



U

LISBOA

UNIVERSIDADE
DE LISBOA



COLÉGIO
de QUÍMICA

1º encontro
**A QUÍMICA
NA INVESTIGAÇÃO
DA ULISBOA**

Book of Abstracts

20 E 21 JULHO 2017
Reitoria da Universidade de Lisboa



UNIVERSIDADE
DE LISBOA



COLÉGIO
de QUÍMICA

Scientific Committee of 1ECQUL

Armando Pombeiro (President), IST

António Almeida, FFUL

Carlos Afonso, FFUL

Carlos Nieto de Castro, FCUL

Cristina Bento, FMH

Francisco Lemos, IST

Helena Pereira, ISA

Manuel Minas da Piedade, FCUL

M^a Fátima Guedes da Silva, IST

Maria José Calhorda, FCUL

Mário Berberan-Santos, IST

Nuno Santos, FMUL

Organizing Committee of 1ECQUL

Maria José Calhorda (President), FCUL

Ana Lourenço, ISA

Carla D. Nunes, FCUL

Carlos Baleizão, IST

Isabel Miranda, ISA

Manuel Almeida, IST

Maria M. M. Santos, FFUL

Pedro Góis, FFUL

Sónia Gonçalves Abreu, FMUL

INDEX

Message from President of the <i>Colégio de Química da Universidade de Lisboa</i>	3
Message from President of the Organizing Committee of 1ECQUL.....	5
Programme	6
Division of Energy & Environment.....	8
Invited Lecturer	9
Oral Communications.....	10
Flash Communications	14
Poster Communications	20
Division of Materials	39
Invited Lecturer	40
Oral Communications.....	41
Flash Communications	47
Poster Communications	53
Division of Technology & Industry.....	93
Invited Lecturer	94
Oral Communications.....	95
Flash Communications	98
Poster Communications	101
Division of Life & Health.....	112
Invited Lecturer	113
Oral Communications.....	114
Flash Communications	123
Poster Communications	129

UNIVERSIDADE
DE LISBOACOLÉGIO
de QUÍMICA

The College of Chemistry of the University of Lisbon (*Colégio de Química da Universidade de Lisboa*, CQUL), by congregating the academic members and researchers of this University with activities in Chemistry (in the broad sense), aims to promote (i) the cohesion in this University and better use of its human and material resources, (ii) the collaboration among its various Schools, (iii) the collaboration with external institutions, (iv) the interdisciplinarity of the various domains of Chemistry and (v) the transdisciplinarity of Chemistry with other sciences in which the former plays an important role.

It concerns a consortium of the following Schools, listed in alphabetical order: Faculdade de Ciências (FCUL), Faculdade de Farmácia (FFUL), Faculdade de Medicina (FMUL), Faculdade de Motricidade Humana (FMH), Instituto Superior de Agronomia (ISA) and Instituto Superior Técnico (IST).

Within the mission of the College, the organization of a first conference (“Chemistry in the Research of the University of Lisbon”) mainly to gather young researchers from these Schools, post-docs and PhD students, as well as invited speakers from external institutions including the industrial sector, should contribute to a better knowledge of their works and to the establishment of collaboration links and networks.

This Conference (the first one organized by this young College and focused on its young members) is of a particular significance at this early stage of the College, although other activities are under way, such as: preparation of a database on the Chemistry research at the University of Lisbon; calls for the award of PhD fellowships for joint research involving at least two Schools and for the award of research prizes; setup of a Newsletter; organization of conferences and summer schools addressed mainly to PhD students, of a workshop with industry and of a major congress of Chemistry; analysis of post-graduation programs; project for the creation of an Institute of Chemistry of the University of Lisbon; etc.

I take the opportunity to acknowledge the efforts of all those who have been involved in the organization of this Conference, represented by the President of the Executive Commission for Research, Prof. Maria José Calhorda, who chairs this event.

I also thank the Rector, Prof. António Cruz Serra, for all his support to this Conference and for his initiative for the creation of this College.

A special welcome word is addressed to all the participants who will be the players in this Conference, hoping that they will benefit from a very fruitful and pleasant scientific event.

Armando Pombeiro

President of the Colégio de Química da Universidade de Lisboa

UNIVERSIDADE
DE LISBOACOLÉGIO
de QUÍMICA

This conference, Chemistry in the Research of the University of Lisbon (ULisbon), is the first event organized within the College of Chemistry of the University of Lisbon (*Colégio de Química da Universidade de Lisboa*, CQUL).

After a series of meetings to define CQUL and to bring it to life, we want to show the science that is being daily performed by the researchers in the six Schools of ULisbon which are part of the College. Despite the short period since we decided to hold this meeting on July 20-21, 2017, more than 200 participants have registered and 168 abstracts for orals (22), flash (24) and poster (124) presentations were accepted. The option for short talks (15 & 5 minutes) gave the possibility for many researchers to present their achievements to all the College members, while PhD and undergraduate students were invited to contribute with posters.

Four invited lectures associated with each Division topic will be delivered by participants from the industry who will emphasize some industrial and environmental challenges and hopefully will contribute to strengthen the links between the two worlds, University and Industry.

I wish that these two days will help the six Schools to get to know one another and to develop new collaborations and joint projects.

Thank you for coming!

Maria José Calhorda

President of the Organizing Committee

PROGRAMME

July 20 th	
08h30	Check-in
09h30-10h00	Opening Session António Manuel da Cruz Serra (Rector of ULisboa) Armando J. L. Pombeiro (Pres. Coordination Council CQUL) Maria José Calhorda (Pres. Organizing Committee 1ECQUL)
Energy & Environment	
10h00-10h30	Invited Lecturer José Bravo Ferreira (Secil)
<i>Coffee Break</i>	
10h30-11h00	Poster Session
11h00-12h30	Oral (15 min) & Flash (5 min) Presentations [F] Tiago A. Fernandes (CQB-FCUL) [O] Bruno Pedras (CQFM-IST) [F] Virgínia C. Ferreira (CQB-FCUL) [O] Tânia Ribeiro (CQFM-IST) [F] Susanta Hazra (CQE-IST) [F] Anirban Karmakar (CQE-IST) [O] Elisabete R. Silva (CQB-FCUL & CERENA-IST) [F] Andreia A. Rosatella (iMed.ULisboa-FFUL) [O] Manas Sutradhar (CQE-IST) [F] João P. C. Tomé (CQE-IST)
<i>Lunch</i>	
Materials	
14h00-14h30	Invited Lecturer Jorge Moniz dos Santos (Resiquímica)
14h30-15h30	Oral (15 min) & Flash (5 min) Presentations [O] José Paulo Farinha (CQFM-IST) [F] Nuno A. G. Bandeira (ICIQ-Espanha, CQE-IST & CQB-FCUL) [O] Ana Maria Ferraria (CQFM/IN-IST) [F] Dulce Belo (C ² TN-IST) [O] António P. Gonçalves (C ² TN-IST) [F] Carlos E. S. Bernardes (CQB-FCUL & CQE-IST)
<i>Coffee Break</i>	
15h30-16h30	Poster Session
16h30-17h30	Oral (15 min) & Flash (5 min) Presentations [O] Ana S. Mestre (CQB-FCUL) [F] Carina I. C. Crucho (CQFM/IN-IST) [O] João Pires (CQB-FCUL) [F] João P. Leal (C ² TN-IST) [O] Sandra Rabaça (C ² TN-IST) [F] Inês F. A. Mariz (CQFM/IN-IST)

July 21 st	
08h30	Check-in
Technology & Industry	
09h00-09h30	Invited Lecturer Miguel Cabral (Corticeira Amorim)
09h30-10h30	Oral (15 min) & Flash (5 min) Presentations [O] Cláudia A. Figueira (CQE-IST) [F] Cátia P. Carvalho (iMed.Ulisboa-FFUL) [O] Liliana M. Martelo (CQFM/IN-IST & DQ/IRS-UCoimbra) [F] Clara S. B. Gomes (CQE-IST) [O] Ana Catarina Sousa (ISEL & CQE-IST) [F] Ana P. C. Ribeiro (CQE-IST)
<i>Coffee Break</i>	
10h30-11h30	Poster Session
Life & Health	
11h30-12h30	Oral (15 min) & Flash (5 min) Presentations [O] Vasco D. B. Bonifácio (CQFM/IN-IST) [F] Filomena A. Carvalho (iMM-FMUL) [O] Marco M. Domingues (iMM-FMUL) [F] Fábio Fernandes (CQFM/IN-IST & UCIBIO/REQUIMTE-FCTUNL) [O] Hélio Faustino (iMed.Ulisboa-FFUL)
<i>Lunch</i>	
14h00-14h30	Invited Lecturer Carlos Romão (Alfama)
14h30-15h30	Oral (15 min) & Flash (5 min) Presentations [O] Joana Ferreira (CEF-ISA) [F] Ana Paula Francisco (iMed.Ulisboa-FFUL) [O] Alexandra Paulo (iMed.Ulisboa-FFUL) [F] Catarina N. Matias (CIPER-FMH & INSA) [O] António Paulo (C ² TN-IST)
<i>Coffee Break</i>	
15h30-16h30	Poster Session
16h30-17h30	Oral (15 min) & Flash (5 min) Presentations [O] Amélia P. Rauter (CQB-FCUL) [F] Adrià Gil (CQB-FCUL) [O] Patrícia Rijo (CBIOS-ULHT & iMed.Ulisboa-FFUL) [F] Sónia Gonçalves (iMM-FMUL) [O] Bruno L. Victor (CQB-FCUL)
17h30-18h00	Closing Session Francisco Lemos (Pres. Division E&E) Mário Berberan-Santos (Pres. Division Mat) Carlos Nieto de Castro (Pres. Division T&I) Helena Pereira (Pres. Division L&H)

Energy & Environment

Chemistry role on cement production, on the control of the associated environmental impacts and on sustainable construction solutions

José Bravo Ferreira

Secil

A brief presentation of the chemistry role all along the cement production cycle in current installations and new alternatives in the cement developing domain.

Best Available Technologies, chemical based, used to control the cement production environmental impacts.

CO₂ emissions mitigation, technologies currently used and new developing trends.

Chemistry role on the election of the current construction cement based materials and reference to new developments towards a more sustainable construction, during all the life cycle.

1. Chemistry role on cement production
 - 1.1. Current cements
 - 1.2. Developing new cements

2. Chemistry role on the control of the associated environmental impacts
 - 2.1. Control of the main impacts according with the Industrial Emissions Directive
 - 2.2. CO₂ mitigation
 - 2.2.1. Current solutions
 - 2.2.2. New developments

3. Chemistry role on sustainable construction solutions
 - 3.1. Current cement based materials
 - 3.2. New developments

Novel phenoxazine and phenothiazine derivatives for OLED applications

Bruno Pedras^a, Faiza Baraket^{a,c}, Érica Torres^{a,b}, Maria João Brites^b, Mohamed Dammak^c,
Mário Nuno Berberan-Santos^a

^a CQFM, Centro de Química-Física Molecular, Instituto Superior Técnico, Universidade de Lisboa, 1049-001
Lisboa, Portugal

^b LNEG, UES Unidade de Energia Solar, Estrada do Paço do Lumiar, 22, 1649-038 Lisboa, Portugal

^c Department of Inorganic Chemistry, University of Sfax, Tunisia

Luminescent materials for organic light-emitting diodes (OLEDs) have been an important subject of both academic and industrial research in recent years.¹ Although OLEDs that employed fluorescent materials have been progressively replaced by metal-based phosphorescent materials, the latter exhibit certain disadvantages, such as cost and the need to use heavy metals. Recently, organic emitters displaying thermally-activated delayed fluorescence (TADF) have become relevant in this field, leading to remarkable results.^{2,3}

In this communication are presented different novel phenoxazine and phenothiazine luminescent derivatives, which were designed having in mind their ability to display TADF, in order to explore their potential application in OLEDs.

Acknowledgements

Support for this work was provided by FCT through FAPESP/20107/2014.

B. Pedras acknowledges financial support from FCT-Portugal, through the post-doctoral grant SFRH/BPD/104295/2014.

References

- [1] S. Reineke, F. Lindner, G. Schwartz, N. Seidler, K. Walzer, B. Lussem, K. Leo, *Nature* 459 (2009) 234.
- [2] H. Uoyama, K. Goushi, K. Shizu, H. Nomura, C. Adachi, *Nature* 492 (2012) 234.
- [3] G. Mehes, H. Nomura, Q. Zhang, T. Nakagawa, C. Adachi, *Angew. Chem. Int. Ed.* 51 (2012) 11311.

Hybrid nanoparticles with application in photovoltaic solar cells

Tânia Ribeiro, Carlos Baleizão, José Paulo S. Farinha

*CQFM-Centro de Química-Física Molecular, IN-Institute of Nanosciences and Nanotechnology,
Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal*

Solar energy conversion based on organic photovoltaic (OPV) cells is a promising clean and sustainable source of energy and exciting research area. A major challenge in the development of better OPV is the trade-off between light absorption and photogenerated exciton collection, requiring that the polymer film has both high absorbance and low thickness. One promising approach to enhance light harvesting in OPVs is based on the use of noble metal nanostructures such as gold or silver, which can act as local field enhancers^{1,2} and/or light scattering centers³. Here, we prepared and characterized gold nanoparticles (spheres and stars) and coated them with insulating silica shell of 7 to 20 nm to avoid charge recombination (Figure 1). A high quantum yield perylenediimide (PDI) dye was attached to the silica surface of the nanospheres avoiding fluorescence quenching. We predicted emission enhancements of 5 to 30 times without change in the dye emission lifetime, attributed to the increased local electromagnetic field around the metal.¹ The nanoparticles were incorporated in the active layer of a OPV device, in order to study the interfacial charge and energy transfer processes at the nanoscale.

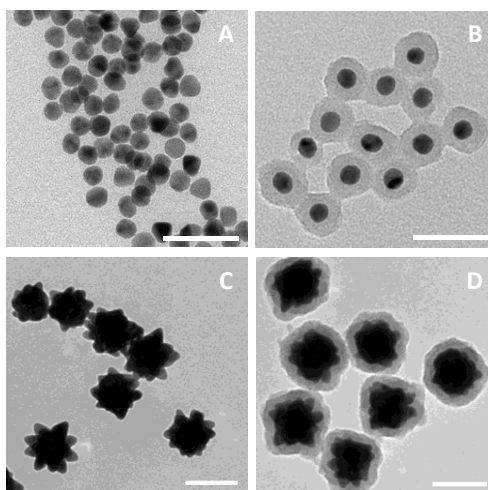


Figure 1. TEM images of hybrid core-shell nanoparticles with gold spheres (**A**) and gold stars (**C**) in the core encapsulated with a silica shell (**B and D**). Scale bar: 50 nm (A and B), 100 nm (C and D).

Acknowledgements

This work was partially supported by Fundação para a Ciência e a Tecnologia (FCT-Portugal) and COMPETE (FEDER), projects UID/NAN/50024/2013, RECI/CTM-POL/0342/2012, PTDC/CTM-POL/3698/2014 and grant SFRH/BPD/96707/2013.

References

- [1] T. Ribeiro, C. Baleizão, J.P.S. Farinha, *Scientific Reports* 7 (2010) 2440.
- [2] R. Alvarez-Puebla, L.M. Liz-Marzán, F.J. García de Abajo, *J. Phys. Chem. Lett.* 1 (2010) 2428.
- [3] E. Stratakis, E. Kymakis, *Materials Today* 16 (2013) 133.

A new Eco-friendly solution for biofouling prevention

O. Ferreira^{1,2}, J. Gomes^{2,3}, J. C. Bordado², M. J. Calhorda¹, E. R. Silva^{1,2}

¹Centro de Química e Bioquímica (CQB), FCUL-UL, 1749-016 Lisboa, Portugal

²Centro de Recursos Naturais e Ambiente (CERENA), IST- UL, 1049-001 Lisboa, Portugal

³Área Departamental de Engenharia Química, ISEL- IPL, 1959-007 Lisboa, Portugal

Contamination with microorganisms (biofouling) causes serious environmental/economic penalties and health risks on several applications (e.g. water circuits, shipping). This work aims to develop a new non-toxic solution able to control biofouling, through innovative approaches such as the immobilization of biocidal agents (e.g. Ecomea) in polymeric coatings for surfaces protection. A recent patented method was used for this purpose, in which non-releasing biocidal systems were developed by providing new functional biocides (e.g. Ecomea-NCO) capable of being tethered in polymeric coatings.¹ Antifouling/antimicrobial polymeric systems were prepared and applied on different materials supports (e.g. ceramic structures polymeric subtracts). Uniform polymeric films were obtained and mechanical tests revealed similar adhesion behaviour for biocidal coatings and their commercial counterpart without biocide. Bioactivity assessment of functional biocides and coatings containing tethered biocides evidenced antimicrobial activity, particularly against *S. aureus* microorganisms, suggesting that the biocide properties were not significantly affected by the immobilization in the polymeric matrix. Antifouling behaviour at simulated and real conditions evidenced promising results (Figure 1). In addition, and in accordance with the European Standards, these coating systems were also classified as non-toxic for the environment and appear to promote a better anticorrosion protection when compared to its reference counterpart without biocide.² Our ultimate goal is to adapt this potential immobilization strategy with proved efficacy for surfaces protection in water treatments circuits.

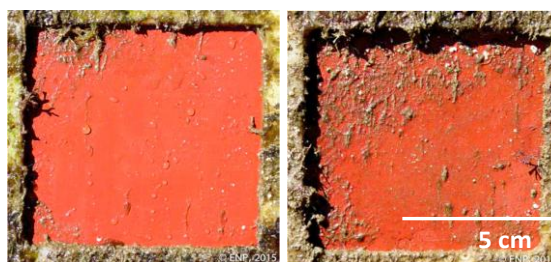


Figure 1. Performance of a commercial silicone marine based coating after 43 months of exposure in Atlantic seawater: (left) containing tethered Ecomea biocide, (right) free of biocide. Photo gently provided by ENP, SA.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and Pest-OE/QUI/UI0612/2013. O. Ferreira and E.R. Silva also acknowledge for the financial support from FCT, PhD Grant PD/BD/128370/2017 and Post-Doc fellowship SFRH/BPD/88135/2012, respectively. The authors also thank HEMPEL A/S and P. Rijo for the work collaboration.

References

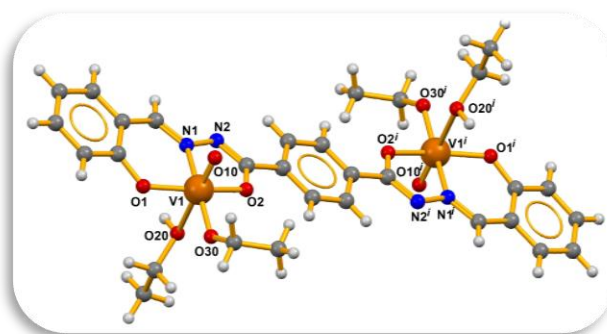
- [1] E.R. Silva, O. Ferreira, J.C. Bordado, Patent Application, WO2016/093719 A1, 2016.
- [2] E.D. Kiosidou, A. Karantonis, D.I. Pantelis, E.R. Silva, J.C. Bordado, J. Coat Technol. Res. 14(2) (2017) 333-345.

Vanadium catalyzed mild oxidation reactions

Manas Sutradhar, Armando J. L. Pombeiro

*Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa,
Av. Rovisco Pais, 1049-001 Lisboa, Portugal*

Vanadium plays an important role as a catalyst or catalyst precursor in many organic transformations. The catalytic activity of vanadium in various peroxidative oxidation reactions under mild conditions in homogeneous or heterogeneous (supported) conditions¹⁻³ is an area of current interest. Existence of variable oxidation states (from -3 to +5, where +4 and +5 are the most stable ones under aerobic conditions and easily interconvertible) may be a key factor behind its activity. Moreover, its Lewis acidic character and the high affinity towards oxygen may enhance the catalytic activity.¹



This presentation mainly deals with some important vanadium catalyzed peroxidative oxidation reactions, e.g. oxidation of alkanes, alcohols, under homogeneous and supported heterogeneous conditions including the use of microwave irradiation in the oxidation reactions. The catalytic activity of oxidovanadium complexes (mainly containing azine fragment (C=N–N=C) ligands) under mild conditions and the effects of different factors with proposed mechanisms will be presented.

Acknowledgements

Authors are grateful to the Fundação para a Ciência e a Tecnologia (FCT), Portugal, for financial support (projects UID/QUI/00100/2013, PTDC/QEQ-QIN/3967/2014 and PTDC/QEQ-ERQ/1648/2014).

M. Sutradhar acknowledges the FCT, Portugal, for a postdoctoral fellowship (SFRH/BPD/86067/2012).

References

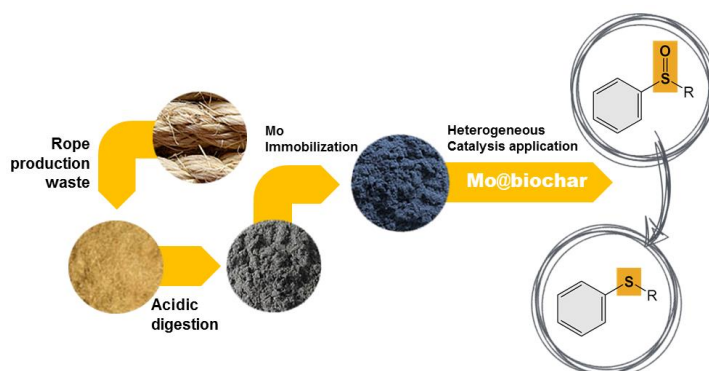
- [1] M. Sutradhar, A.J.L. Pombeiro, *Coord. Chem. Rev.* 265 (2014) 89-24.
- [2] M. Sutradhar, L.M.D.R.S. Martins, M.F.C. Guedes da Silva, A.J.L. Pombeiro, *Coord. Chem. Rev.* 301 (2015) 200-239.
- [3] M. Sutradhar, L.M.D.R.S. Martins, S.A.C. Carabineiro, M.F.C. Guedes da Silva, J.G. Buijnsters, J.L. Figueiredo, A.J.L. Pombeiro, *ChemCatChem* 8 (2016) 2254-2266.

Mo catalysts supported on sisal derived biochars (Mo@biochar) for heterogeneous reductive deoxygenation

Tiago A. Fernandes¹, Tiago A. G. Duarte^{1,2}, Ana S. Mestre¹,
Ana P. Carvalho¹, Maria J. G. Ferreira², Maria José Calhorda¹
¹Faculdade de Ciências, Centro de Química e Bioquímica, ULisboa, Portugal
²Instituto Superior Técnico, Centro de Química Estrutural, ULisboa, Portugal

The deoxygenation of sulfoxides is rather important from both the synthetic and the biological point of view, owing to their potential as intermediates in a variety of synthetic transformations, mainly as chiral auxiliaries for the synthesis of biologically active compounds.¹ Thus there is a continuous interest in developing new deoxygenation methods.²

The current work aims at obtaining two new Mo@biochar materials to be tested in sulfoxides deoxygenation. The biochar support was obtained by acidic carbonization of sisal residues.³ The material has an acid surface, as demonstrated by the pH_{zpc} values (1.8), allowing it to be considered as support for two oxomolybdenum(VI) compounds, [MoO₂Cl₂(H₂O)₂] and Na₂MoO₄·2H₂O. The immobilized catalysts were characterized by IR spectroscopy, elemental analysis, inductively coupled plasma mass spectrometry (ICP-OES), solid state NMR, and SEM, and evaluated for their catalytic activity in sulfoxides reduction (Scheme 1). The Mo@biochar materials acted as efficient catalysts in the heterogeneous reduction of aryl sulfoxides to the corresponding sulfides in the presence of a reducer agent, such as phenylsilane. The reaction parameters were investigated (e.g. type and loading of catalyst, temperature, solvent, reductant, acid promoter (HCl), and substrate), and total conversion into products was achieved after 24 h. This use of a carbon recycled materials as a support, besides being a clever and environmentally sustainable idea, proved to be a good strategy to develop new heterogeneous catalysts.



Scheme 1

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013.

References

- [1] C. Chatgililoglu, K.D. Asmus (Eds.), Sulfur Centered Reactive Intermediates in Chemistry and Biology, Nato ASI series, Plenum Press, New York, 1990.
- [2] a) A.C. Fernandes, J.A. Fernandes, C.C. Romão, L.F. Veiros, M.J. Calhorda, *Organometallics* 29 (2010) 5517-5525; b) T.A. Fernandes, A.C. Fernandes, *ChemCatChem* 7 (2015) 3503-3507.
- [3] L. Wang, Y. Guo, Y. Zhu, Y. Li, Y. Qu, C. Rong, X. Ma, Z. Wang, *Bioresource Technol.* 101 (2010) 9807-9810.

In situ synthesis and modification of fibers with photoactive semiconducting nanoparticles for pollutants removal

Virgínia C. Ferreira, Inês Ferreira, Olinda C. Monteiro

Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

The development of textile fibers modified with nanoparticles (NPs) has been subject of intense research in recent years due to the possibility of conferring new and improved properties to those materials, such as antibacterial and antifungal, control of the wettability, self-cleaning, photocatalytic, magnetic shielding and UV blocking.¹ A wide variety of semiconducting nanoparticles (NPs) has been used, for example metal oxides, chalcogenides and other.¹⁻³ The resulting composite materials have shown interesting properties such as phototacalalytic activity imparted by the semiconducting nanoparticles.^{2,3}

In this work, the successful modification of fibers with semiconducting NPs was achieved using *in situ* approaches. Here, different NPs were used, for example BiOCl and Bi₂S₃, and the resulting composites were structural, morphological and optically characterised using several techniques. This allowed establishing structure/properties relationships. The prepared materials were then used for the removal of dye molecules, for example those used in the leather industry. The composites displayed good photocatalytic response indicating to be suitable for the degradation of pollutants using UV and/or visible light irradiation.

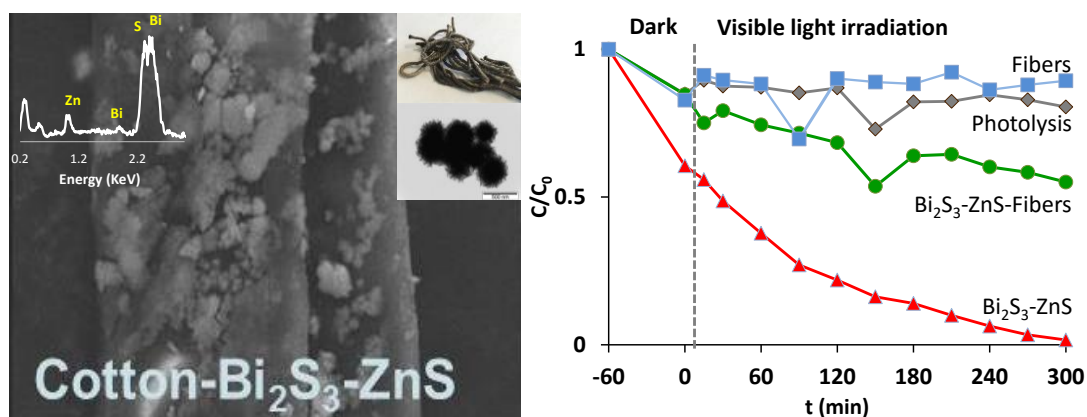


Figure 1. Example of modified fibers with NPs and their photocatalytic response under visible light.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. V.C. Ferreira acknowledges financial support from Fundação para a Ciência e a Tecnologia through grant SFRH/BPD/77404/2011.

References

- [1] A.K. Yetisen, H. Qu, A. Manbachi, H. Butt, M.R. Dokmeci, J.P. Hinstroza, M. Skorobogatiy, A. Khademhosseini, S.H. Yun, *ACS Nano* 10 (2016) 3042-3068.
- [2] M. Abid, S. Bouattour, D.S. Conceição, A.M. Ferraria, L.F.V. Ferreira, A.M. Botelho do Rego, M.R. Vilar, S. Boufi, *RSC Adv.* 6 (2016) 58957-58969.
- [3] Z. Du, R. Guo, J. Lan, X. Jiang, S. Lin, C. Cheng, L. Zhao, *Surf. Coat. Technol.* 319 (2017) 219-229.

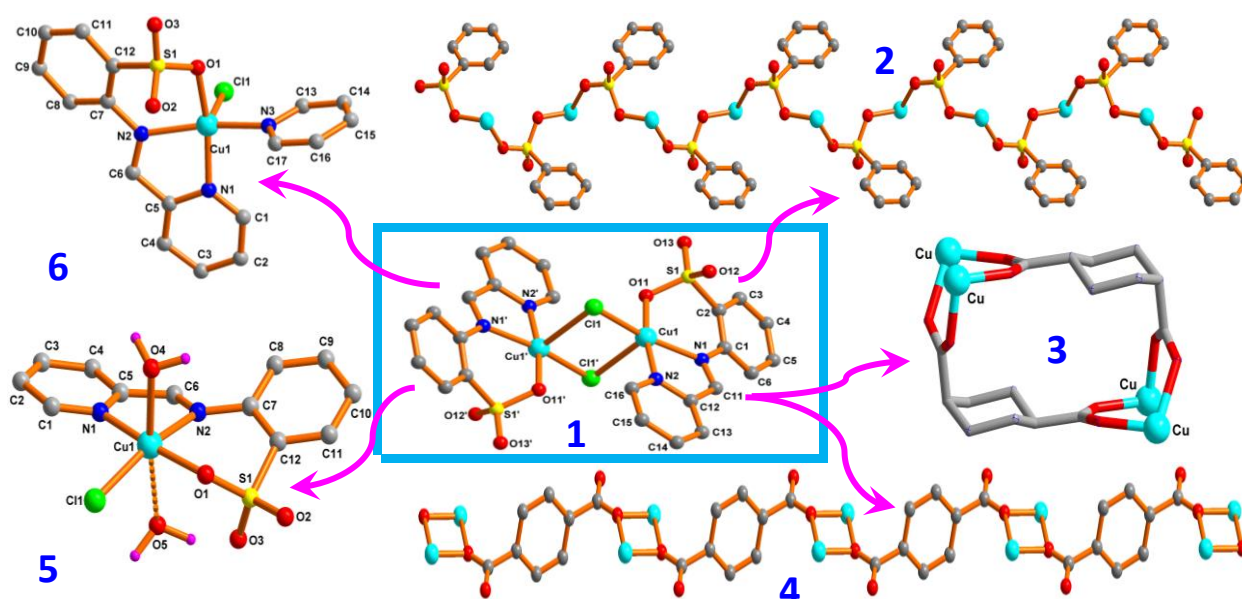
A versatile dicopper precursor for catalysts and bio-active molecules

Susanta Hazra^a, Ana P. C. Ribeiro^a, Anup Paul^a, Gunjan Sharma^b, Biplob Koch^b,
M. Fátima C. Guedes da Silva^a and Armando J. L. Pombeiro^a

^a Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais,
1049-001 Lisboa, Portugal

^b Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi-221005, India

Reaction of a dicopper(II) complex (**1**) with di- to tetracarboxylic acids produces polynuclear systems (**2-4**) which are catalysts¹⁻³ for cyclohexane oxidation in both conventional (CH₃CN) and non-conventional (ionic liquid) solvents. In the presence of coordinating solvents (pyridine or water) the compound **1** collapses into mononuclear systems (**5** and **6**), one of which (**6**) shows better cytotoxic activity than the standard drug *cis*-platin against breast cancer cells.⁴



Acknowledgements

Financial support for this work was provided by FCT through PEst-OE/QUI/UI0100/2013 and UID/QUI/00100/2013. S. Hazra, A.P.C. Ribeiro and A. Paul acknowledge financial support from FCT, Portugal, for their fellowship grants (SFRH/BPD/78264/2011, SFRH/BPD/90883/2012 and SFRH/BPD/88450/2012, respectively). B. Koch and G. Sharma acknowledge partial financial supports from CAS-UGC phase V, New Delhi, India and Interdisciplinary School of Life Sciences (ISLS), Banaras Hindu University, for access to FACS facility.

References

- [1] S. Hazra, A.P.C. Ribeiro, M.F.C. Guedes da Silva, C.A. Nieto de Castro, A.J.L. Pombeiro, Dalton Trans. 45 (2016) 13957-13968.
- [2] S. Hazra, S. Mukherjee, M.F.C. Guedes da Silva, A.J.L. Pombeiro, RSC Adv. 4 (2014) 48449-48457.
- [3] A.P.C. Ribeiro, L.M.D.R.S. Martins, S. Hazra, A.J.L. Pombeiro, Compt. Rend. Chim. 18 (2015) 758-765.
- [4] A. Paul, S. Hazra, G. Sharma, M.F.C. Guedes da Silva, B. Koch, A.J.L. Pombeiro, J. Inorg. Biochem. 174 (2017) 25-36.

Metal Organic Frameworks based on Amidoisophthalic acid ligands: a useful material for heterogeneous catalysis

Anirban Karmakar, M. Fátima C. Guedes da Silva and Armando J. L. Pombeiro
*Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais,
1049-001, Lisbon, Portugal*

Metal-organic frameworks (MOFs) are crystalline coordination networks consisting of metal ions or clusters and multidentate organic ligands.¹ This area of research is currently undergoing a rapid growth due to their potential applications as functional materials in heterogeneous catalysts, magnetism, nonlinear optics, gas storage and separation, etc.² Moreover, MOFs constructed from amide based linkers have attracted considerable attention due to their interesting topologies as well as catalytic properties.³ Thus, we have synthesized three different amidoisophthalic acid ligands, such as 5-acetamidisophthalic acid, 5-propionamidisophthalic acid and 5-benzamidisophthalic acid (Figure 1A), and employed them for the construction of various MOFs. Solvothermal reaction of zinc(II) and cadmium(II) salts with these ligands in presence or absence of an auxiliary ligand gives rise to a series of 1D, 2D and 3D Zn(II) or Cd(II) MOFs (Figure 1B). We have characterized them by X-ray single crystal diffraction, elemental microanalysis, IR spectroscopy, thermogravimetric analysis and powder X-ray diffraction analysis. These MOFs act as effective heterogeneous catalysts for various organic transformations, for example Knoevenagel condensation, Henry and transesterification reactions under mild conditions and can be recycled without losing activity.

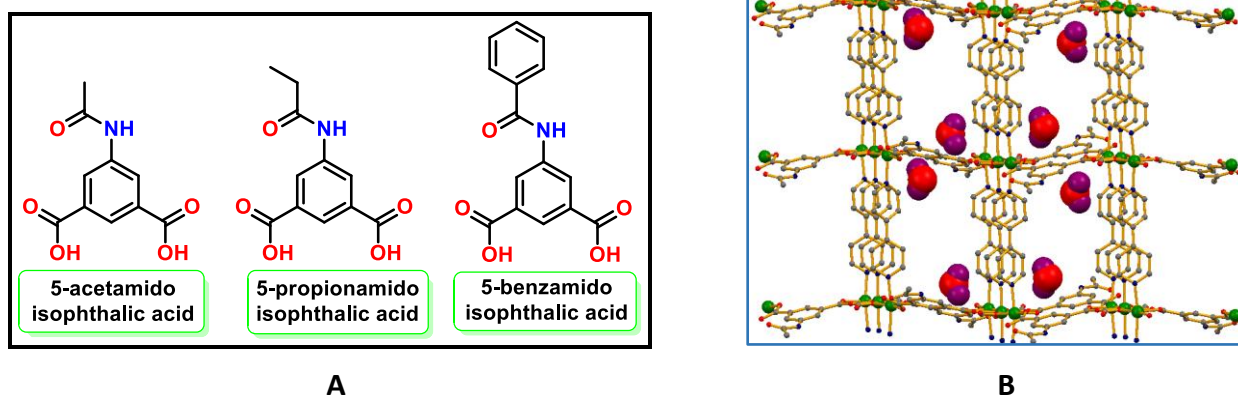


Figure 1: (A) Chemical diagrams of three amidoisophthalic acid ligands; (B) Representative example of a 2D MOF obtained by the reaction amidoisophthalic acid linker and a Zn(II) salt.

Acknowledgements

This work has been supported by the Foundation for Science and Technology (FCT), Portugal (project UID/QUI/00100/2013). A. Karmakar acknowledges financial support from FCT for post-doctoral fellowship (SFRH/BPD/76192/2011).

References

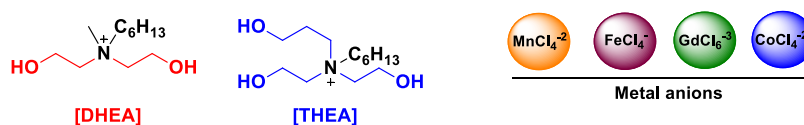
- [1] A. Karmakar, H.M. Titi, I. Goldberg, *Cryst. Growth Des.* 11 (2011) 2621-2636.
- [2] H.-C. Zhou, S. Kitagawa, *Chem. Soc. Rev.* 43 (2014) 5415-5418.
- [3] A. Karmakar, M.F.C. Guedes da Silva, A.J.L. Pombeiro, *Dalton Trans.* 43 (2014) 7795-7810.

A New Family of Magnetic Ionic Liquids

Andreia A. Rosatella, Filipa Siopa, Raquel F. M. Frade, Carlos A. M. Afonso
iMed.UL, Faculdade de Farmácia, ULisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal

In 2004 was described a new type of magnetic materials based on paramagnetic metal salts – Magnetic Ionic Liquids (MILs).¹ Several MILs have been reported as combination of different organic cations with anionic metal complexes possessing magnetic properties.² In spite of the high propensity to crystalize of the anionic metal complexes, there are few reported MILs that are liquid at rt. In addition the cation can also contribute for the MIL high tendency to crystalize, thus for cations with strong hydrogen bond donor (like imidazolium) the formation of an organized network of hydrogen bonding is enhanced resulting in a more organized structure. On the other hand, cations that don't have this hydrogen bonding network (e.g. tetraalkylphosphonium) have a low tendency to crystalize,³ although these cations are quite toxic.⁴ Different applications have been reported for MILs, for example, in collaboration with this laboratory, Crespo *et al.* have reported the preparation of supported MILs membranes for CO₂ separation and also observed a remarkable reduction of the MILs viscosity in the presence of an applied magnetic field.⁵

In this work is presented a new family of cholinium based MILs (Scheme) that are liquid at rt, even in combination with paramagnetic anions FeCl₄⁻, CoCl₄²⁻, MnCl₄²⁻ and GdCl₆³⁻.⁶ We have studied the viscosity of these MILs and it was very interesting to observe that the insertion of one and two ethanol chains ([DHEA] and [THEA]) largely decreases the viscosity of the MILs. Indeed, at 298 K, [THEA]Fe presents a viscosity of 142 mPa s, which is lower than the reported value for [P_{6,6,6,14}]Fe, 650 mPa s. Additionally, we have also reported that these new family of MILs are prone to generate low toxicities on human cell lines (even at high concentrations)^{4,6} and we have evaluated their ecotoxicity towards the luminescent bacteria *Vibrio fischeri*.⁷



Scheme: Synthesis of Magnetic Ionic Liquids based on cholinium cations.

Acknowledgements

We thank the Fundação para a Ciência e Tecnologia for financial support (SFRH/BPD/75045/2010, SFRH/BPD/73822/2010, SFRH/BPD/88666/2012, PTDC/QEQ-PRS/2824/2012).

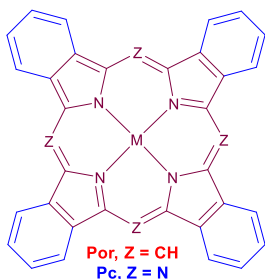
References

- [1] S. Hayashi, H.O. Hamaguchi, Chem. Lett. 33 (2004) 1590-1591.
- [2] E. Santos, J. Albo, A. Irabien, Rsc Advances 4 (2014) 40008-40018.
- [3] R.E. Del Sesto, T.M. McCleskey, A.K. Burrell, G.A. Baker, J.D. Thompson, B.L. Scott, J.S. Wilkes, P. Williams, Chem. Commun. (2008) 447.
- [4] i) R.F.M. Frade, S.P. Simeonov, A.A. Rosatella, F. Siopa, C.A.M. Afonso, Chemosphere 92 (2013) 100; ii) R.F.M. Frade, C.A.M. Afonso, Hum. Exp. Toxicol. 29 (2010) 1038.
- [5] i) A.J. Albo, E. Santos, L.A. Neves, S.P. Simeonov, C.A.M. Afonso, J.G. Crespo, A. Irabien, Sep. Purif. Technol. 97 (2012) 26-33; ii) E. Santos, J. Albo, C.I. Daniel, C.A.M. Afonso, J.G. Crespo, A. Irabien, J. Membr. Sci. 430 (2013) 56-61.
- [6] A.A. Rosatella, F. Siopa, R.F.M. Frade, C.A.M. Afonso, New J. Chem. 40 (2016), 3124-3129.
- [7] T.E. Sintra, M. Nasirpour, F. Siopa, A.A. Rosatella, F. Gonçalves, J.A.P. Coutinho, C.A.M. Afonso, S.P.M. Ventura, Ecotoxicol. Environ. Saf. 143 (2017) 315-321.

Light on chemistry: photoactive materials for light-based technologies

João P. C. Tomé

CQE, Departamento de Engenharia Química, Instituto Superior Técnico, Universidade de Lisboa,
1049-001 Lisboa; E-mail: jtome@tecnico.ulisboa.pt



Light-based technologies, in the last decades, have been mostly developed and implemented in many different areas, such as on: photomedicine, photoinduced energy- and electron-transfer materials, photocatalysis and on optical sensor devices.¹⁻⁶ In our lab we have been working on the synthesis of novel porphyrin (Por) and phthalocyanine (Pc) dyes with different motifs, at the periphery of their cores, and metals. These molecular refinements allow us to prepare more efficient drugs, to build novel metal coordination

polymers and/or to combine them with different nanomaterials, all of them with unique properties for the above applications. Many of these (photo)active functional molecules and materials have been evaluated in cancer photodynamic therapy (PDT)¹ and microorganism photodynamic inactivation (PDI),² in both cases acting as singlet oxygen generators. Others have been studied in electronic and light-harvesting devices,³ to reduce the fossil energy needs, or in photocatalysis,⁴ trying to have more sustainable chemical processes than the century old ones. More recently, with the tremendous need to control pollutants and dangerous materials, these dyes have been explored as optical (chemo)sensors, such as for anions⁵ and nitroaromatic compounds.⁶ In this communication some of our most recent works will be shown, highlighting the used synthetic strategies and the obtained results in the indicated applications.

Acknowledgements

Thanks are due to FCT/MEC for the financial support to CQE (FCT UID/QUI/0100/2013) and QOPNA (FCT UID/QUI/00062/2013) research units, through national funds and where applicable co-financed by the FEDER, within the PT2020 Partnership Agreement. I further wish to thank FCT for funding the projects PTDC/QUI/65228/2006 and PTDC/CTM/101538/2008; CNPq (Brazil) for funding the program “Ciência sem Fronteiras/2012” (4802069445108663); and to Seventh Framework Programme (FP7-People-2012-ITN) for funding the SO₂S project (grant agreement number: 316975).

References

- [1] a) B. Korsak *et al.*, *Int. J. Cancer* (2017), *accepted*; b) P.M.R. Pereira *et al.*, *PlosOne* (2017) 1-21; c) J.T. Ferreira *et al.*, *J. Mat. Chem. B* (2017), *accepted*; d) P.M.R. Pereira *et al.*, *Bioconjug. Chem.* 27(11) (2016) 2762-2769; e) P.M.R. Pereira *et al.*, *Eur. J. Cancer* 68 (2016) 60-69.
- [2] a) A. Almeida *et al.*, *Future Med. Chem.* 7(10) (2015) 1221-1224; b) L.M.O. Lourenço *et al.*, *Photochem. Photobiol. Sci.* 14 (2015) 1853-1863.
- [3] a) L. Wibmer *et al.*, *Nanoscale* 7 (2015) 5674-5682; b) L.M.O. Lourenço *et al.*, *ChemPlusChem* 80(5) (2015) 832-838; c) A.E. Schuckman *et al.*, *J. Phys. Chem. C* 119(24) (2015) 13569-13579.
- [4] a) K.A.D.F. Castro *et al.*, *ChemCatChem* (2017), *accepted*; b) L. Fernández *et al.*, *Dyes and Pigments* (2017) 535-543; c) K.A.D.F. Castro *et al.*, *J. Catal.* 344 (2016) 303-312; d) K.A.D.F. Castro *et al.*, *Inorg. Chem.* 54(9) (2015) 4382-4393.
- [5] a) F. Figueira *et al.*, *Chemistry - A European Journal* 22(40) (2016) 14349-14355; b) F. Figueira *et al.*, *ChemComm* 52 (2016) 2181-2184; c) J.M.M. Rodrigues *et al.*, *Sensors & Actuators B* 224 (2016) 81-87.
- [6] a) N. Venkatramaiah *et al.*, *Anal. Chem.* 87(8) (2015) 4515-4522; b) N. Venkatramaiah *et al.*, *J. Mater. Chem. C* 3 (2015) 1056-1067; c) N. Venkatramaiah *et al.*, *Chem. Commun.* 50 (2014) 9683-9686.

The role of cascade complexes in the activation of CO₂

Janaína C. Almeida^a, Sara Realista^a, Sónia Barroso^b, Maria José Calhorda^a,
Paulo N. Martinho^a

^a Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal

^b Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Avenida Rovisco Pais,
1049-001 Lisboa, Portugal

Host-guest structures have proved to be useful for the recognition and activation of small molecules.¹ Cascade complexes with polyaza ligands have demonstrated ability to bind different small molecules by adapting their binding sites towards these molecules. Nelson's cryptands² are an example of a dynamic structure with useful applications, which demonstrated the ability to capture and convert CO₂ to carbonate and methyl carbonate following its coordination to encapsulated metal ions. Here we explore the fixation chemistry of small molecules by derivatised dinuclear Cu(II), Ni(II) cryptands (Figure 1) where the phenyl ring was modified towards engineering these metal-organic structures into supramolecular assemblies. Attaching electron withdrawing or electron donating groups to the phenyl ring proved to affect their ability to capture CO₂. Synthesis of the cryptates were performed under N₂ and CO₂ atmosphere, to understand the substituent effect, DFT studies were performed, and their behaviour was studied by cyclic voltammetry.

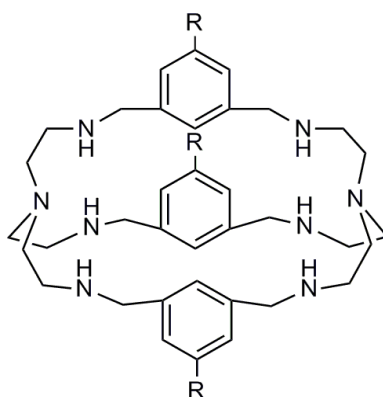


Figure 1. Derivatised cryptands.

Acknowledgements

Support for this work was provided by Fundação para a Ciência e a Tecnologia (UID/MULTI/00612/2013, PTDC/QEQ-QIN/3414/2014).

P.N. Martinho (SFRH/BPD/73345/2010) and S. Realista (PD/BD/52368/2013) thank FCT for financial support.

References

- [1] D.-C. Zhongab, T.-B. Lu, Chem. Comm. 52 (2016) 10322-10337.
- [2] Y. Dussart, C. Harding, P. Dalgaard, C. McKenzie, R. Kadirvelraj, V. McKee, J. Nelson, J. Chem. Soc., Dalton Trans. (2002) 1704.

Chemical effects of a mild torrefaction on the wood of eight *Eucalyptus* species
Solange de Oliveira Araújo¹, Duarte M. Neiva¹, Jorge Gominho¹, Bruno Esteves²,
Helena Pereira¹

¹ Centro de Estudos Florestais, Instituto Superior de Agronomia, Universidade de Lisboa, Tapada da Ajuda,
1349-017 Lisboa, Portugal

² Escola Superior de Tecnologia e Gestão de Viseu, Instituto Politécnico de Viseu, Av. Cidade Politécnica,
Campus Politécnico, 3504-510, Viseu, Portugal

Forest biomass is one renewable source that can be converted into energy via e.g. thermochemical and biochemical conversions.¹ However, the chemical features of biomass may negatively influence the energy properties of the material, e.g. high oxygen content, low calorific value, hydrophilic nature and high moisture content. One way to improve the biomass quality for use as biofuel is to perform a thermal pre-treatment such as torrefaction. Torrefaction corresponds to a mild pyrolysis. It is a pre-carbonization process occurring in the endothermic pyrolysis phase, between 200 and 300 °C, carried out with low heating rate, in an environment with reduced or absent oxygen concentrations, for short residence times of a few hours at the most, thereby allowing to retain the volatile higher heating value in the product.²

This study compared the wood of eight eucalypt species (*Eucalyptus botryoides*, *E. globulus*, *E. grandis*, *E. maculata*, *E. propinqua*, *E. rudis*, *E. saligna* and *E. viminalis*) during a mild torrefaction. The mass loss during torrefaction, and the equilibrium moisture content, density, chemical composition and FTIR of the initial and torrefied woods were determined. The average mass loss was 11% and the heat-treated woods had an overall 10% density decrease. All the heat-treated woods presented lower equilibrium moisture content values corresponding to an average reduction of 50%. The chemical changes induced by the heat treatment were an increase of extractives, a 20% higher lignin content and a 16% decrease of holocellulose in relation to the untreated wood. The hemicelluloses were affected by torrefaction with a decrease of xylose, galactose and acetyl groups in the torrefied woods. The FTIR spectra reflected the chemical changes of the heating treatment. Similar results were reported by other authors.³ The different eucalypt species showed a similar behavior during this mild torrefaction, therefore allowing considering a mixed eucalypt feedstock as biofuel.

Acknowledgements

Support for this work was provided by FCT through UID/AGR/00239/2013. S.O. Araújo acknowledges financial support from CNPq (National Council for Scientific and Technological Development, Brazil) and D.M. Neiva doctoral grant under the FCT SUSFOR doctoral programme (PD/BD/52697/2014). The authors also thank the Industry Santos & Santos, belonging to the group Catarino, for the heat treatment of the wood samples.

References

- [1] M.J.C. van der Stelt, H. Gerhauser, J.H.A. Kiel, K.J. Ptasinski, Biomass Energy 35 (2011) 3748-3762.
- [2] M. van de Velden, J. Baeyens, A. Brems, B. Janssens, R. Dewil, Renew. Energy 35 (2010) 232-242.
- [3] B. Esteves, A. Velez Marques, I. Domingos, H. Pereira, Wood Sci. Technol. 42(5) (2008) 369-384.

Microwave-assisted peroxidative oxidation of toluene by Cd(II)-aroylhydrazone complexes

Tannistha Roy Barman^a, Manas Sutradhar^a, Elisabete C. B. A. Alegria^{a,b},
M. Fátima C. Guedes da Silva^a, Armando J. L. Pombeiro^a

^a Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais,
1049-001 Lisboa, Portugal

^b Chemical Engineering Department, ISEL – Instituto Superior de Engenharia de Lisboa, Instituto Politécnico de Lisboa, 1959-007 Lisboa, Portugal

The Cd(II)-aroylhydrazone complexes $[\text{Cd}(\text{HL}^1)(\text{OAc})_2]$ (**1**) and $[\text{Cd}(\text{HL}^2)(\text{DMF})_n]$ (**2**), derived from the Schiff bases 2-amino-(2-hydroxybenzylidene)benzohydrazide¹ (H_2L^1) and 2-hydroxy-(2-hydroxybenzylidene)benzohydrazide² (H_2L^2), have been synthesized under hydrothermal conditions and characterized by IR spectroscopy, elemental analysis and X-ray crystallographic analysis. Figure 1 represents the X-ray structure of the polymeric compound **2**. Both complexes have been studied as catalysts towards the microwave-assisted peroxidative oxidation of toluene under heterogeneous conditions. A highly favorable effect of MW-irradiation is observed. Under a low microwave power (5 W) with the **2**/TBHP/MW system, 49% of total product yield was achieved after 3 hours reaction at 50°C in acetonitrile.

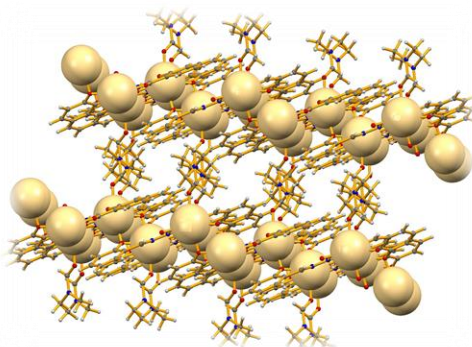


Figure 1.

Acknowledgements

Authors are grateful to the Fundação para a Ciência e a Tecnologia, FCT (projects UID/QUI/00100/2013, PTDC/QEQ-QIN/3967/2014 and PTDC/QEQ-ERQ/1648/2014), Portugal, for financial support. M. Sutradhar acknowledges the FCT, Portugal, for a postdoctoral fellowship (SFRH/BPD/86067/2012).

References

- [1] R. Dinda, P. Sengupta, S. Ghosh, T.C.W. Mak, *Inorg. Chem.* 41 (2002) 1684-1688.
- [2] M. Sutradhar, G. Mukherjee, M.G.B. Drew, S. Ghosh, *Inorg. Chem.* 45 (2006) 5150-5161.

Seven-coordinate allylic Mo(II) complexes: structure, bonding and CO₂ reduction

M. J. Calhorda, P. J. Costa, S. Realista, M. S. Saraiva, P. N. Martinho

Centro de Química e Bioquímica, DQB, Faculdade de Ciências, Universidade de Lisboa,

Campo Grande, 1749-016 Lisboa, Portugal

E-mail: mjc@ciencias.ulisboa.pt

The allylic complexes $[\text{Mo}(\eta^3\text{-C}_3\text{H}_5)(\text{CO})_2\text{X}(\text{LL}')]]$ were reported in the 1960s,^{1,2} and can be described as pseudo-octahedral, assuming that the centroid of the allyl group corresponds to one ligand. A search in the Cambridge Crystallographic Data Base³ has shown that two main isomers, equatorial and axial, are usually observed. They are depicted in Figure 1 for $[\text{Mo}(\eta^3\text{-C}_3\text{H}_5)(\text{CO})_2\text{Br}(\text{phen})]$ (phen = 1,10-phenanthroline) in a scheme and a 3-D representation. The experimentally determined structure (single crystal X-ray diffraction) is the equatorial one. In both isomers the facial arrangement of the two carbonyl and the allyl centroid is observed, the exo conformation of the allyl being also preferred. This complex is fluxional in solution. Both isomers are detected, as well as the exo conformer of the equatorial isomer. We analyze the structural preferences of this family of formally seven-coordinate Mo(II).⁴ We also report the activity of the 1,10-phenanthroline and dipyridophenazine derivatives in CO₂ electroreduction.

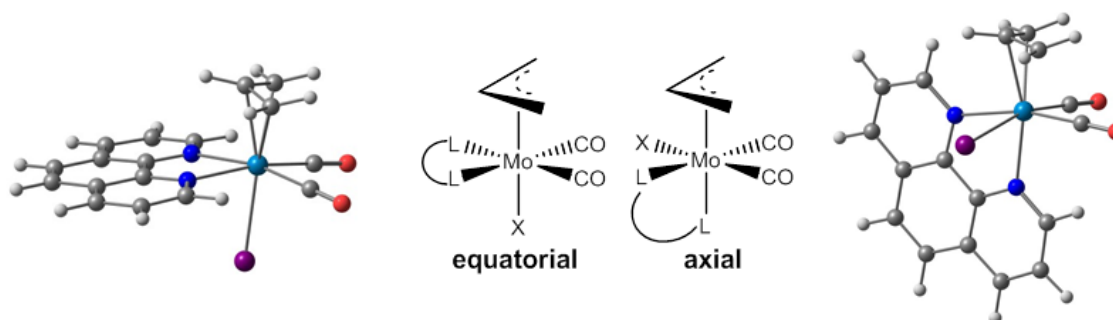


Figure 1. Two isomers of $[\text{Mo}(\eta^3\text{-C}_3\text{H}_5)(\text{CO})_2\text{Br}(\text{phen})]$.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013 and COST Action CM 1205. P.J. Costa, S. Realista, M.S. Saraiva and P.N. Martinho acknowledge financial support from FCT (IF/00069/2014, PD/BD/52368/2013, SFRH/BPD/73345/2010, SFRH/BPD/88082/2012).

References

- [1] H. tom Dieck, H. Friedel, *J. Organomet. Chem.* 14 (1968) 375.
- [2] C.G. Hull, M.H.B. Stiddard, *J. Organomet. Chem.* 9 (1967) 519-525.
- [3] C.R. Groom, I.J. Bruno, P. Lightfoot, S.C. Ward, *C. Acta Cryst.* B72 (2016) 171-179.
- [4] M.J. Calhorda, P.J. Costa, *Coord. Chem. Rev.* 344 (2017) 83-100.

Double benefit biodiesel from low grade fats and Ca rich wastes based heterogeneous catalysts

Mónica Catarino^a, Marta Ramos^{a,b}, Ana Paula Soares Dias^a

^a IDMEC, IST, Universidade de Lisboa, Av. Rovisco Pais, s/n, 1049-001 Lisboa, Portugal

^b ISEL, Rua Conselheiro Emídio Navarro, 1, 1959-007 Lisboa, Portugal

The continuous use of fossil fuels has led the society to a decisive moment. Global warming, mainly caused by anthropogenic carbon emissions, and the instability of oil and derivatives market urge the search for renewable and sustainable fuels. Biodiesel, fatty acid methyl esters (FAME) mixture, is reported to be a feasible substitute for diesel fuel.

Presently, biodiesel production is achieved by a homogeneous basic catalyzed transesterification, with the foremost used feedstock being vegetable oils. However, the use of these edible oils raises issues related with the use of arable lands to grow crops destined to biofuels production. To solve this problem, low grade feedstocks, such as waste frying oils (WFOs) and animal fats, can be used, allowing, simultaneously, the valorization of these wastes.¹

Another problem associated with currently biodiesel production is the large amount of waste water generated by catalyst removal from the final reaction mixture and the impossibility of reuse this catalyst. The use of heterogeneous catalysts reduces water consumption and, because their simple separation process, it is possible to reuse them without any regeneration step.²

In this study, transesterification was carried out using a methanol:fat molar ratio of 12:1 and 5% (based on fat weight) of Ca based catalyst prepared from scallop shells. The reaction was performed for 2.5 h at methanol reflux temperature. More details about the experimental procedure are given elsewhere.³

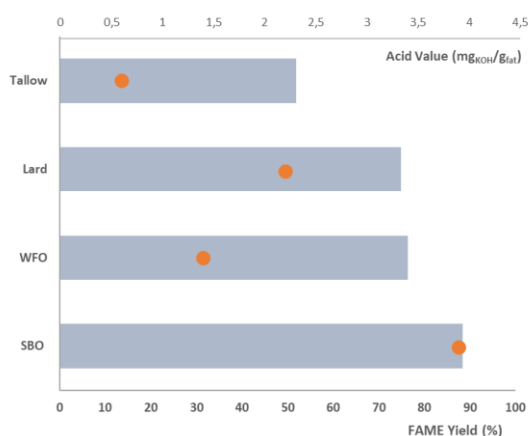


Figure 1. FAME yield and acid value (●) for different feedstocks.

The use of low grade fats was tested in order to obtain a more sustainable biodiesel. As expected, their acidity and water contents promoted a decay of the catalytic performances of Ca based catalysts (Figure 1). The semi-refined oil presented in the tested conditions the highest FAME yield and the lowest soap formation. As reported in the literature the fats acidity and water contents are responsible for soap formation during transesterification.² Co-processing of low grade fats with semi-refined oil showed to be smart strategy to attenuate such drawbacks.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. The authors acknowledge FCT for funding project PTDC/EMS-ENE/4865/2014.

References

- [1] I.J. Stojković, I.B. Banković-Ilić, A.V. Veličković, J.M. Avramović, O.S. Stramenković, D.S. Povrenović, V.B. Veljković, *Chem. Eng. Technol.* 39 (2016) 741-750.
- [2] G. Knothe, L.F. Razon, *Prog. Energ. Combust.* 58 (2017) 36-59.
- [3] A.P.S. Dias, J. Puna, J. Gomes, M.J.N. Correia, J. Bordado, *Renew. Energ.* 99 (2016) 622-630.

New non-releasing biocidal coatings for biofouling prevention:
An environmental compatibility study

Ana E. Ferreira¹, Cátia Vilas Boas², R. Bayón³, A. Igartua³, Marta Correia-da-Silva^{2,4},
Maria José Calhorda¹, Elisabete R. Silva^{1,5}

¹ Faculdade de Ciências, CQB/DQB, Universidade de Lisboa, Lisboa, Portugal

² Laboratório de Química Orgânica e Farmacêutica, Faculdade de Farmácia, Universidade do Porto,
Porto, Portugal

³ Fundación TEKNIKER, IK4-TEKNIKER, Eibar, Guipuzcoa, Spain

⁴ Centro Interdisciplinar de Investigação Marinha e Ambiental (CIIMAR/CIMAR), Universidade do Porto,
Porto, Portugal

⁵ Instituto Superior Técnico, DEQ, CERENA, Universidade de Lisboa, Lisboa, Portugal

Marine Biofouling is the undesirable accumulation of a diversity of organisms on underwater surfaces, corroding and impairing structures and systems, and being responsible for adverse ecological and economic impacts, especially consequential in the marine transport industry.¹ Strategies that target the surface protection against this marine biofouling have been widely pursued. Hitherto, the most effective antifouling strategies employ coatings acting through controllable biocide releasing mechanisms. However, the ecotoxicity of the applied biocides has led to strict regulations for their use, and in the future even more restricted guidelines are expected (BPR, EU Regulation nº528/2012). For that reason, a rigid environmental compatibility study is imperative for any new developed antifouling systems. Their intrinsic properties should envisage a low environmental risk. In this work, a recent developed non-releasing strategy,¹ based on the chemical immobilisation of proved bioactive agent(s) (e.g. Econeal) in marine coatings has been assessed in terms of environmental compatibility, namely an accurate ecotoxicity determination of biocidal coatings following standards included in the EU hazard assessment of substances and European Eco-label.² In addition, leaching tests of the developed formulations were performed (standard ISO15181) to confirm the effective biocide immobilisation of coatings, and the presence and amount of the biocide was accurately analysed in the leaching waters (HPLC-DAD, UV-VIS). The overall results evidenced the low ecotoxicity and non-releasing potential of the new developed biocidal coatings.

Acknowledgements

Support for this work was provided by Fundação para a Ciência e a Tecnologia (FCT) through UID/MULTI/00612/2013, PEst-OE/QUI/UI0612/2013 and PTDC/AAG-TEC/0739/2014, and by European Regional Development Fund through the COMPETE (POCI-01-0145-FEDER-016793) and RIDTI (Project 9471). The authors also acknowledge Sara Cravo and Olga Ferreira for technical support in HPLC and leaching tests, respectively. E.R. Silva also acknowledges for FCT support (SFRH/BPD/88135/2012).

References

- [1] E.R. Silva, O. Ferreira, J.C. Bordado, Patent Application, WO2016/093719 A1, 2016.
- [2] E.R. Silva, O. Ferreira, A.V. Tulcidas, R. Bayon, A. Igartua; Non-releasing biocidal coatings: A new eco-friendly strategy to prevent marine biofouling; Conference scientific paper, Shipping in Changing Climates Conference, Vol. 2, 307-317, Glasgow, Scotland, UK, 24-26th November 2015.

In an era where the chemistry has to be green...

Luís M. T. Frija

Centro de Química Estrutural (CQE), Instituto Superior Técnico, Universidade de Lisboa,
Av. Rovisco Pais, 1049-001 Lisboa, Portugal; E-mail: luisfrija@tecnico.ulisboa.pt

Science and technology should, undoubtedly, use all the instruments available in the genesis of a superior quality of life globally. Historically, chemistry, as a central science, has always tried to be governed by this principle. Nevertheless, chemistry expanded in the last decades of the 20th century, guided by a growing awareness of the necessity to preserve the environment, even aiming for an improvement in the quality of life through reflections on its *modus operandi*. The ends no longer justify all means, and the “*clean chemistry* perception” has emerged!

In 1962, Rachel Carson “threw the first stone” in this area by publishing the environmentally oriented book, *Silent Spring*.¹ This served as an alert for the public and scientific community and stimulated the development of the modern environmental movement. In 1969, President Richard Nixon established the U.S. Environmental Protection Agency (EPA), a federal regulatory agency responsible for protecting human health and the environment...

Over the last two decades, much has been written and reflected on green chemistry. This includes its principles, benefits, utility, need for good practices, or technological advances based on sustainable chemistry protocols. The significance of green chemistry is also reflected by the continuing increase in high quality scientific publications.² The greatest practical contributions for society within this research field are, obviously, perceived to be those made visible to public opinion. However, too much research globally has been presented as green- or sustainable chemistry without obeying its minimum principles or undergoing rigorous evaluation. We are talking, in this case, of “*pseudo-green chemistry*”, which has been wrapped up in a fashion where almost everything that happens within the chemistry domain must have something “*greenish*”. Unfortunately, reference to all research of this type is unfeasible, just as any kind of generalization would be unfair. In the vast majority of these cases, “the part” instead of the “whole” of the question is highlighted. The line dividing green chemistry from *pseudo-green chemistry* becomes tenuous. The pressures to present as quickly as possible results in scientific and business spheres, associated with the incessant search for funding in strategic areas, such as the Environment and Health, leads to the development of “*fast science*”, which is not always accurate.³⁻⁵ With all the obvious benefits to society achieved in recent decades through the use of sustainable chemistry procedures, it is crucial to reflect on what is less good in this research field to avoid entering into irretrievable anarchy.

References

- [1] R. Carson, *Silent Spring*, Houghton Mifflin, Boston, 1962.
- [2] a) P.T. Anastas, D.T., Allen, *ACS Sustainable Chem. Eng.* 4 (2010) 5820; b) P.T. Anastas, M.M. Kirchoff, *Acc. Chem. Res.* 35 (2002) 686; c) P.T. Anastas, N. Eghbali, *Chem. Soc. Rev.* 39 (2010) 301; d) D.J. Constable *et al.*, *Green Chem.* 9 (2007) 411; e) M. Poliakoff, J.M. Fitzpatrick, T.R. Farren, P.T. Anastas, *Science* 297 (2002) 807; f) M. Toda *et al.*, *Nature* 438 (2005) 178.
- [3] S. Elliott, *J. Pharm. Sci.* 105 (2016) 1358; b) A. Kerr, R. Prescott, T. Theologis, *Gait & Posture* 42 (2015) 224.
- [4] J.T. Trevors, M.H. Saier Jr., *Water Air Soil. Pollut.* 189 (2008) 1.
- [5] M.J. Müller, B. Landsberg, J. Ried, *Eur. J. Clin. Nutr.* 68 (2014) 411.

MoO₃ nanoparticles as catalysts to sulfoxides reduction

Mafalda Geraldes, Tiago A. Fernandes, Carla D. Nunes

*Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa,
1749-016 Lisboa, Portugal*

The development of sustainable catalytic protocols for the deoxygenation of organic compounds, frequently involved in the synthesis of bioactive targets, is very important. Particularly, the deoxygenation of sulfoxides is of extraordinary relevance in biological processes, as well as in organic synthesis as a key step in several reaction sequences. Accordingly, numerous catalytic methods have been developed in the past decades to perform this transformation.¹ In this sense, considerable efforts have been done in the catalyst development for sulfoxide reduction and, therefore, significant achievements have been accomplished including the use of non-metal or abundant, inexpensive and non-toxic Mo, Zn, Cu or Fe based catalysts. Dioxomolybdenum(VI) complexes have been extensively studied, much of the interest in these compounds is derived from their oxygen atom transfer chemistry. Recyclable, inexpensive, and stable catalysts are desirable for industrial and synthetic applications. With this in mind, in this work MoO₃ nanoparticles have been synthesized and characterized, they were prepared by a hydrothermal method using molybdenum chloride (V) (MoCl₅). Molybdenum trioxide (MoO₃) nanoparticles were obtained and characterized by infrared spectroscopy (DRIFT) and X-ray diffraction (XRD).² Resulting material was tested as catalyst in the reduction of sulfoxides to its corresponding sulfide. Studies were made by varying several parameters such as the solvent (which, in turn, made it necessary to also vary the reactional temperature), the presence or absence of a reducing agent, an acid promoter, and the substrate effect. Throughout the studies, the same catalyst was used in the same percentage. In most of the reactions, the conversion of sulfoxide in sulfide had a low percentage. However, there were some tests which presented highly satisfactory results.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013.

References

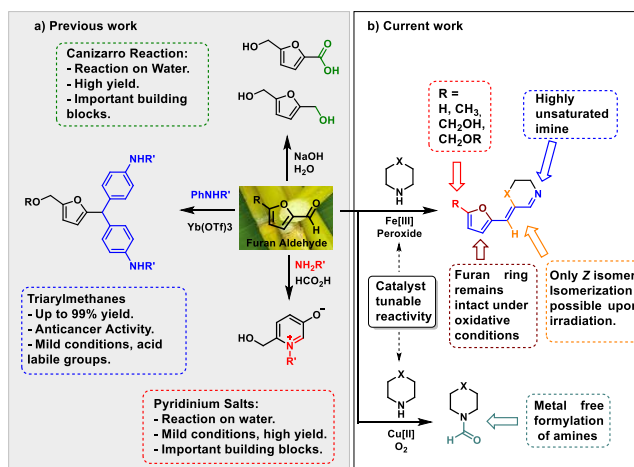
- [1] F.J. Arnáiz, R. Agudo, M.R. Pedrosa, A. De Cian, *Inorg. Chim. Acta* 347 (2003) 33-40.
- [2] C.I. Fernandes, S.C. Capelli, P.D. Vaz, C.D. Nunes, *Appl. Catal. A: Gen.* 504 (2015) 344-350.

Catalyst Tunable Oxidative β -Functionalization of Secondary Amines with Furan Derivatives from Biomass to Highly Unsaturated Imines

Rafael F. A. Gomes, Jaime A. S. Coelho, Carlos A. M. Afonso

iMed.UL, Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal

The ever increasing population growth, aligned with the concomitant industrial development leads to an increased demand for chemicals and energy. The fact that oil reservoirs are being depleted is a concern and the increased demand will hasten this depletion. New sustainable sources for fuels and bulk chemicals are of the highest interest, and biomass is the most attractive alternative for oil based products. Furan aldehydes such as 5-hydroxymethylfurfural (HMF) and furfural, easily obtained from fructose or glucose, are included in the U.S. Department of Energy top 10+4 list of biobased materials.¹ We have been involved on the synthesis of HMF² and the transformation of this important furan to other interesting building blocks such as dihydroxymethylfuran (DHMF), hydroxymethylfuran carboxylic acid (HMFCFA), pyridinium salts, dimers³ and more recently the transformation of HMF to bioactive anticancer triarylmethanes⁴. Herein we report the first methodology for the direct oxidative β -functionalization of secondary amines, with different biomass derived furan aldehydes providing interesting highly unsaturated imines. We can tune the reactivity by changing the catalyst, achieving the formylation of the amine up to 99% yield, and changing the aldehyde to a benzaldehyde derivative, achieving the oxidative amidation of the aldehyde group.



Scheme 1. Catalyst tunable oxidation of biomass derivatives containing furan ring.

Acknowledgements

We thank the Fundação para a Ciência e Tecnologia for financial support and European Research Area Network; ERANet LAC (ref. ELAC2014/BEE-0341).

References

- [1] a) J. Bozell, G. Petersen, *Green Chem.* 12 (2010) 539-554; b) T. Werpy, G. Petersen, *Top Value Added Chemicals from Biomass Vol. I-Results of Screening for Potential Candidates from Sugars and Synthesis Gas*, NREL/TP-510-35523, 2004.
- [2] a) S. Simeonov, C.A.M. Afonso, *ChemSusChem* 5 (2012) 1388-1391; b) S. Simeonov, C.A.M. Afonso, *Org. Synth.* 93 (2016) 29-36.
- [3] a) S. Subbiah, J. Esperança, L. Rebelo, C.A.M. Afonso, *Green Chem.* 15 (2013) 2849-2853; b) S. Subbiah, L.F. Veiros, J. Esperança, L. Rebelo, C.A.M. Afonso, *Org. Lett.* 17(21) (2015) 5244-5247; c) J. Coelho, M. Duarte, L.F. Veiros, C.A.M. Afonso, *Org. Biomol. Chem.* 12 (2014) 9324.
- [4] R.F.A. Gomes, J.A.S. Coelho, R. Frade, A.F. Trindade, C.A.M. Afonso, *J. Org. Chem.* 80(20) (2015) 10404-10411.

Hydrosoluble copper complexes for homogeneous catalysis

Abdallah G. Mahmoud¹, M. Fátima C. Guedes da Silva¹, Piotr Smoleński²,
Armando J. L. Pombeiro¹

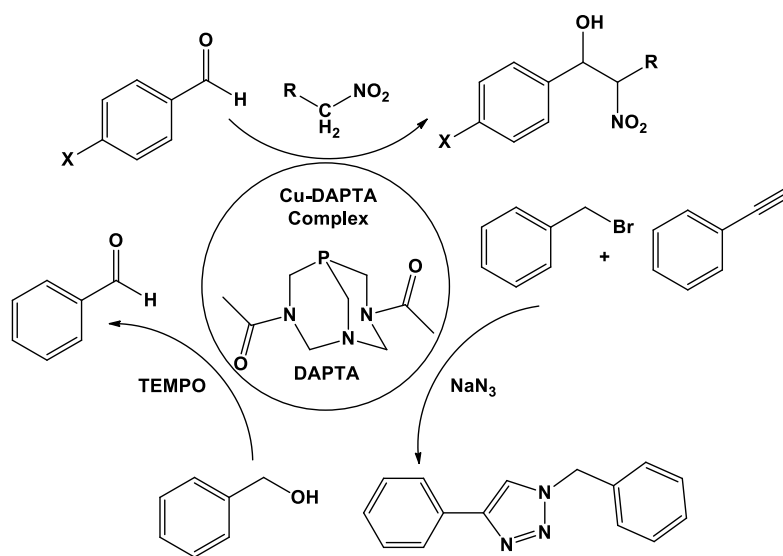
¹ Instituto Superior Técnico, Universidade de Lisboa, Centro de Química Estrutural, Complexo I,
Av. Rovisco Pais, 1049-001 Lisboa, Portugal

² University of Wrocław, Faculty of Chemistry, Ul. F. Joliot-Curie 14, 50-383 Wrocław, Poland

E-mail: abdallah.mahmoud@tecnico.ulisboa.pt

As part of our interest on water soluble transition metal complexes with applications in catalysis, we have obtained novel compounds by reacting Cu(II) or Cu(I) salts with the water soluble aminophosphine 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane (DAPTA).

The obtained complexes were fully characterized and applied as catalysts, under mild conditions, for nitroaldol condensation of aldehydes with nitroalkanes (Henry reaction), aerobic TEMPO-mediated oxidation of benzyl alcohol and azide-alkyne 1,3 dipolar cycloaddition (Huisgen reaction) in homogeneous aqueous systems.



Acknowledgements

This work has been partially supported by the Foundation for Science and Technology (FCT), Portugal (UID/QUI/00100/2013). A.G. Mahmoud is thankful to the CATSUS doctoral program of FCT for his PhD fellowship (SFRH/BD/106006/2014).

CO₂ capture by functionalised carbon nanotubes

Sofia A. Milheiro^a, Sara Realista^a, Ana M. Botelho do Rego^b, Maria José Calhorda^a,
Paulo N. Martinho^a

^a Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal

^b Centro de Química-Física Molecular (CQFM), Institute of Nanoscience and Nanotechnology (IN), Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal

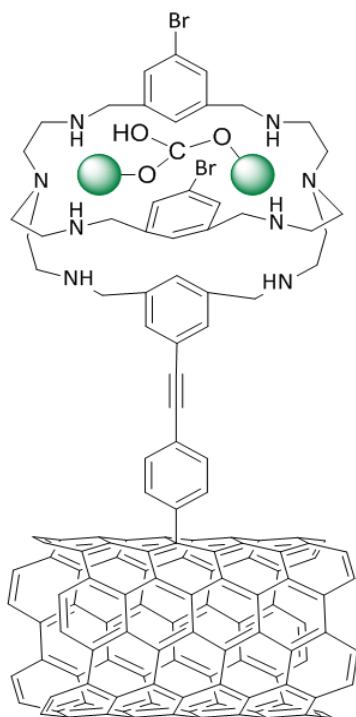


Figure 2. Modified carbon nanotube with Co(II) cryptate.

Cascade complexes are formed stepwise by reaction of ligands with metal ions, which may in turn bind small molecules. Polyaza ligands have shown their versatility in creating, after coordinating two or three 3d cations, depending on their topological properties, a small cavity to bind anions. Nelson's cryptands¹ provide an example of a dynamic structure with useful applications, demonstrated by their ability to capture and convert CO₂ to carbonate following their coordination to two metal ions. On the other hand, the electrochemical reduction of CO₂ to other products with well-defined molecular catalysts has selectively produced compounds such as CO, formic acid, methane and methanol.² One of the strategies for catalytic CO₂ reduction is based on carbon nanotubes functionalisation through covalent grafting of metal complexes. Here we explore the conversion of CO₂ into CO by carbon nanotubes modified with Co(II) cryptates (Figure 1) that can capture CO₂ from the atmosphere. The syntheses of different Co(II) cryptates were performed under N₂ and CO₂ atmosphere. The new species characterised by FTIR, elemental analysis, and XPS. The redox properties of both the complexes and the modified carbon nanotubes were studied by cyclic voltammetry. The behaviour of the new materials under exposure to a CO₂ saturated atmosphere was investigated in aqueous medium.

Acknowledgements

Support for this work was provided by Fundação para a Ciência e a Tecnologia (UID/MULTI/00612/2013, PTDC/QEQ-QIN/3414/2014). P.N. Martinho (SFRH/BPD/73345/2010) and S.Q. Realista (PD/BD/52368/2013) thank FCT for financial support.

References

- [1] Y. Dussart, C. Harding, P. Dalgaard, C. McKenzie, R. Kadirvelraj, V. McKee, J. Nelson, J. Chem. Soc. Dalton Trans. (2002) 1704-1713.
- [2] A. Maurin, M. Robert, J. Name 00 (2013) 1-3.

Heterometallic alkoxo-bridged Cu/Fe complex with a rare hexanuclear $M_6(\mu-X)_7(\mu_3-X)_2$ core for alkane C–H catalytic activation

Dmytro S. Nesterov, Oksana V. Nesterova, Armando J. L. Pombeiro

Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Avenida Rovisco Pais, 1049-001 Lisboa, Portugal

The search towards novel molecule-based materials, able to combine useful (physico-)chemical properties, such as magnetism and catalysis, has led to a particular interest in polynuclear coordination compounds.¹ Following our interest in the preparation of mono- and polynuclear complexes with N,O-donor ligands^{2,3} we have explored the synthetic system containing *N*-tert-butyl-diethanolamine (H₂tBuDea) and pivalic (trimethylacetic) acid (HPiv) ligands.

The reaction of zerovalent metal and iron chloride with H₂tBuDea, HPiv and triethylamine in acetonitrile solution lead to the formation of the novel heterometallic complex [Cu^{II}₄Fe^{III}₂(OH)(Piv)₄(tBuDea)₄Cl]·0.5CH₃CN (**1**) (Figure 1). It acts as a catalyst in the mild oxidation of cyclohexane with H₂O₂, showing the yields of products, cyclohexanol and cyclohexanone, up to 17% using pyrazinecarboxylic acid as promoter. In the oxidation of *cis*-1,2-dimethylcyclohexane with *m*-chloroperoxybenzoic acid (*m*-CPBA) catalysed by **1**, 70% of retention of stereoconfiguration was observed for tertiary alcohols. Incorporation of ¹⁸O from H₂¹⁸O at 2% level into the *cis*-alcohol was detected. The compound **1** was also tested as catalyst in the intramolecular amidation of cyclohexane with benzamide revealing *N*-cyclohexyl benzamide as the main product.

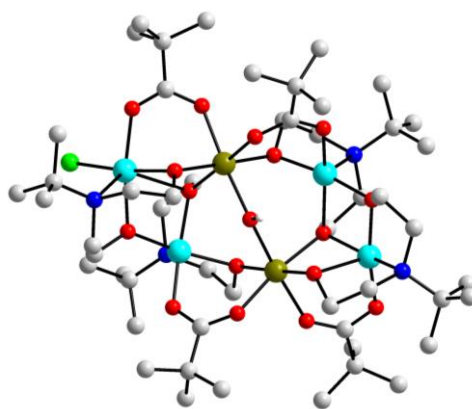


Figure 1. Molecular structure of [Cu^{II}₄Fe^{III}₂(OH)(Piv)₄(tBuDea)₄Cl]·0.5CH₃CN (**1**)

Acknowledgements

This work was supported by FCT (projects PTDC/QEQ-QIN/3967/2014 and UID/QUI/00100/2013; fellowship SFRH/BPD/99533/2014).

References

- [1] H. Li, Z.J. Yao, D. Liu, G.X. Jin, *Coord. Chem. Rev.* 293 (2015) 139-157.
- [2] D.S. Nesterov, J. Jezierska, O.V. Nesterova, A.J.L. Pombeiro, A. Ozarowski, *Chem. Commun.* 50 (2014) 3431-3434.
- [3] D.S. Nesterov, O.V. Nesterova, V.N. Kokozay, A.J.L. Pombeiro, *Eur. J. Inorg. Chem.* (2014) 4496-4517.

Cu(II) aminoalcohol Schiff base complexes: synthesis, crystal structures and catalytic activity

Oksana V. Nesterova, Dmytro S. Nesterov and Armando J. L. Pombeiro

*Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais,
1049-001 Lisboa, Portugal*

Design and preparation of copper coordination compounds still remain a main topic since such complexes have recognized applications as magnetic and catalytic materials, as well as bioactive objects. Copper is found in active centres of many bioenzymes, for example in superoxide dismutase (dismutation of superoxide)¹ and particulate methane monooxygenase (methane oxidation)². Also, complexes of copper with polydentate amine and aminoalcohol ligands are recognized catalysts in oxidative catalysis, particularly in C–H functionalization of various substrates.³ Following our interest in the preparation of polynuclear compounds with N,O-donor ligands⁴ we have synthesised two novel binuclear complexes, $[\text{Cu}_2(\text{HL}^1)(\text{L}^1)(\text{N}_3)_3]\cdot\text{DMF}$ (**1**) and $[\text{Cu}_2\text{L}^2(\text{N}_3)_2]\cdot\text{CH}_3\text{OH}$ (**2**) (Figure 1), by reactions of copper(II) chloride or nitrate, respectively, with sodium azide in non-aqueous solutions of the Schiff base aminoalcohols. In the case of **1**, the *in situ* condensation of the salicylaldehyde and 1-(2-aminoethyl)piperazine afforded the expected N,N,O-donor ligand HL^1 . However, in the case of **2**, the unexpected *in situ* C–N bond formation with subsequent forming of the hexa-dentate Schiff base H_2L^2 was observed. We propose that the formation of H_2L^2 occurs through the (i) catalytic aerobic oxidation of methanol solvent to formaldehyde and (ii) condensation of formaldehyde with amine groups of the piperazine.

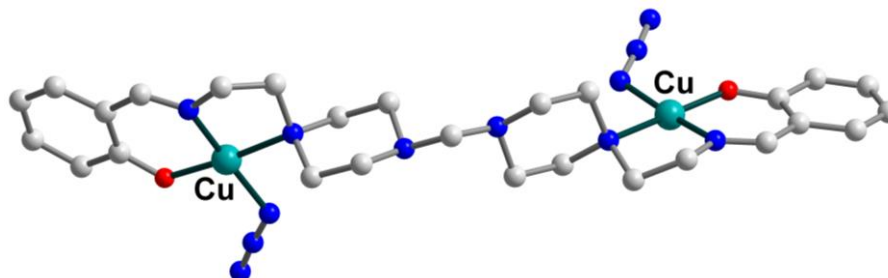


Figure 1. Molecular structure of $[\text{Cu}_2\text{L}^2(\text{N}_3)_2]\cdot\text{CH}_3\text{OH}$ (**2**).

The results of catalytic investigations of the compounds **1** and **2** towards oxidation of cyclohexane with hydrogen peroxide in the presence of various promoters under mild conditions, as well as in the reaction of amidation of cyclohexane with benzamide, in benzene medium, are also discussed.

Acknowledgements

This work was supported by Fundação para a Ciência e Tecnologia (FCT), Portugal (projects PTDC/QEQ-QIN/3967/2014 and UID/QUI/00100/2013; fellowship SFRH/BPD/99533/2014).

References

- [1] J.A. Tainer, E.D. Getzoff, J.S. Richardson, D.C. Richardson, *Nature* 306 (1983) 284-287.
- [2] S. Sirajuddin, A.C. Rosenzweig, *Biochemistry* 54 (2015) 2283-2294.
- [3] A.M. Kirillov, M.V. Kirillova, A.J.L. Pombeiro, *Coord. Chem. Rev.* 256 (2012) 2741-2759.
- [4] D.S. Nesterov, O.V. Nesterova, V.N. Kokozay, A.J.L. Pombeiro, *Eur. J. Inorg. Chem.* (2014) 4496-4517.

Biodiesel production from beef tallow

Marta Ramos^{a,b}, Mónica Catarino^b, Ana Paula Soares Dias^b

^a ISEL, Rua Conselheiro Emídio Navarro, 1, 1959-007 Lisboa, Portugal

^b IDMEC, IST, Universidade de Lisboa, Av. Rovisco Pais, s/n, 1049-001 Lisboa, Portugal

Biodiesel, a mixture of fatty alkyl esters, is a renewable substitute for fossil fuels. Currently, biodiesel is mainly produced by methanolysis of vegetable oils using homogeneous basic catalysis. Vegetable oils not only are expensive, representing 75-90% of biodiesel production costs¹, as the use of these oils for biodiesel production is controversial. The use of arable lands for its production raise several sustainability issues.²

In order to improve the biodiesel sustainability and reduce the production costs, different animal fats, such as beef tallow, pork lard, chicken fat and grease, can be used.¹ Biodiesel produced from animal fats has a higher cetane number (advantage) comparing with fuel made from vegetable oils. However, because animal fats have a significant content of saturated fatty acids the produced fuel presents a higher cloud point (disadvantage).³

In this study, biodiesel was produced from beef tallow and 50 % w/w beef tallow/soybean oil mixture using a scallop shells derived catalyst. The beef tallow was obtained from waste bovine fat tissues by boiling water rendering. The methanolysis tests were carried out for 150 minutes, at methanol reflux temperature using 5 % w_{cat}/w_{fat} of catalyst and methanol/fat = 12 molar ratio. In addition, for comparison, the methanolysis of the soybean oil was also carried out under the same conditions.



Figure 3. Rendering process of waste beef tallow.

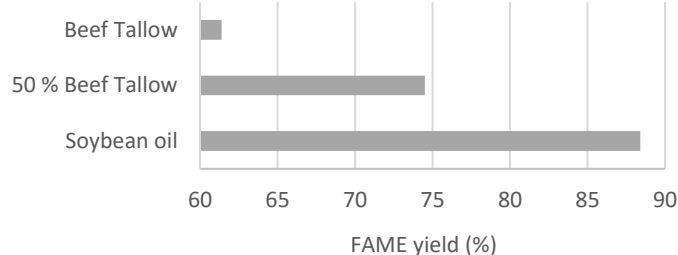


Figure 2. FAME yield (%) assessed by ATR-FTIR.

The biodiesel from beef tallow was successfully produced using basic heterogeneous Ca catalyst. These type of catalyst are also efficient in the production of biodiesel by oil methanolysis.⁴ Although, as reported in the literature,³ the high level of free fatty acids and water content in beef tallow using an alkaline catalyst promoted the soap formation and consequently reduced the FAME yield. The co-processing of beef tallow with soybean oil minimized these drawbacks.

Acknowledgements

The authors acknowledge FCT (Fundação para a Ciência e Tecnologia, Portugal) for funding project PTDC/EMS-ENE/4865/2014.

References

- [1] I.B. Banković-Ilić *et al.*, Renewable and Sustainable Energy Reviews 32 (2014) 238-254.
- [2] P. Adewale, M. Dumont, M. Ngadi, Renewable and Sustainable Energy Reviews 45 (2015) 574-588.
- [3] J.M. Encinar *et al.*, Bioresource Technology 102 (2011) 10907-10914.
- [4] A.P.S. Dias *et al.*, Renewable Energy 99 (2016) 622-630.

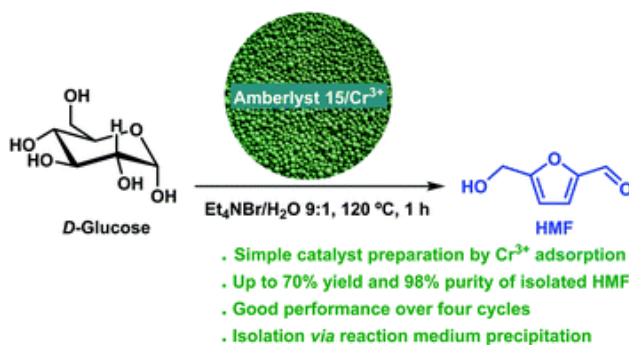
Production and isolation of 5-hydroxymethylfurfural from glucose using bifunctional Cr³⁺ modified ion exchange resins

João M. J. M. Ravasco^a, Jaime A. S. Coelho^a, Svilen P. Simeonov^{*a,b} and Carlos A. M. Afonso^{*a}

^a *iMed.UL, Faculdade de Farmácia da ULisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*

^b *Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Acad. G. Bonchev str., bl. 9, Sofia, Bulgaria*

5-hydroxymethylfurfural (HMF) has been recognized as a key biorefining building block derived from carbohydrates, such as cellulose, glucose, inulin, fructose, etc. Among them, fructose is currently the only carbohydrate that can be readily dehydrated into HMF, typically in high yield and selectivity.¹⁻² However, fructose has a low abundance in nature resulting in high cost, whereas glucose has much higher abundance and is readily available from non-food cellulosic biomass, thus being a highly desirable feedstock.³ Conversion of glucose to HMF is a twostep process where first the glucose is isomerized to fructose and the last undergoes subsequent dehydration to form HMF. The isomerization step is typically enzymatic, base or metal salt catalysed, while dehydration is an acid catalysed process. In the recent years a considerable number of bifunctional catalysts have been reported allowing this one pot transformation. Tetraethylammonium bromide (TEAB)/water is an efficient reaction media for fructose dehydration, which allowed quantitative HMF isolation via simple TEAB crystallization and subsequent recycling of both TEAB and organic solvents.⁴⁻⁵ Herein we report Cr³⁺ modified readily available cation exchange resins explored as heterogeneous bifunctional catalysts for the dehydration of glucose to 5-hydroxymethylfurfural (HMF) in tetraethyl ammonium bromide (TEAB)/water as reaction medium. Excellent HMF isolated yields of up to 70% were achieved using simple crystallization of the reaction medium (TEAB) from ethyl acetate/ethanol which allowed the isolation of HMF in high purity. The best identified catalyst (Amberlyst 15/Cr³⁺) exhibited high activity over 4 cycles. The loss of activity was attributed to the decreased number of acidic sites of the catalyst, thus a simple treatment of the catalyst with 10% HCl efficiently restored its activity in the following cycles.



Scheme 1. Production and isolation of 5-hydroxymethylfurfural from glucose using bifunctional Cr³⁺ modified ion exchange resins.

Acknowledgements

The authors acknowledge Fundação para a Ciência e a Tecnologia (FCT) (ref. SFRH/BPD/109476/2015, SFRH/BD/120829/2016 and UID/DTP/04138/2013), European Research Area Network; ERANet LAC (ref. ELAC2014/BEE-0341), and REDE/1518/REM/2005 (FF-UL) for the mass service.

References

- [1] A.A. Rosatella, S.P. Simeonov, R.F.M. Frade, C.A.M. Afonso, *Green Chem.* 13 (2011) 754.
- [2] S.P. Simeonov, C.A.M. Afonso, *ChemSusChem* 5 (2012) 1388-1391.
- [3] J. Wang, J. Xi, Y. Wang, *Green Chemistry* 17 (2015) 737.
- [4] S.P. Simeonov, J.A.S. Coelho, C.A.M. Afonso, *ChemSusChem* 5 (2012) 1388.
- [5] J.A.S. Coelho, S.P. Simeonov, C.A.M. Afonso, *Org. Synth.* 93 (2016) 29.

Salphen inspired complexes and materials for CO₂ reduction

Sara Realista^a, Priscila C. Ramgi^a, Bernardo P. Cardoso^{a,b}, Ana S. Viana^a, Claudio Cometto^c, Marc Robert^c, Paulo J. Costa^a, Maria José Calhorda^a, Paulo N. Martinho^a

^a Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal

^b Université de Strasbourg, École Européenne de Chimie, Polymères et Matériaux, CNRS, LCM UMR 7509, Equipe de Chimie Organométallique Appliquée, 25 Rue Becquerel, 67087 Strasbourg, France

^c Université Paris Diderot, Sorbonne Paris Cité, Laboratoire d'Electrochimie Moléculaire, UMR 7591 CNRS, 15 rue Jean-Antoine de Baïf, F-75205 Paris Cedex 13, France

The versatility of salen-type (salen = N,N-bis(salicylidene)ethylenediamine) complexes has been shown, among others, in their extensive applications in electrochemistry owing to their electrochromic¹, sensor² and catalytic³ properties. These features are complemented by their easy electropolymerisation without significant modifications of the metal environment.⁴ This reaction requires that there are no substituents at the phenolate *para* position and the mechanism involves oxidation of the metal coordinated to the unsubstituted salphen, followed by C-C coupling. DFT calculations show the high spin density of the oxidised complex at those positions. Mono and binuclear complexes were synthesised being the later prepared by a template procedure. A template synthesis allowed the preparation of homobinuclear complexes and a newly developed stepwise procedure led to heterobinuclear complexes, with two distinct environments for the metal centres.^{5,6} The compounds were characterised by FTIR spectroscopy, elemental analyses and HR-mass spectrometry. Studies with these complexes were performed on the homogeneous and heterogeneous conversion of CO₂. Modified electrodes based on metallopolymers and nafion were produced and characterised by cyclic voltammetry and the study of the morphologic properties performed by atomic force microscopy. For the CO₂ reduction, bulk electrolysis experiments were performed and gas chromatography with thermal conductivity detector was used to detect and quantify the reduction products.

Acknowledgements

The authors thank FCT for financial support (UID/MULTI/00612/2013) and P.N. Martinho and S. Realista for fellowships SFRH/BPD/73345/2010 and PD/BD/52368/2013, respectively. CMST COST Action CM1205 (CARISMA), CATSUS doctoral programme and Fundação Calouste Gulbenkian are also gratefully acknowledged.

References

- [1] D.T. Whipple, P.J.A. Kenis, *The Journal of Physical Chemistry Letters* 1 (2010) 3451.
- [2] G.W. Coates, D.R. Moore, *Angew. Chem. Int. Ed.* 43 (2004) 6618.
- [3] J. Meléndez, M. North, R. Pasquale, *Eur. J. Inor. Chem.* 21 (2007) 3323.
- [4] J. Qiao, Y. Liu, F. Hong, J. Zhang, *Chem. Soc. Rev.* 43 (2014) 631-675.
- [5] S. Realista, A.S. Viana, B.P. Cardoso, A.M. Botelho do Rego, P.D. Vaz, A.I. Melato, P.N. Martinho, M.J. Calhorda, *RSC Adv.* 5 (2015) 39495.
- [6] S. Realista, P. Ramgi, B.P. Cardoso, A.I. Metalo, M.J. Calhorda, P.N. Martinho, *Dalton Trans.* 45 (2016) 14725.

Mo structured materials to sulfides oxidation

Rita Sales, Carla D. Nunes

Centro de Química e Bioquímica Faculdade de Ciências, Universidade de Lisboa,
1749-016 Lisboa, Portugal

Since the first report on the synthesis of sulfoxides by Marcker in 1865¹, many processes for the conversion of sulfides to sulfoxides using nitric acid, hydrogen peroxide, dinitrogen tetroxide, ozone, peracids, hydroperoxides and many other reagents have been developed. Sulfoxides and sulfones have found many applications in pharmacy and other fields such as engineering plastics and polymers. Oxidation of sulfides is the most direct approach for the synthesis of sulfoxides and sulfones. Many different catalysts have been applied for oxidation of organic substrates but in order to make this process rapid, selective and consist of higher yields of products, the use of catalysts is mandatory. As a result of the apparent interest in the perfection of oxidation product synthesis, many explorations have been commenced to develop catalysts for oxidation, e.g. supported metal oxides as well as homogeneous transition metal complexes.²

In this work new nanostructured materials were synthesized and characterized. Their application as catalysts in the oxidation of sulfides to sulfoxides has been studied afterwards. The catalyst was prepared from molybdenum(V) chloride (MoCl_5) using a hydrothermal method. Molybdenum trioxide (MoO_3) nanoparticles were obtained, which were characterized by infrared spectroscopy (DRIFT) and powder X-ray diffraction (XRD).

The use of the MoO_3 nanoparticles as catalysts was then aimed at the oxidation of sulfides to sulfoxides. The reactions were studied by varying some key parameters, namely the oxidizing agent (*tert*-butyl hydroperoxide and hydrogen peroxide), the oxidizing agent ratio, temperature (room temperature, 55, 80 and 110 °C), solvent (dichloromethane, toluene and acetonitrile) and the substrate (diphenyl sulfide, dimethyl sulfide and methylphenyl sulfide).

In most reactions, oxidation to sulfoxide occurs selectively when using *tert*-butyl hydroperoxide. When using hydrogen peroxide as oxidizing agent only in a single reaction the transformation of sulfoxide to sulfone is observed. From the set of substrates tested, dimethyl sulfide seems to be the one for which the catalytic system is not ideal, as no conversion was observed even after tests at 110 °C. It was possible to verify that most of the catalytic studies were finished after 6h30, at most. However, some of them were very fast reactions, being completed in just 10 or 15 minutes.

In summary, the best reaction conditions obtained were at lower temperatures, at 55 °C, where the conversion of sulfoxide was 100% in dichloromethane and using 200% *tert*-butyl hydroperoxide obtained after just only 5 minutes reaction time.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013.

References

[1] C. Marcker, Ann. 136 (1865) 75.

[2] M.M. Javadi, M. Moghadam, I. Mohammadpoor-Baltork, S. Tangestaninejada, V. Mirkhani, H. Kargar, M. N. Tahir, Polyhedron 72 (2014) 19.

Use of inorganic calcium wastes materials as nanocatalysts to produce biodiesel

Samuel Santos^a, Jaime Puna^{a,b}, João Gomes^{a,b}, Rosa Quinta-Ferreira^c, João Bordado^a

^a CERENA, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1, Lisboa, 1049-001, Portugal

^b Instituto Superior de Engenharia de Lisboa, R. Conselheiro Emídio Navarro, 1, Lisboa, 1959-007, Portugal

^c Faculdade de Ciências e Tecnologia, Universidade de Coimbra, R. Sílvio Lina s/n, 3030-790 Coimbra, Portugal

In terms of industrial application for biodiesel production, homogeneous catalysts, such as NaOH and KOH, are usually preferred, but their removal is rather complex and very pollutant, bringing extra cost to the final product.¹⁻³ On the other hand, heterogeneous catalysts are, for the time being, somewhat time consuming, still inefficient, and present some mass transfer limitations. One solution to this problem might be the use of nanocatalysts, as these new heterogeneous catalysts present high surface area and high catalytic activity.⁴

Nanocatalysts have recently become the focus of recent research. Reddy *et al.* (2006)⁵ stated that a nanocrystalline CaO was an efficient catalyst to produce biodiesel with high yields at room temperature using soybean oil and poultry fat as raw materials. For instance, Hu *et al.* (2011)⁶ developed a nano-magnetic solid base catalyst KF/CaO-Fe₃O₄ based on a magnetic Fe₃O₄ core, achieving a biodiesel yield over 95% with 3 hours of reaction time. Wen *et al.* (2010)⁷ concluded that the solid base catalyst KF/CaO can be used for biodiesel production with a yield of more than 96%. Kaur *et al.* (2011)⁸ prepared a 1.75 Li-CaO catalyst which, in the optimized conditions for transesterification of Karanja and Jatropha oils, could achieve over 99% conversion of oils to FAME.

Residual inorganic materials have potential to be used as catalysts, especially in their nanostructured form thus allowing to achieve a significant improvement on transesterification efficiency, translating into faster reactions i.e., shorter reaction times, low reaction temperatures and lower catalyst concentration, and WFOs and animal fats can be used as raw materials in the transesterification reaction for biodiesel production, turning it into an eco-friendly and cost-effective process.

Acknowledgements

Support for this work was provided by FCT through PTDC/SEM-ENE/4865/2014.

S. Santos acknowledges financial support from FCT by PhD grant PD/BD/128450/2017.

References

- [1] C. Liu, P. Lv, Z. Yuan, F. Yan, W. Luo, *Renewable Energy* 35 (2010) 1531-1536.
- [2] A.K. Singh, S.D. Fernando, *Energy & Fuels* 22 (2008) 2067-2069.
- [3] L. Wang, J. Yang, *Fuel* 86 (2007) 328-333.
- [4] S. Chatuverdi, P.N. Dave, N.K. Shah, *Journal of Saudi Chemical Society* 16 (2012) 307-325.
- [5] C.R.V. Reddy, R. Oshel, J.G. Verkade, *Energy & Fuels* 20 (2006) 1310-1314.
- [6] S. Hu, Y. Guan, Y. Wang, H. Han, *Applied Energy* 88 (2011) 2685-2690.
- [7] L. Wen, Y. Wang, D. Liu, S. Hu, H. Han, *Fuel* 89 (2010) 2267-2271.
- [8] M. Kaur, A. Ali, *Renewable Energy* 36 (2011) 2866-2871.

Synthesis and applications of molybdenum(II) organometallic phenanthroline complexes

Jiawei Wang^{a,b}, Armando J. L. Pombeiro^b, Maria José Calhorda^a,
Luísa M. D. R. S. Martins^{b,c}, Ana P. C. Ribeiro^b, Marta S. Saraiva^{a*}

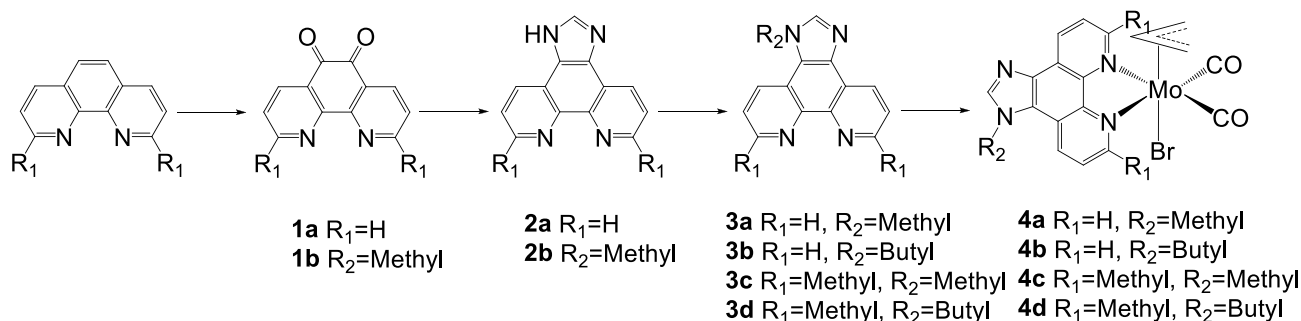
^a Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande,
1749-016 Lisboa, Portugal

^b Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais,
1049-001 Lisboa, Portugal

^c Departamento de Engenharia Química, Instituto Superior de Engenharia de Lisboa, Instituto Politécnico de
Lisboa, Rua Conselheiro Emídio Navarro, 1959-007 Lisboa, Portugal

E-mail: mssaraiva@fc.ul.pt

A set of phenanthroline derivatives was synthesized from 1,10-phenanthroline and 2,9-dimethyl-1,10-phenanthroline as shown in Scheme 1.¹ These ligands reacted in inert atmosphere and at room temperature with the precursor complex $[\text{Mo}(\eta^3\text{-C}_3\text{H}_5)\text{Br}(\text{CO})_2(\text{CH}_3\text{CN})_2]$ resulting in the formation of the new family of molybdenum(II) organometallic complexes $[\text{Mo}(\eta^3\text{-C}_3\text{H}_5)\text{Br}(\text{CO})_2(1\text{-R}_1\text{-imidazo}[4,5\text{-f}]\text{-R}_2\text{-[1,10]phenanthroline})]$ (**4**, R_1 =butyl, methyl, R_2 =dimethyl, H).² All the ligands and complexes prepared were characterized by FTIR, ¹H and ¹³C NMR. The new complexes prepared were used as homogeneous catalysts for the oxidation of *cis*-cyclooctene, styrene, *cis*-3-hexen-1-ol, *trans*-2-hexen-1-ol, *R*(+)-limonene, geraniol and 1-octene with TBHP (*tert*-butyl hydroperoxide) as the oxidant. The data were collected through GC-MS. The effects of reaction time, temperature and amount of catalysts are discussed.



Scheme 1. Synthesis of the molybdenum organometallic complexes **4**.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013, PEst-OE/QUI/UI0612/2013, UID/QUI/00100/2013, PTDC/QEQ-ERQ/1648/2014 and PTDC/QEQ-QIN/3967/2014. A.P.C. Ribeiro acknowledges FCT for SFRH/BPD/90883/2012. J. Wang acknowledges financial support from FCT through PD/BD/114397/2016. M.S. Saraiva thanks FCT for grant SFRH/BPD/88082/2012.

References

- [1] A.A. Webster, S.K.K. Prasad, J.M. Hodgkiss, J.O. Hoberg, Dalton Trans. 44 (2015) 3728-3736.
- [2] M.S. Saraiva, S. Quintal, F.C.M. Portugal, T.A. Lopes, V. Félix, J.M.F. Nogueira, M. Meireles, M.G.B. Drew, M.J. Calhorda, J. Organomet. Chem. 693 (2008) 3411-3418.

Materials

Moving back to nature

Jorge Moniz dos Santos

Resiquímica

Before oil exploration, materials and coatings already existed.

The petrochemical industry created an enormous toolbox that, among others, led to the chemistry of synthetic polymers. Different materials with completely new properties emerged and became commodities.

Nowadays, environmental concerns, consumer awareness and legislative regulations prompt scientists and engineers to develop greener materials with high renewable contents, while keeping or even improving performance.

Optical and Multifunctional Materials

José Paulo Farinha, Ermelinda Maçôas, Carlos Baleizão, José Gaspar Martinho
*CQFM – Instituto de Nanociências e Nanotecnologias,
Instituto Superior Técnico, Universidade de Lisboa, Portugal*

Our group is focused on the development, characterization and applications of multifunctional nanostructured materials, in particular those with optical response. We have developed nanomaterials based on different combinations of polymers, silica, semiconductors, gold, carbon materials and fluorescent dyes. We target applications in fields from advanced optical imaging, to sensing, optical data storage, clean energy, structural color, theranostics, separation, etc.

Some examples of our nanomaterials include: hybrid silica nanoparticles (SNPs)¹ with new fluorescent dyes of increased brightness and photostability for laser-scanning imaging;² stimuli-responsive polymers (SRP)³ for sensing,⁴ biodiagnosis⁵ and separation;⁶ mesoporous silica nanoparticles (MSNs) with fluorescent dyes and SRPs for theranostics;⁷ metal-organic frameworks for clean energy;⁸ gold nanoparticles with silica and dyes,⁹ and with polymer and semiconductor nanoparticles¹⁰ for photonic applications; gold clusters;¹¹ fluorescence upconversion materials based on two-photon absorption (TPA) for bioimaging¹² and 3D-data storage.¹³

Acknowledgements

We are grateful for the commitment and dedication of the many students and young researchers that contributed to this work. Financial support provided by FCT projects PTDC/CTM/101627/2008, PTDC/CTM-NAN/115110/2009, PTDC/CTM-POL/114367/2009, PTDC/CTM-NAN/2354/2012, PTDC/CTM-NAN/6249/2014, PTDC/CTM-POL/3698/2014, RECI/CTM-POL/0342/2012, and UID/NAN/50024/2013, and EU projects SAFUEL (contract 314032) and GUIDENANO (contract 604387).

References

- [1] Analytical Chem. 89 (2017) 681-687.
- [2] RSC Advances 3 (2013) 9171-9174; Dyes & Pigments 110 (2014) 227-234.
- [3] Polymer 116 (2017) 261-267; Colloids and Surfaces B: Biointerfaces 112 (2013) 264-271.
- [4] Analytical Methods 6 (2014) 5450-5453; PCT WO/2014/123436; RSC Advances 7 (2017) 4627-4634.
- [5] Polymer Chem. 4 (2013) 2968-2981; Org. Biomol. Chem. 12 (2014) 3181-3190.
- [6] Langmuir 28 (2012) 5802-5809; Biotechnology J. 8 (2013) 709-717; Chem. Eng. J. 319 (2017) 31-38.
- [7] Microscopy Microanal. 19 (2013) 1216-1221; Nanomedicine 10 (2015) 2311-2314; Eur. J. Inorg. Chem. 27 (2015) 4579-4587; PCT/PT2017/000003.
- [8] RSC Advances 6 (2016) 35191-35196.
- [9] Nature Scientific Reports 7 (2017) 2440.
- [10] J. Phys. Chem. C 117 (2013) 3122-3133.
- [11] Nano Letters 10 (2010) 4217-42221; J. Colloid Interf. Sci. 455 (2015) 154-162.
- [12] Dyes & Pigments 99 (2013) 642-652; J. Mater. Chem. B 1 (2013) 2169-2177; Dyes & Pigments 95 (2012) 713-722; J. Phys. Chem. A 119 (2015) 2351-2362; Chem. Commun. 47 (2011) 7374-7376.
- [13] Mater Chem. C 3 (2015) 10775.

XPS application to the study of graphene-like materials

Ana Maria Ferraria, Ana Maria B. Rego

CQFM and IN, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal

X-ray photoelectron spectroscopy (XPS), a surface specific technique of analysis, can be used to study very different systems. The carbonaceous nanostructures mentioned here are just two examples.

I) Graphene and its derivative N-graphene have attracted an exceptional interest due to their unique chemical and physical properties. Nanosheets in the form of free-standing graphene flakes with just a few atomic monolayers find applications where an alternative to horizontal graphene supported by solid surfaces is needed. While in supported-graphene only one surface is available, free-standing graphene has the advantage of having both free surfaces and at least three open edges that can effectively be utilized.^{1,2}

II) Onion-Like Carbon (OLC) has been extensively studied due its electronic and self-lubricating properties, which may be interestingly explored at larger scales by dispersing these carbon nanostructures in metallic matrices. Diamond nanoparticles can be successfully dispersed by attrition milling and a similar processing route can be devised for OLC [P.A. Carvalho *et al.*, work in progress].

Among the battery of analytical techniques, XPS can help to evaluate the quality of the nanostructures, namely by quantifying the sp^2/sp^3 carbon ratio and/or the doping efficiency. Another useful parameter is the one obtained from the 1st derivative of the C KLL Auger structure, called the D parameter, which is the energy difference between absolute maximum and minimum (Figure 1).

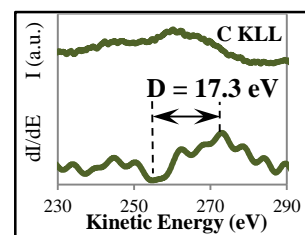


Figure 1. C KLL and 1st derivative of graphene.

Table 1. D parameters (eV) reported for different carbon structures³

Graphite	Diamond	SWCNT	DLC	Carbonized Wood	Carbon-black pellets
21.2	13.7	17.5	14.7	14.3	14

Acknowledgements

Support for this work was provided by FCT through UID/NAN/50024/2013. A. M. Ferraria acknowledges FCT for grant SFRH/BPD/108338/2015.

References

- [1] E. Tatarova, A. Dias, J. Henriques, A.M. Botelho do Rego, A.M. Ferraria, *et al.* J. Phys. D: Appl. Phys. 47 (2014) 385501.
- [2] D. Tsyganov, N. Bundaleska, E. Tatarova, A. Dias, J. Henriques, A. Rego, A. Ferraria, *et al.* Plasma Sources Sci. Technol. 25 (2016) 015013.
- [3] A. Mezzi, S. Kaciulis. Surf. Interface Anal. 42 (2010) 1082.

Study of Thermoelectric Materials at C²TN

A. P. Gonçalves, E. B. Lopes

*C²TN, Instituto Superior Técnico, Universidade de Lisboa, Estrada Nacional 10,
2695-066 Bobadela LRS, Portugal*

Thermoelectric materials can directly convert heat into electricity (via the Seebeck effect) and, vice versa, heating or cooling through the passage of an electrical current (via the Peltier effect). As a result, thermoelectric technology is seen as having great potential to contribute for the recovery of waste heat, increasing the energy efficiency, reducing the greenhouse gas emissions and promoting a more sustainable world.¹ The performance of a material for thermoelectrics can be estimated from its dimensionless figure of merit, $zT = \sigma\alpha^2T/\lambda$, which depends only on the material properties, the Seebeck coefficient (α), electrical conductivity (σ) and thermal conductivity (λ), and on the absolute temperature (T). It must have the highest zT over the wider possible temperature range in order to optimize the power generating efficiency. Actual commercial devices are composed of materials with $zT \approx 1$, being mostly based on scarce or toxic raw materials. Therefore, an increasing focus on the development of new thermoelectric materials made of non-toxic earth-abundant elements was lately seen.²

In this talk the activities related with the investigation of thermoelectric materials at C²TN are presented. These studies go from the preparation of borides, pnictides and chalcogenides, to their structural, electrical and thermal characterizations. Compounds and composites are prepared as amorphous, nanostructured, microstructured and single crystal materials. The existing phases and crystal structures are characterized by X-ray diffraction at room temperature and the electrical and thermal transport properties are studied from 20 K to 350 K (600 K in the case of electrical conductivity). The example of tetrahedrites will be given in more detail.

Acknowledgements

This work was partially supported by FCT through UID/Multi/04349/2013, POCI-01-0145-FEDER-016674 and M-ERA-NET2/0010/2016. We would also like to acknowledge the support given by the ANR project "PROGELEC", Verre Thermo-Générateurs "VTG".

References

- [1] K. Hiromasa, K. Takeshi, F. Shinichi, M. Kazuya, and H. Hirokuni, *Komatsu Tech. Rep.* 57 (2011) 164.
- [2] A.P. Gonçalves, E.B. Lopes, J. Monnier, E. Alleno, C. Godart, M.F. Montemor, J.B. Vaney, B. Lenoir, *Solid State Phenom.* 257 (2017) 135.

From biomass to carbon materials: synthetic routes and properties

Ana S. Mestre, Ana P. Carvalho

Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Portugal

Biomass is a valuable feedstock for numerous industrial sectors and its processing leads to wastes still with value for other economic sectors. The use of a waste as raw material for other industry is the ground for a more circular economy that will certainly play a key role in the development of more sustainable processes and societies.

The Adsorption and Adsorbent Materials Group of Chemistry and Biochemistry Center (Faculty of Sciences of Lisbon University) has been exploring the use of biomass residues as precursors for the synthesis of carbon materials successfully tested as adsorbents or as catalyst supports. Initial studies focused on the preparation of activated carbon materials from cork waste by chemical activation with KOH and K_2CO_3 . Under the framework of a QREN Project coordinated by Corticeira Amorim, the team also tested industrially pre-treated cork wastes as activated carbon precursors [Fig. 1(a)].¹ To obtain more specialized carbon materials innovative synthetic routes have been explored, namely, hydrothermal carbonization of sucrose followed by chemical or physical activation² [Fig.

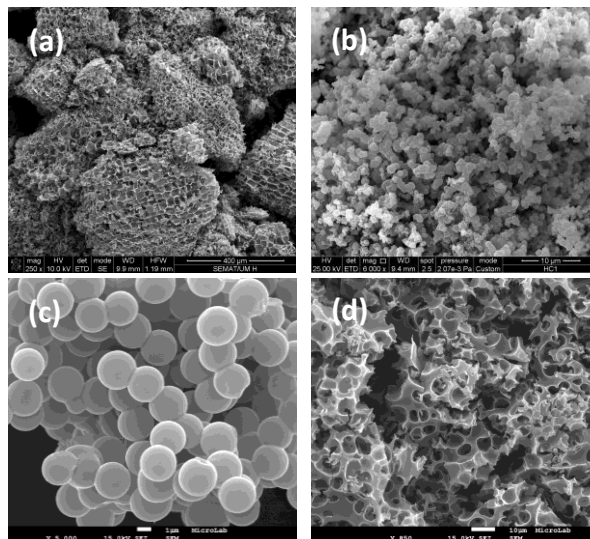


Figure 1. SEM images of lab-made carbon materials: Steam activated carbon from industrial pre-treated cork (a); Sisal-derived biochar by acid digestion of sisal residues (b); and sucrose-derived activated carbons obtained by hydrothermal carbonization followed by K_2CO_3 (c) or KOH (d) activation.

1(c) and (d)], or acid digestion of biomass and further activation [Figure 1(b)].³ The use of eutectic salt mixtures as porogens under low and high temperature is currently being addressed.

The carbon materials have been extensively characterized namely regarding pore structure and surface chemistry and these data have allowed a comprehensive analysis of their performance as adsorbents of pharmaceutical compounds with very distinct chemical moieties and dimensions, as enrichment phases previous to analytical quantification of pollutants in water matrices, and also as catalyst supports for greener processes.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013, and by COMPETE, AdI – QREN Project WaterCork (nº 5523). A.S. Mestre acknowledges financial support to FCT from Post-doc grant SFRH/BPD/86693/2012.

References

- [1] A.S. Mestre, R.A. Pires, I. Aroso, E.M. Fernandes, M.L. Pinto, R.L. Reis, M.A. Andrade, J. Pires, S.P. Silva, A.P. Carvalho, *Chem. Eng. J.* 253 (2014) 408-417.
- [2] A.S. Mestre, E. Tyszko, M.A. Andrade, M. Galhetas, C. Freire, A.P. Carvalho, *RSC Adv.* 5 (2015) 19696-19707.
- [3] A.S. Mestre, F. Hesse, C. Freire, C.O. Ania, A.P. Carvalho, Extended Abstract, Penn State (US): The world conference on Carbon 2016.

Materials for the Ethane-Ethylene Separation by Gas Adsorption

João Pires¹, Joana Fernandes¹, Ana Fernandes¹, Moisés L. Pinto²

¹Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal

²CERENA, Departamento de Engenharia Química, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal

Short-chain unsaturated hydrocarbons such as ethylene have major importance in petrochemical industry. Yearly, nearly 50 million tons of polyethylene were produced worldwide, using ethylene as raw material.¹ The separation of ethylene from ethane in an ethane-ethylene mixture is made by cryogenic distillation. However, 75 to 85% of the ethylene costs are due to the high energy consumption that is needed to separate it from ethane,² being one of the most energy-intensive single distillations practiced in industry.

Adsorption processes can be in principle used for the separation of ethylene from ethane. Nevertheless, the use of adsorption is still not economically viable, the main reason being related with the adsorption operation process implementation. Because most of the known adsorbents display preferential adsorption of ethylene over ethane, an additional desorption step is needed, which makes the implementation difficult due to economic reasons.³ Therefore, if the alkane is preferentially adsorbed, pure alkene is directly obtained during the adsorption step, and the whole separation scheme becomes much simpler.

In this communication we review part of recent work, and present new results, obtained in the Faculty of Sciences of ULisboa regarding the study of materials for the separation of ethylene from an ethane-ethylene mixture. We give emphasis, but not exclusively, to the ethane selective materials, that is, materials that show preferential adsorption of ethane over ethylene. The types of studied adsorbents range from clay based materials⁴ to zeolites⁵, metal-organic frameworks (MOFs)^{5,6} and, more recently, silica xerogels.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013.

References

- [1] L. Lloyd, Handbook of Industrial Catalysts, Springer, New York, 2011.
- [2] A. Miltenburg, W. Zhu, F. Kapteijn, J.A. Moulijn, Chem. Eng. Res. Des. 84 (2006) 350-354.
- [3] C. Gücüyener, J. van den Bergh, J. Gascon, F. Kapteijn, J. Am. Chem. Soc. 132 (2010) 17704-17706.
- [4] V. Saini, M.L. Pinto, J. Pires, Sep. Sci. Tech. 46 (2011) 1-10.
- [5] J. Pires, J. Fernandes, A.C. Fernandes, M.L. Pinto, Sep. Sci. Tech. 52 (2017) 51-57.
- [6] J. Pires, M.L. Pinto, V.K. Saini, ACS App. Mater. Interfaces 6 (2014) 12093-12099.

Self-Assembled Bilayer Molecular Metals (CNB-TTF-type donors)₄X: Polymorphism and Superconductivity

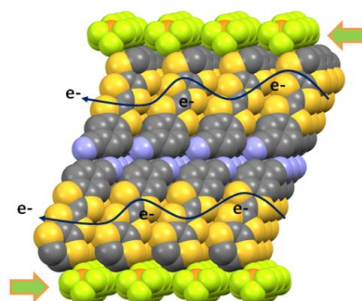
S. Rabaça^a, S. Oliveira^a, A. C. Gonçalves^a, G. Lopes^a, V. Gama^a, E. B. Lopes^a,
G. Oliveira^a, I. C. Santos^a, J. A. Paixão^b, D. Belo^a, E. Canadell^c and M. Almeida^a

^a C²TN, I.S.T., Univ. Lisboa, E.N. 10 (km 139,7), P-2695-066 Bobadela LRS, Portugal

^b Departamento de Física, Univ. Coimbra, P-3004-516 Coimbra, Portugal

^c ICMAB (CSIC), Bellaterra, Spain

In this contribution a novel type of 2D electronic systems based on charge transfer salts with a donor bilayer structure is described. These bilayer systems are an entirely new type of structures among molecular materials, observed in charge transfer salts of an electronic donor asymmetrically substituted with CN groups. These solids exhibit unprecedented properties associated with a direct coupling between two adjacent layers of donor molecules interconnected by relatively weak but direct interactions induced by head-to-head C–N⋯H pairing interactions associated with a combination of R²₂(10) and R²₄(10) synthons between donors in nearby layers.^{1,2} The formation of partially oxidized donor bilayers with metallic properties is observed in salts with composition (CNB-TTF-Type)₄X with different small anions such as X= ClO₄⁻, PF₆⁻, I₃⁻, BF₄⁻, ReO₄⁻, SbF₆⁻, Br⁻. However different polymorphs of salts with the 4:1 stoichiometry, depending on the solvent and crystallization conditions, can be obtained.^{3,4} These 4:1 charge transfer salts present 2D metallic properties with unusual characteristics derived both from the unusual stoichiometry and the weak interaction between paired donor layers. These bilayer structures constitute a new model for 2D electronic systems, intermediate between the single layer and 3D solids.



Bilayer molecular metals (CNB-EDT-TTF)₄X.

Acknowledgements

Work partially supported by FCT through contracts UID/MULTI/04349/2013 and RECI/QEQ-QIN/0189/2012 and grants SFRH/BPD/113344/2015, SFRH/BD/72722/2010 and SFRH/PD/BD/127804/2016 to S. Rabaça, S. Oliveira and A.C. Gonçalves, respectively.

References

- [1] S. Oliveira, D. Belo, I.C. Santos, S. Rabaça, M. Almeida, *Beil. J. Organic Chemistry* 11 (2015) 951-956.
- [2] S. Oliveira, J. Ministro, I.C. Santos, D. Belo, E.B. Lopes, S. Rabaça, E. Canadell, M. Almeida, *Inorg. Chem.* 54 (2015) 6677-6679.
- [3] S. Rabaça, S. Oliveira, V. Gama, I.C. Santos, D. Belo, E.B. Lopes, E. Canadell, M. Almeida, *Inorg. Chem.* 55 (2016) 10343-10350.
- [4] S. Rabaça, S. Oliveira, A.C. Gonçalves, V. Gama, I.C. Santos, D. Belo, M. Almeida, *Cryst. Growth Design* 17 (2017) 2801-2808.

Notes on the nature of the chemical bond in actinide di-sulfides
of the type $\eta^2\text{-AnS}_2^{2+}$ (An = Th, U, Np, Pu)

Nuno A. G. Bandeira^{1,2,3}, Ana Lucena⁴, Cláudia C. L. Pereira⁴, Joaquim Marçalo⁴,
John K. Gibson⁵

¹ Institute of Chemical Research of Catalonia (ICIQ), Avda. Països Catalans, 16 - 43007 Tarragona, Spain

² Centro de Química Estrutural – Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais,
1049-001 Lisboa, Portugal

³ Centro de Química e Bioquímica – Faculdade de Ciências, Universidade de Lisboa, Campo Grande,
1749-016 Lisboa, Portugal

⁴ Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa,
2695-066 Bobadela LRS, Portugal

⁵ Chemical Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, California 94720, USA
E-mail: nuno.bandeira@ciencias.ulisboa.pt

The recent discovery¹ that di-cationic uranium di-sulphide possesses a triangular geometry (Figure 1) as opposed to the well-known linear uranyl (UO_2^{2+}) poses the question of whether this trend is maintained with the immediate neighbours of uranium in the same period namely neptunium and plutonium. These species were produced in the gas phase by ionic collisions. To provide insight into their geometric and bonding scenarios high level multiconfigurational (CASPT2) electronic structure calculations were performed to assess the structures and bonding of the new AnS_2^{2+} cations for An = Th, U, Np and Pu, to examine trends along the actinide period. The CASPT2 results showed that, like in the case of uranium, the new AnS_2^{2+} ions have ground states with triangular geometries, corresponding to the presence of a persulphide in the case of thorium that formally leads to a stable $\text{Th}^{\text{IV}}\text{S}_2^{2+}$ species, while a super-sulphide appears to be present in the case of U, Np and Pu, formally leading to a $\text{An}^{\text{III}}\text{S}_2^{2+}$ species. The computations also revealed that linear thioactinyl structures are higher in energy, with a difference that increases fourfold upon moving from U to Pu.

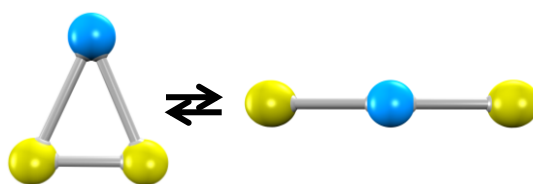


Figure 1. Linear versus triangular actinide di-sulfides.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. N.A.G. Bandeira acknowledges financial support from grants SFRH/BPD/110419/2015 (FCT) and CTQ2014-52824-R (MINECO).

References

[1] C.C.L. Pereira, M.C. Michelini, J. Marçalo, Y. Gong, J.K. Gibson, *Inorg. Chem.* 52 (2013) 14162-14167.

Single Component Molecular Conductors Based on Thiophene-dithiolene Ligands

D. Belo, M. M. Andrade, R. Santos, R. A. L. Silva, E. B. Lopes, L. C. J. Pereira,
J. T. Coutinho, I. C. Santos, S. Rabaça, M. Almeida

*C²TN, Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa,
E.N. 10 ao km 139, 7, 2695-066 Bobadela, Portugal*

The report of the first Single Component Molecular Conductors (SCMC) in 2001, contributed to a renewal of the interest in the chemistry of Transition Metal bisdithiolenes, as all known SCMC are based on this type of complexes. Our group initially reported a small gold complex based on a simple thiophene-dithiolate (α -tpdt = 2,3-thiophenedithiolate) $[\text{Au}(\alpha\text{-tpdt})_2]$, that even in the poly-nano-crystalline form displays a very high room temperature conductivity of 7 S/cm. Subsequently we focused on complexes with more extended and delocalised thiophene-dithiolate ligands, which besides the thiophenic ring also incorporated a fused TTF moiety. The best results were obtained with $[\text{Ni}(\text{dtdt})_2]$ (dtdt = 2-(dihydro-5H-thieno[3,2-d][1,3]dithiol-2-ylidene)-1,3-dithiolane-4,5-dithiol), that as a polycrystalline sample shows a room temperature conductivity of 200 S/cm. These two examples besides being among the first reported SCMC, were also the first of such compounds tested as components in electronic devices:

- Thin films were prepared by self-metallizing polycarbonate films with $[\text{Au}(\alpha\text{-tpdt})_2]$. Electromechanical tests demonstrated that these films are strain-resistive materials with advanced elastic properties, making them potentially useful for engineering flexible, lightweight, strain and pressure sensors;
- $[\text{Ni}(\text{dtdt})_2]$, as a fine suspension, processed by a drop casting technique, can be used as a conductive ink with a resistance of ~ 0.3 k Ω /sq, one order of magnitude better than commercial carbon based conductive inks.

In spite these two successful examples, SCMC processing is still limited by their very poor solubility in organic solvents. To overcome this handicap, we explored several new families of transition metal neutral complexes based on alkyl substitute thiophene-dithiolate ligands, which as expected, are more soluble in their neutral form. In this communication our most recent work concerning this topic will be presented and discussed.

Acknowledgements

Support for this work was provided by FCT through UID/Multi/04349/2013, PTDC/QEQ-SUP/1413/2012 and RECI/QEQ-QIN/0189/2012. R. A. L. Silva and J. T. Coutinho acknowledges financial support from FCT (PhD grants SFRH/BD/86131/2012 and SFRH/BD/84628/2012, respectively).

References

- [1] D. Belo, H. Alves, E.B. Lopes, M.T. Duarte, V. Gama, R.T. Henriques, M. Almeida, A. Perez-Benitez, C. Rovira, J. Veciana, Chem. Eur. J. 7 (2001) 511-519.
- [2] J.P.M. Nunes, M.J. Figueira, D. Belo, I.C. Santos, B. Ribeiro, E.B. Lopes, R.T. Henriques, C. Rovira, M. Almeida, Chem. Eur. J. 13 (2007) 9841-9849.
- [3] D. Belo, M. Almeida, Coord. Chem. Rev. 254 (2010) 1479-1492.
- [4] M.M. Andrade, R.A.L. Silva, I.C. Santos, E.B. Lopes, S. Rabaça, L.C.J. Pereira, J.T. Coutinho, J.P. Telo, C. Rovira, M. Almeida, D. Belo, Inorg. Chem. Front. 4 (2017) 270-280.

Polymorphism in Active Pharmaceutical Ingredients

Carlos E. S. Bernardes^{1,2}, Catarina T. António¹, Gabriel L. B. Araújo³,
Manuel E. Minas da Piedade¹

¹ *Centro de Química e Bioquímica, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Portugal*

² *Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Portugal*

³ *Universidade de São Paulo, Brasil*

Since the middle of the last century, it has been widely recognized that many organic compounds can be obtained in more than one crystal structure, a phenomenon known as polymorphism. It also became apparent that the adopted crystal structure often exerts a significant effect in the solid-state properties of the compounds, so that, in fact, each polymorph should be regarded as a different material. The lack of control over polymorphism may, therefore, wreak havoc with the production, safe use, shelf life, and patenting of fine chemicals such as organic conductors, explosives, pigments, and pharmaceuticals. Polymorphism has, in fact, been of particular concern in the pharmaceutical industry since various examples have been reported where the unexpected appearance of new polymorphic forms at the production stage led to the recall of marketed medicines with enormous financial losses (e.g. the ritonavir and avalide cases).

Organic polymorphs can often coexist at the same temperature and pressure conditions, but they may evolve over time to the most thermodynamically stable one. Thus, once polymorphism has been identified and structurally characterized it is very important to define a stability hierarchy among different forms.

In this work, a small overview of ongoing polymorphism studies involving active pharmaceutical ingredients, will be given. This will include the very recent determination of the relative stability of two known polymorphs of the anticancer drug erlotinib hydrochloride (Figure 1).

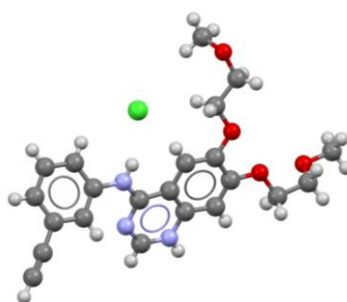


Figure 1. Molecular structure of erlotinib hydrochloride.

Acknowledgements

This work was supported by projects UID/MULTI/00612/2013 and UID/QUI/00100/2013 from Fundação para a Ciência e a Tecnologia (FCT), Portugal. Post-Doctoral grants from FCT are also gratefully acknowledged by C.E.S. Bernardes (SFRH/BPD/101505/2014). We also thank to Prati-Donaduzzi Pharmaceutical company (Brazil) for the donation of erlotinib hydrochloride.

Ligand characterization and functional group conversion in nanostructured silica by $^1\text{H-NMR}$

C. I. C. Crucho, C. M. Baleizão, J. P. S. Farinha

*Optical and multifunctional materials 1, CQFM, Centro de Química-Física Molecular, IN — Institute of
Nanosciences and Nanotechnology, Instituto Superior Técnico, 1049-001 Lisboa, Portugal*

E-mail: carina.crucho@tecnico.ulisboa.pt

Nanoscale materials offer excellent opportunities for bio-imaging and therapeutic applications. Particularly, silica-based nanoparticles (SiNPs) are a promising class of materials due to their well-defined and tunable structures and versatile functionalization chemistry, which improves their chemical and physical properties.¹ An accurate quantification of active functional groups on a nanoparticle surface is important to know the number of molecules that can be linked to the surface. Solid-state NMR methods have been used to investigate functionalized nanomaterials, however, an important drawback of these methods is that they are very time consuming, need a large amount of sample for analysis and are generally carried out on the dried powders.

Here, we present a fast and simple method for quantification of surface ligands and for tracking chemical modifications on silica nanoparticles. This is based on solution NMR spectroscopy, combining *in-situ* dissolution of the SiNPs and standard $^1\text{H-NMR}$ experiments.²

Quantitative analysis of the NMR spectra for functionalized SiNPs agrees well with the TGA results and the obtained results revealed the sensitivity of solution NMR spectroscopy for tracking small amounts of surface bound ligands on the SiNPs. Extension of this method to other silica based nanomaterials can also be envisaged.

Acknowledgements

This work was partially supported by Fundação para a Ciência e a Tecnologia (FCT-Portugal) and COMPETE (FEDER), projects RECI/CTM-POL/0342/2012, UID/NAN/50024/2013 and PTDC/CTM-POL/3698/2014.

C. Crucho thanks to FCT for her postdoctoral grant SFRH/BPD/120548/2016.

References

- [1] A. Liberman, N. Mendez, W.C. Trogler, A.C. Kummel, *Surf. Sci. Rep.* 69 (2014) 132-158.
- [2] C.I.C. Crucho, C. Baleizão, J.P.S. Farinha, *Anal. Chem.* 89 (2017) 681-687.

From fundamentals to applications:

f- Elements – a fascinating part of the Periodic Table

J. P. Leal, J. Marçalo, J. B. Branco, J. M. Carretas,

L. Maria, B. Monteiro, A. C. Ferreira, A. Cruz

Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico

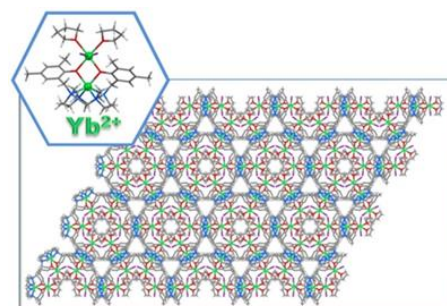
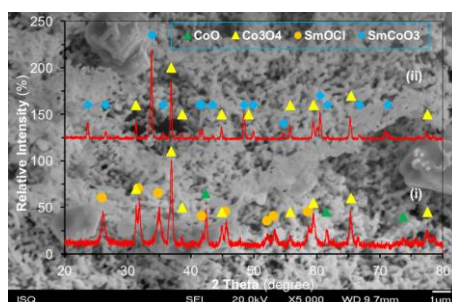
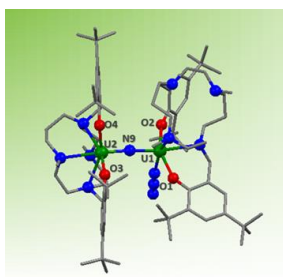
Universidade de Lisboa, 2695-066 Bobadela, Portugal

The *f*-Element Chemistry Group (QE*f*)¹ is part of Centro de Ciências e Tecnologias Nucleares (C²TN), a research unit of Instituto Superior Técnico (IST). The research activities of the QE*f* Group are centered in the study of lanthanide and actinide chemistry at fundamental and applied levels, with focus on topics of relevance in environmental, nuclear and materials sciences.

The activities comprise the synthesis of new *f*-element compounds and materials, the study of their structural, optical and magnetic properties, and reactivity and catalysis studies aiming the elimination/activation of major gaseous pollutants such as carbon dioxide, methane and nitrous oxide. Different aspects of the chemistry of elementary lanthanide and actinide species are examined using molecular mass spectrometry. Investigation of the thermodynamic properties of key species in condensed and gas phases are studied as well as methods for their prediction.

During its almost 40 years of life (under different names but always focused on *f*-element chemistry), in the group or under supervision of group members a significant number of PhD and MSc theses were produced, a few hundred publications were published and 5 patents were registered.

The QE*f* Group has active collaborations with other research groups inside and outside C²TN, e.g. IPFN, CQB-FCUL, LAQV@REQUIMTE, CQE-IST, and other external research groups in the framework of the Portuguese Mass Spectrometry Network (RNEM - ROTEIRO/0028/2013), the FCT Doctoral Programme CATSUS-Catalysis and Sustainability, and the European Project “ENVIRONMENTALLY friendly and efficient methods for extraction of Rare Earth Elements from secondary sources” (ENVIREE).



Acknowledgements

Support for the work was partially provided by Fundação para a Ciência e a Tecnologia (FCT) through project UID/Multi/04349/2013UID/MULTI/00612/2013.

References

[1] <http://c2tn.tecnico.ulisboa.pt/en/r-d/research-groups/chemistry-of-f-elements> .

Nonlinear emission in molecular materials: where we have been and where we are going

Inês F. A. Mariz, Carla Santos, Cátia Correia, Tiago Silva, Carlos Baleizão,

José M. G. Martinho and Ermelinda M. S. Maçôas

Centro de Química-Física Molecular and IN-Institute of Nanoscience and Nanotechnology, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal

The two-photon absorption (TPA) process is a third-order nonlinear optical process that requires high excitation powers and/or systems with high third order susceptibility coefficients.¹ The quadratic dependence of the TPA probability on the light intensity can confine absorption to a highly localized focal volume simultaneously allowing for a greater depth of penetration of light due to the use of longer wavelengths when compared to linear excitation. TPA finds an increasing use in fluorescence microscopy, 3D optical data storage, nanofabrication, optical power limiting, and photodynamic therapy. These applications crucially rely on the development of new materials with well-characterized and optimized TPA properties.

Our work has been focused on the development and the characterization of fluorescence upconversion materials based on two-photon excitation. Different systems such as oxazolone derivatives, molecules base on quinolizinium cation, triazine molecules and polymers, perylenediimide (PDIs) derivatives, water soluble hybrid polymer nanoparticles and graphene quantum dots were studied.

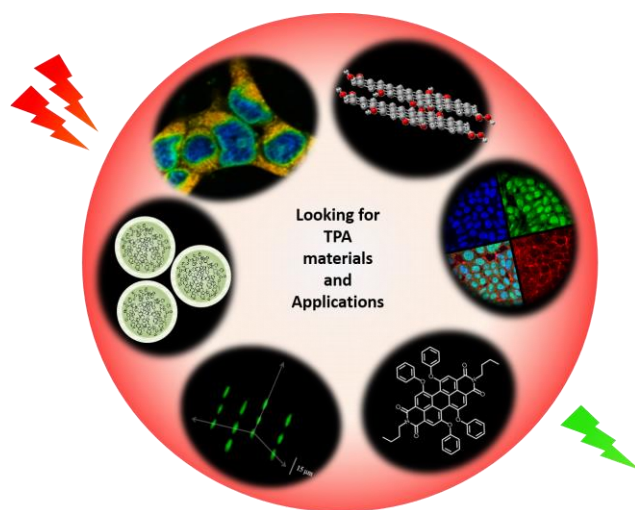


Figure 1. Representation of some TPA materials (quinolizinium cation, PDIs, water soluble nanoparticles and graphene quantum dots) and some applications in bioimaging and 3D optical data storage.

Acknowledgements

This work was partially supported by Fundação para a Ciência e a Tecnologia (FCT-Portugal) (IF/00759/2013, SFRH/BPD/75782/2011, SFRH/BPD/1054/2014 and PD/BD/127805/2016) and COMPETE (FEDER), project UID/NAN/50024/2013.

References

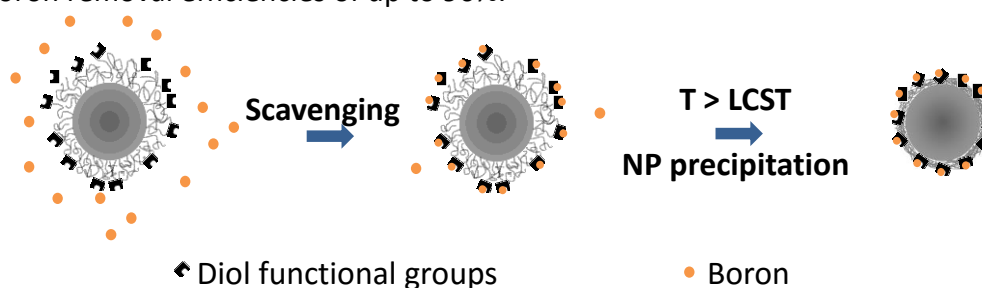
[1] G.S. He, L.-S. Tan, Q. Zheng, P.N. Prasad, *Chem. Rev.* 108 (2008) 1245.

Smart Polymeric Nanoparticles for Boron Scavenging

Sérgio P. C. Alves, Catarina Santos, André Pontes da Costa, Mara Soares da Silva,
Carlos Baleizão, José Paulo S. Farinha
*CQFM, Centro de Química-Física Molecular, IN—Institute of Nanosciences and Nanotechnology,
Instituto Superior Técnico, 1049-001 Lisboa, Portugal*

Boron is a trace element essential to human health and agriculture in trace quantities, but becomes toxic when in excess.¹ Boron compounds are used in many industries, including in the manufacture of glass and ceramics, semiconductors, fertilizers, insecticides, pharmaceutical drugs, high duress compounds, soaps and detergents, and flame retardants. A high boron contents in water might be a result from industrial wastewaters or leaching from rocks and soils containing borates and borosilicates.¹

It is difficult to detect^{2,3} and remove boron from water⁴, a step which is sometimes required in the treatment of residual waters. We have synthesized thermoresponsive core-shell polymer nanoparticles containing vicinal diol groups for boron scavenging. The particles have a core of poly(methyl methacrylate) (PMMA) and a thermosensitive shell with a brush composed of a copolymer of N-isopropylacrylamide (NIPAM), 2-aminoethyl methacrylate (AEMH), and either D-gluconoamidoethyl methacrylate (GAEM) or monodiol methacrylate (MDM) boron-chelating diol-containing monomers. The nanoparticles revealed good boron chelation capacity, both for the removal of boric acid and phenylboronic acid from water. At temperatures above about 35°C the particle shell collapses, inducing particle flocculation that facilitates particle separation. We observed boron removal efficiencies of up to 96%.⁵



Scheme 1. Boron scavenging process.

Acknowledgements

This work was partially supported by Fundação para a Ciência e a Tecnologia (FCT-Portugal) and COMPETE (FEDER), projects RECI/CTM-POL/0342/2012, UID/NAN/50024/2013 and PTDC/CTM-POL/3698/2014. S. Alves acknowledges a postdoctoral grant from FCT (SFRH/BPD/74654/2010).

References

- [1] World Health Organization, Guidelines for drinking-water quality, 4th ed., World Health Org., 2011.
- [2] S. Alves, C. Baleizão, J.P.S. Farinha, *Analytical Methods* 6 (2014) 5450-5453.
- [3] J.P.S. Farinha, C. Baleizão, S. Alves, WO2014123436, 2014.
- [4] J. Wolska, M. Bryjak, *Desalination* 310 (2013) 18-24.
- [5] S.P.C. Alves, C. Santos, A.P. Costa, M. Silva, C. Baleizão, J.P.S. Farinha, *Chem. Eng. J.* 319 (2017) 31-38 (featured article, journal cover).

Glucose-derived nanoporous carbons as supports of a C-scorpionate Fe^{II} catalyst

Marta A. Andrade^a, Ana S. Mestre^b, Ana P. Carvalho^b, Armando J. L. Pombeiro^a,
Luísa M. D. R. S. Martins^{a,c}

^a Centro de Química Estrutural, IST, Universidade de Lisboa, Portugal

^b Centro de Química e Bioquímica, Faculdade de Ciências da Universidade de Lisboa, Portugal

^c Chemical Engineering Department, Instituto Superior de Engenharia de Lisboa, Portugal

Metal complex-catalyzed oxidation reactions are quantitatively the most important homogeneously catalyzed reactions in chemical industry.¹ However, as all homogeneous processes, these reactions present major drawbacks, as the difficult separation of the relatively expensive catalysts from the reaction medium, their recycling and reuse. The immobilization of a catalyst on solid supports is nowadays a convenient and suitable strategy to overcome these limitations, combining the advantages of homogeneous and heterogeneous catalysis.^{2,3}

The sustainable development of chemical processes is leading to the search for efficient, selective, environmentally benign and economic catalytic oxidation processes. In this context, the use of transition metal complexes bearing tris(pyrazolyl)methanes in oxidation catalysis has attracted much interest, given their ability to act as catalysts or catalyst precursors for relevant alkane oxidation reactions, namely peroxidative oxygenations and carboxylations.⁴ In the present study the Fe^{II} complex, lithium [tris(1-pyrazolyl)methanesulfonate]dichloroferrate, Li[FeCl₂{SO₃C(pz)₃}], was immobilized in two carbon materials. The nanoporous carbons were prepared by hydrothermal carbonization (HTC), a green and sustainable process, since it uses water as solvent, mild temperatures, self-generated pressure and generates no CO₂ emission. The carbon precursor was glucose (G) and a LiCl/ZnCl₂ eutectic salt mixture was used as a porogen agent.⁵

The heterogenization process onto the carbon materials was performed through the dissolution of the necessary amount of Fe scorpionate in water to achieve a Fe catalyst at 2 % (wt) per mass of carbon. The mixture was stirred for 24 h, at room temperature. The catalytic behaviour of the immobilized catalysts for the oxidation of cyclohexane will be presented and discussed. The effect of temperature, time, oxidant and catalysts amount will be optimized to obtain the best performing systems. Recycling studies are also foreseen.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013, UID/QUI/00100/2013, PTDC/QEQ-ERQ/1648/2014 and PTDC/QEQ-QIN/3967/2014 projects. M.A. Andrade and A.S. Mestre acknowledge financial support from [BL/CQE-2017-022] and Post-doc grant (FCT) SFRH/BPD/86693/2012, respectively.

References

- [1] Ullmann's Encyclopedia of Industrial Chemistry, 6th ed., John Wiley and Sons, Inc.
- [2] Appl. Catal. A: Gen. 464-465 (2013) 43-50.
- [3] ChemCatChem 5 (2013) 3847-3856.
- [4] Coord. Chem. Rev. 265 (2014) 74-88.
- [5] J. Mat. Chem. A 1 (2013) 9418.

Crystal engineering and supramolecular coordination chemistry: a powerful combination to improve drug's performance

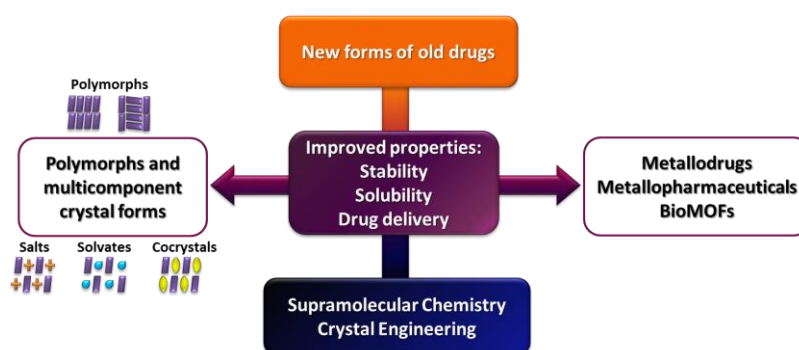
Vânia André, Sílvia Quaresma, Inês C. B. Martins, M. Teresa Duarte

Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal

Over the last years, our group has been dedicated to combine the principles of crystal engineering and supramolecular chemistry to develop new crystal forms of active pharmaceutical ingredients (API), envisaging the improvement of specific properties, such as stability and solubility, as well as new materials for controlled drug delivery and release.

Several polymorphs, hydrates, solvates, salts and cocrystals of multiple APIs were disclosed and specific properties have been studied, showing in most cases improvements in the stability and/or solubility of the pharmaceutical compounds.¹⁻³ Metallodrugs, metallopharmaceuticals and bio-inspired metal-organic frameworks (BioMOFs) are another branch of work that we are successfully exploring, from which we highlight the study with bismuth subsalicylate⁴ and the development of novel BioMOFs with azelaic and nalidixic acids. Systems made of APIs and room temperature ionic liquids are further being investigated for applications in polymorphic control.⁵

It is also worth mentioning that the main synthetic technique used in our group is mechanochemistry, which proved to be an efficient, environmental-friendly, cleaner, and faster procedure.



Acknowledgements

Authors acknowledge Fundação para a Ciência e a Tecnologia for funding (PEst-OE/QUI/UI0100/2013, RECI/QEQ-QIN/0189/2012, SFRH/BD/100029/2014, SFRH/BD/93140/2013 and SFRH/BPD/78854/2011)

References

- [1] C. Maheshwari, V. André, S. Reddy, L. Roy, M.T. Duarte, N. Rodríguez-Hornedo, *CrystEngComm* 14 (2012) 4801-4811.
- [2] V. André, L. Cunha-Silva, M.T. Duarte, P.P. Santos, *Cryst. Growth Des.* 11(9) (2011) 3703-3706.
- [3] I.C.B. Martins, M. Sardo, S.M. Santos, A. Fernandes, A. Antunes, V. André, L. Mafra, M.T. Duarte, *Cryst. Growth Des.* 16(1) (2016) 154-166.
- [4] V. André, A. Hardeman, I. Halasz, R.S. Stein, G.J. Jackson, D.G. Reid, M.J. Duer, C. Curfs, M.T. Duarte, T. Frišćić, *Angew. Chem. Int. Ed.* 50(34) (2011) 7858-7861.
- [5] I.C.B. Martins, J.R.G. Gomes, M.T. Duarte, L. Mafra, *Cryst. Growth Des.* 17(2) (2017) 428-432.

Structurally colored photonic pigments by soft lithography droplet microfluidics technology

Laurinda R. P. Areias and José Paulo S. Farinha

CQFM, Centro de Química-Física Molecular, IN—Institute of Nanosciences and Nanotechnology, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal

Colloidal photonic crystals (PCs) are receiving increased attention due to the fundamental aspects of their formation, their numerous applications (e.g., as waveguides and light manipulators in optoelectronic, photovoltaics and sensoric applications), and also because of their artistic beautiful colors. Their shining structural coloration arises from the modulation of the electromagnetic waves by means of Bragg reflection from photonic band gaps (PBG). The PBGs are due to repeating regions of low and high dielectric constants obtained by the periodical arrangement of nanoparticles that is used to control the propagation of light.¹

In this work our aim is to develop uniformly sized colloidal spherical assemblies that exhibit structural coloration throughout the visible spectrum light range. To this end we synthesized differently sized colloidal building blocks by emulsion polymerization. The polymeric nanoparticles are composed of a hard core made of cross-linked polystyrene and a soft shell composed of poly(methyl methacrylate-co-acrylic acid) [P(St-MMA-AA)] in a size range from ≈ 100 to 300 nm with very low polydispersity.

To obtain photonic pigments within the spherical confinement of emulsion droplets, we used a bottom-up approach, where the self-assembly of colloidal nanoparticles is controlled by means of microdroplet W/O and W/O/W emulsification in PDMS microfluidic devices. Microfluidic devices were fabricated via conventional soft lithographic techniques. The microchannel architecture was transferred to high resolution aluminium masks and the master mold was fabricated using the negative photoresist SU-8, from which we developed 50 μm height PDMS microchannels.² Different sized emulsion droplets can be obtained by adjusting the flow rates of the continuous and dispersed phases. After water evaporation from the emulsion droplets, different photonic pigments can be obtained by using differently sized polymeric nanoparticles.

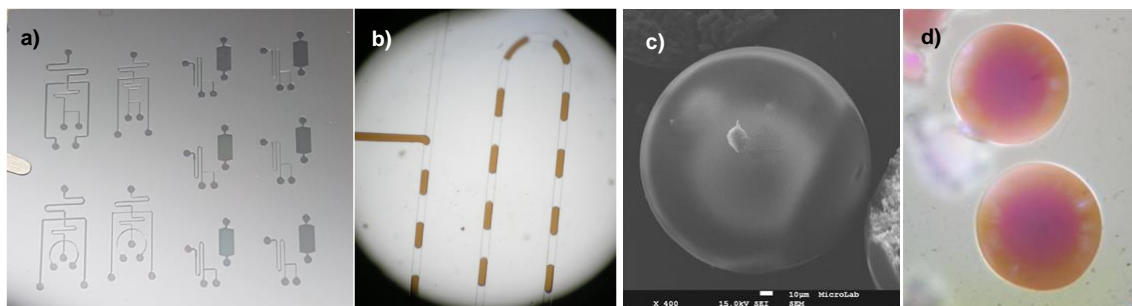


Figure 1. **a)** Photograph of the SU-8 hard mask; **b)** Emulsification process for droplet formation inside the PDMS circuits; **c)** SEM image of a microsphere after water removal and assembling of the polymeric nanoparticles; **d)** Pink-Orange color displayed by a macrosphere composed of 270 nm polymeric nanoparticles under optical microscope (10x objective).

Acknowledgements

This work was partially supported by Fundação para a Ciência e a Tecnologia (FCT-Portugal) and COMPETE (FEDER) within projects UID/NAN/50024/2013 and PTDC/CTM-POL/3698/2014. L. Areias also thanks FCT for a ChemMat Doctoral Program PhD grant, PD/BD/113533/2015.

References

- [1] J.-G. Park, S.-H. Kim, S. Magkiriadou, T.M. Choi, Y.-S. Kim, V.N. Manoharan, *Angew. Chem. Int. Ed.* 53 (2014) 2899.
- [2] J.-T. Wang, J. Wang, J.-J. Han, *Small* 13 (2011) 1728.

The effect of Ru-doping in titanate elongated nanostructures photocatalytic performance

B. Barrocas¹, M. Conceição Oliveira², O. C. Monteiro¹

¹ Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal

² Centro Química Estrutural, Instituto Superior Técnico, ULisboa, 1049-001 Lisboa, Portugal

In this work, titanate nanotubes and nanowires (TNT and TNW) were doped with ruthenium aiming to enhance their photocatalytic properties. The materials were prepared using a hydrothermal approach^{1,2}, and were structural, morphological and optical characterized by XRD, TEM, DRS, XRF and XPS. No modifications on the structure and morphology were detected in the Ru-doped materials but an increase on the visible light absorption was observed. The photocatalytic activity was evaluated on the hydroxyl radical ($\bullet\text{OH}$) production, using terephthalic acid as probe molecule, and on the photocatalytic removal of caffeine and sulfamethazine aqueous solutions. Based on the photodegradation experiments, it is suggested that Ru-doped materials were the best catalysts for all the degradation processes studied. The results show that, within 60 min under UV-vis radiation, the RuTNT sample was the best catalyst, achieving 100% of photodegradation efficiency for caffeine (20 ppm solution) and for sulfamethazine (10 ppm solution), and all the secondary products were identified. A mechanism for the charge-transfer in RuTNT nanoparticles is proposed and discussed.

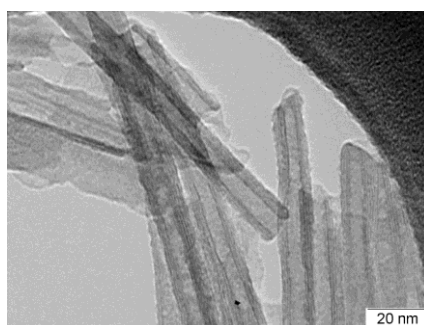


Figure 1. TEM image of the RuTNT sample.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. B. Barrocas acknowledges financial support from SFRH/BD/101220/2014 and O.C. Monteiro from IF/01210/2014. The authors also thank the Portuguese Mass Spectrometry Network (Node IST-Campus Alameda) for facilities. XPS analyses were performed at CEMUP – Centro de Materiais da Universidade do Porto.

References

- [1] M.R. Nunes, O.C. Monteiro, A.L. Castro, D.A. Vasconcelos, A.J. Silvestre, *Eur. J. Inorg. Chem.* 28 (2008) 961-965.
- [2] E.K. Ylhäinen, M.R. Nunes, A.J. Silvestre, O.C. Monteiro, *J. Mater. Sci.* 47 (2012) 4305-4312.

Hybrid Silica Nanoparticles to Target the Blood-Brain Barrier for Controlled Drug Release

Susana Cecílio, Pankaj Karande, Carlos Baleizão and José Paulo S. Farinha

^a *Centro de Química-Física Molecular (CQFM), Institute of Nanoscience and Nanotechnology (IN), Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal*

^b *Department of Chemical and Biological Engineering, Rensselaer Polytechnic Institute, Troy, NY, USA*

There is a huge number of neurological disorders responsible for the impairment and the degeneration of several areas of the central nervous system (CNS). Despite the existence of physical and chemical methods used to treat CNS diseases, new strategies have been emerging to successfully overcome the Blood-Brain Barrier (BBB) for the treatment of these disorders.¹⁻² The use of silica-based nanoparticles has largely increased in the material science and biomedical fields.³ The use of nanoparticles to overcome the BBB in order to encapsulate a range of therapeutic agents, with low levels of toxicity, and to deliver higher drug ratio in the target CNS compartment in an effective manner has been performed in the last years.⁴⁻⁶

The purpose of this work is to design a strategy to treat CNS diseases based on the development of silica nanoparticles with a perylene-3,4,9,10-tetracarboxylic diimide (PDI) dye in the silica structure for traceability and the surface modified with a peptide that targets the BBB tight junctions. Particles of different diameter, with low size dispersity and uniform fluorescent intensity for traceability were obtained (Figure 1a and 1b). The nanoparticles were surface-modified with a PEPDART (Permeability Enhancing Peptides for the Disruption, Attenuation and Recovery of Tight-Junctions) peptide (Figure 1c) in order to specifically target the transmembrane protein claudin-5 (cldn-5) expressed on endothelial cells of the BBB, enhancing the permeability of the barrier. Our results highlight the feasibility of functionalize hybrid silica particles with PEPDARTs to modulate the permeability and disruption of the BBB for imaging of the CNS and drug delivery across the barrier.

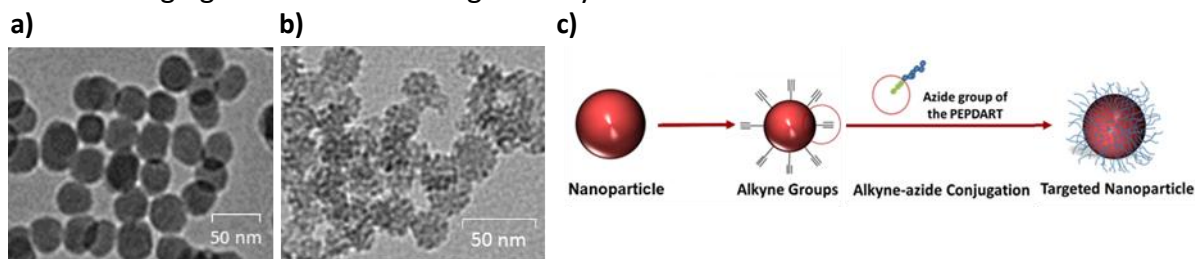


Figure 1. Images of **a)** non-porous silica nanoparticles and **b)** mesoporous silica nanoparticles by Transmission Electron Microscopy (TEM) and **c)** schematic representation of the subsequent functionalization by PEPDART peptide of the non-porous silica particles.

Acknowledgements

We thank Fundação para a Ciência e a Tecnologia (FCT-Portugal) and COMPETE (FEDER) project PTDC/CTM-POL/3698/2014. S. Cecílio thanks FCT and Stem Cell Manufacturing for Bioengineering – Cell Therapies and Regenerative Medicine Doctoral Program for PhD grant PD/BD/105793/2014.

References

- [1] D.J. McCarthy, M. Malhotra, A.M. O'Mahony, J.F. Cryan, C.M. O'Driscoll, *Pharm. Res.* 32 (2015) 1161-1185.
- [2] A.C. Anselmo, S. Mitragotri, *AAPS J.* 17(5) (2015) 1041-54.
- [3] J.A. Bonventre, J.B. Pryor, B.J. Harper, S.L. Harper, *J. Nanoparticle Res.* 16 (2014) 2761.
- [4] K. Ulbrich, T. Knobloch, J. Kreuter, *J. Drug Target.* 19 (2011) 125-132.
- [5] D. Liu, B. Lin, W. Shao, Z. Zhu, T. Ji, C. Yang, *ACS. Appl. Mater. Interfaces* 6 (2014) 2131-2136.
- [6] M. Shilo, M. Motiei, P. Hana, R. Popovtzer, *Nanoscale* 6 (2014) 2146-215.

Carbon Dots: Who is the Brightest of Them All

Carla Santos, Inês Mariz, Cátia Correia*, José Martinho, Ermelinda Maçôas
*Centro de Química-Física Molecular and IN-Institute of Nanoscience and Nanotechnology,
Instituto Superior Técnico, Av. Rovisco Pais, 1049-001 Lisboa, Portugal*

The origin of photoluminescence in carbon dots is under intense debate. Understanding the photoluminescence mechanism of carbon dots is one of the most important issues to be solved in adapting this material to novel applications. Our interest is in using carbon dots as near-infrared antenna in functional materials, taking advantage of their exceptional nonlinear absorption and emission properties. Nitrogen doped, crystalline carbon dots have been reported with high Two-Photon Absorption (TPA) values (on the 10^4 GM range).¹ In contrast, very modest values (<100 GM) have been reported for undoped amorphous carbon dots.² At the moment, the limited number of studies where the TPA properties have been addressed in a systematic and quantitative way preclude a conclusive analysis about the critical factors for an effective two-photon brightness. In this paper we discuss the TPA properties of carbon dots produced by either top-down methods, involving the conversion of a graphite based material to graphite oxide sheets, or bottom-up methods, involving the synthesis of quantum dots from the pyrolysis of organic compounds. The material that is produced using different methods can be quite different in terms of structure, crystallinity and types of oxygen containing functional groups decorating the edges or the surface of the carbonaceous core (Figure 1). In this poster we discuss the TPA properties in connection with the structure of the different types of dots investigated.

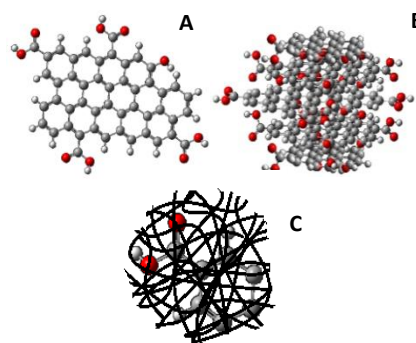


Figure 1. Different types of dots produced: **A)** sheet like graphene quantum dots, **B)** crystalline carbon quantum dots and **C)** amorphous polymer dots.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. Financial support from FCT is acknowledged (SFRH/BPD/75782/2011, SFRH/BPD/105478/2014, IF/00759/2013, PD/BD/127805/2016 and UID/NAN/50024/2013).

References

- [1] Q. Liu, B. Guo, Z. Rao, B. Zhang, J.R. Gong, *Nano Lett.* 13(6) (2013) 2436.
- [2] G.S. Tong, J.X. Wang, R.B. Wang, X.Q. Guo, L. He, F. Qiu, G. Wang, B.S. Zhu, X.Y. Zhu, T.J. Liu, *Mater. Chem.* B 3 (2015) 700.

Formaldehyde-Scavenging Nanoparticles for High Performance Resins

Inês V. M. Ponce Dentinho^a, João Ferra^b, Carlos Baleizão^a, José Paulo S. Farinha^a

^a CQFM-Centro de Química-Física Molecular, IN-Institute of Nanosciences and Nanotechnology, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal

^b Euroresinas – Indústrias Químicas S.A., 4470-909 Maia, Portugal

Mesoporous silica nanoparticles have been developed in order to carry a strong acid, used as a catalyst, into the curing step of urea formaldehyde (UF) resin synthesis.

One of the challenges of this process is the reduction of formaldehyde emissions (a carcinogenic agent¹). In the final product, different attempts to decrease the emissions have been tried in the plywood industry, in particular the reduction of formaldehyde: urea molar ratio² and the use of melamine as a resin fortifier agent³. Both approaches were unsuccessful in their final goal because of the loss of mechanical properties and the increase of the product cost, respectively.

By using a strong acid as a catalyst, formaldehyde emissions can be efficiently reduced. However, the acid must be encapsulated until the hot pressing/curing of the resin in order to avoid pre-curing⁴. Mesoporous silica nanoparticles with thermo-responsive behaviour are a promising solution to catalyse the resin at the right moment.

Mesoporous-nanoparticles with 50 nm diameter were filled with a strong acid and coated with a polymeric shell. The morphology was evaluated by TEM and the stability in water and upon drying was determined by Dynamic Light Scattering (DLS).

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013.

References

- [1] A. Tullo, Chemical and Engineering News 91(32) (2013) 20.
- [2] H. Duan, T. Qiu, L. Guo, J. Ye, X. Li, Journal of Hazardous Materials 293 (2015) 46-53.
- [3] N. Paiva, A. Henriques, P. Cruz, J. Ferra, L.H. Carvalho, F. Magalhães, Journal of Applied Polymer Science 124 (2012) 2311-2317.
- [4] N. Costa, J. Pereira, J. Martins, J. Ferra, P. Cruz, F. Magalhães, A. Mendes, L. Carvalho, International Journal of Adhesion & Adhesives 33 (2012) 56-60.

Synthesis and characterization of Carbon Dots

Catarina B. B. B. Gonçalves^{a,b}, Ana S. M. L. Dias^{a,b}, Ana Paula C. Ribeiro^{a,*},

Elisabete C. B. A. Alegria^{a,b}, Rui P. Oliveira-Silva^c and Armando J. L. Pombeiro^a

^a Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal

^b Chemical Engineering Department, Instituto Superior de Engenharia de Lisboa,
Instituto Politécnico de Lisboa, Rua Conselheiro Emídio Navarro, 1959-007 Lisboa, Portugal

^c IBB, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal

E-mail: apribeiro@tecnico.ulisboa.pt

The synthetic process for producing carbon dots will be addressed, especially the power applied and the reaction time and how these parameters affect their fluorescence. The prepared carbon dots were characterized by TEM, SEM, UV and fluorescence techniques.

Carbon quantum dots are a type of nanoparticles of less than 10 nm in size. Due to their unique properties, like size-dependent fluorescence, non-toxicity and biocompatibility, carbon quantum dots possess a potential in fields such as chemical sensing or catalysis.



Scheme 1. Schematic representation of the synthesis of carbon dots by microwave irradiation.

Acknowledgements

Funding from FCT (Fundação para a Ciência e a Tecnologia, Portugal) (UID/QUI/00100/2013, PTDC/QEQ-ERQ/1648/2014 and PTDC/QEQ-QIN/3967/2014 projects). A.P.C. Ribeiro also acknowledges FCT for the SFRH/BPD/90883/2012 grant.

References

[1] X. Gao, C. Du, Z. Zhuang, W. Chen, *J. Mater. Chem. C* 4 (2016) 6927.

Study of enthalpies of sublimation of organometallic compounds

Mariana T. Donato, Carlos E. S. Bernardes and Manuel E. Minas da Piedade

*Centro de Química e Bioquímica e Departamento de Química e Bioquímica, Faculdade de Ciências,
Universidade de Lisboa, 1749-016 Lisboa, Portugal*

The ability to study the behaviour of a system at the molecular level to predict macroscopic properties is a long-term goal in chemistry and engineering, since it has the potential to reduce the need for expensive and time-consuming experimentation. Molecular dynamics (MD) is perhaps the most promising cost-effective computational technique to perform these studies. It is a general approach that, based on simple atom-atom pair's potential calculations, currently allows the investigation of many physical processes. The key aspect of this methodology is the definition of an intermolecular potential function capable of accurately describing the interactions. However, although a large set of parameters exist for e.g. hydrocarbon compounds, no reliable parametrization exists for materials containing transition metals, which are extremely important to model, for example, proteins. Thus, the work here described is part of an ongoing project at the Molecular Energetics Group (CQB-FCUL), to produce a parametrization suitable for the study of compounds containing transition metals, by MD simulations.

One way to accurately establish interaction potentials involves the determination of a set of parameters that reproduce the cohesive energy of materials – which can be obtained from the enthalpy of sublimation of the compounds – and the spatial arrangement of the molecules (e.g. crystal structures). Although values of enthalpies of sublimation can be found in the literature, these are frequently not assigned to a well characterized crystal structure, leading to large discrepancies between published data. Thus, in this work, enthalpies of sublimation of organometallic compounds were determined for well characterized materials, both in terms of chemical and phase purity. A focus was employed to compounds containing rhenium (e.g. methyltrioxorhenium and decacarbonyl-di-rhenium) due to the importance of this metal in the development of new non-radioactive materials for imaging in nuclear medicine and radiotherapy, for the diagnostic and treatment of cancer.

Acknowledgements

This work was supported by Fundação para a Ciência e a Tecnologia, Portugal (Project UID/MULTI/00612/2013 and UID/QUI/00100/2013).

Different Approaches for Surface Functionalization of S-Doped Hydrochars

Tiago A. G. Duarte^{a,b,*}, Luísa M. D. R. S. Martins^{a,c}, Armando J. L. Pombeiro^a,
Ana P. Carvalho^b

^a Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais,
1049-001 Lisboa, Portugal

^b Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande,
1749-016 Lisboa, Portugal

^c Chemical Engineering Department, Instituto Superior de Engenharia de Lisboa,
Instituto Politécnico de Lisboa, R. Conselheiro Emídio Navarro, 1959-007 Lisboa, Portugal

*E-mail: tiago.gomes.duarte@tecnico.ulisboa.pt

Hydrochars are carbon materials that are prepared from renewable biomasses, e.g, glucose, maltose, sucrose or starch, that can present spherical morphology. These materials have been tested in different areas showing high electrical conductivity and excellent chemical stability. As-synthesised and further activated samples have also been used as adsorbents, catalysts or catalyst supports.¹

The aim of this study was to evaluate the catalytic properties of sucrose, glucose and fructose derived hydrochars in esterification of butanol with acetic acid. Even though the materials present acidic surface properties, as demonstrated by the Boehm titration results, and pH_{PZC} values of ca. 2.0, the catalytic assays revealed that the nature of acid surface groups is a determinant factor for this type of reaction. In fact, according to the literature, to achieve high catalytic activities it is necessary to have a high number of sulfonic groups.² In this sense, S-doped hydrochars were synthesized by different ways: one-pot synthesis where the mixture of the sugars aqueous solution and different amounts of S-containing compound (p-toluenesulfonic acid, isethionic acid sodium salt, 4-sulfophtalic acid) were submitted to hydrothermal treatment; post-synthesis treatment of the sugar derived hydrochars (a) with concentrated H_2SO_4 , and (b) by impregnation with S-containing compound followed by a second hydrothermal treatment.

The H_2SO_4 treated sucrose derived hydrochar allowed a quicker reaction (80% conversion after 2h), and achieved almost total conversion after 6h of contact time.

Acknowledgements

This work has been partially supported by the Foundation for Science and Technology (FCT), Portugal (UID/QUI/00100/2013, PTDC/QEQ-ERQ/1648/2014, PTDC/QEQ-QIN/3967/2014 and UID/MULTI/00612/2013). T.A.G. Duarte is thankful to FCT for his CATSUS Ph.D. fellowship (PD/BD/105993/2014). The authors acknowledge the Portuguese NMR Network (IST-UTL Centre) for access to the NMR facility.

References

- [1] R.J. White, V. Budarin, R. Luque, J.H. Clark, D.J. Macquarrie, Chem. Soc. Rev. 38 (2009) 3401.
- [2] L. Roldán, E. Pires, J.M. Fraile, E. García-Bordejé, Catal. Today 249 (2015) 153.

Efficient oxidation of benzoin to benzil catalyzed by mechanically prepared vanadium oxide composites

F. Ferretti^a, E. C. B. A. Alegria^{a,b*}, A. P. C. Ribeiro^a, M. F. C. Guedes da Silva^a,
F. Marchetti^c and A. J. L. Pombeiro^{a*}

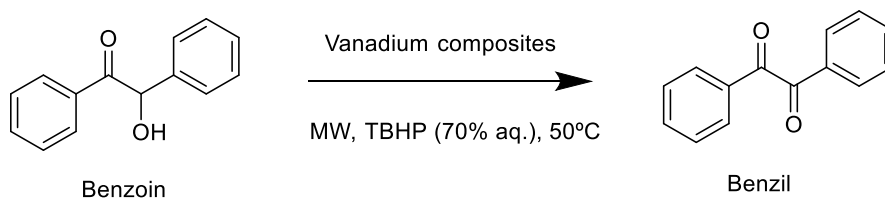
^a Centro de Química Estrutural, Complexo I, IST, Universidade de Lisboa, Portugal

^b Chemical Engineering Department, ISEL, Instituto Politécnico de Lisboa, Portugal

^c School of Science and Technology, Chemistry Section, University of Camerino, Italy

In this work we prepared vanadium containing composites with different ratios of additives (TiO₂, Al₂O₃ or SiO₂) by a simple and solvent-free mechanochemical method, *i.e.*, ball-milling^{1,2}. The thus prepared composites materials were characterized by XPS, SEM, FEGSEM, EDX and TEM microscopy techniques and were screened for the microwave-assisted peroxidative oxidation of benzoin to benzil, with TBHP (Scheme).

The effects of time, solvent, temperature and amount of catalyst were optimized to obtain maximum yield. The catalytic activity results demonstrate that these catalytic systems are both highly active and selective for the oxidation of benzoin under mild reaction conditions.



Scheme - Microwave-assisted peroxidative oxidation (TBHP) of benzoin into benzil

Acknowledgements

We thank the Fundação para a Ciência e Tecnologia (fellowship SFRH/BPD/90883/2012 to A.P.C. Ribeiro and the UID/QUI/00100/2013 and PTDC/QEQ-QIN/3967/2014 projects) and the Instituto Politécnico de Lisboa (IPL/2016/MechSynCat_ISEL project) for financial support.

References

- [1] A.P.C. Ribeiro, E. Fontolan, E.C.B.A. Alegria, M.N. Kopylovich, R. Bertani, A.J.L. Pombeiro, *J. Mol. Catal. A Chem.* 426 (2017) 557.
- [2] E. Fontolan, E.C.B.A. Alegria, A.P.C. Ribeiro, M.N. Kopylovich, R. Bertani, A.J.L. Pombeiro, *Inorg. Chim. Acta* 455 (2017) 653.

The influence of different additives on the catalytic activity of copper metalloporphyrins towards 1-phenylethanol oxidation

D. Fonte^{a,b}, F. Figueira^c, A. J. L. Pombeiro^b, M. F. C. Guedes da Silva^b, J. P. C. Tomé^b
and E. C. B. A. Alegria^{a,b}

^a Chemical Engineering Department, ISEL–Instituto Superior de Engenharia de Lisboa,
Instituto Politécnico de Lisboa, 1959-007 Lisboa, Portugal

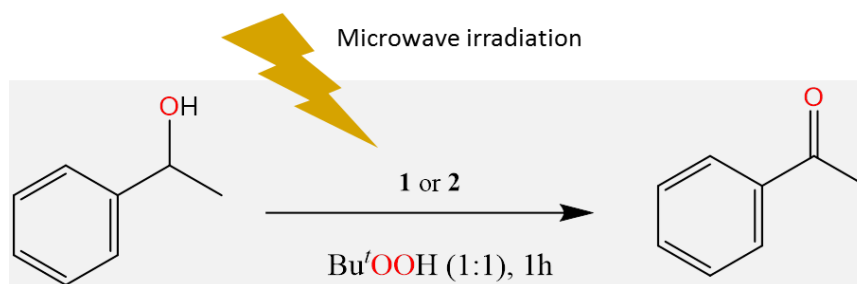
^b Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal

^c QOPNA and Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal

E-mail: daniela.fonte90@gmail.com

The selective oxidation of alcohols to carbonyl compounds is very important in the synthesis of relevant compounds and fine chemicals.¹ We recently synthesized two Cu(II)-based metalloporphyrins, CuTPyP (**1**) and CuTPPF₁₆(SPy)₄ (**2**), by reacting Cu(AcO)₂·H₂O with H₂TPyP (for **1**) or H₂TPPF₁₆(SPy)₄ (for **2**) porphyrins^{2,3} in a CHCl₃/MeOH (2:1) solvent mixture and fully characterized them by UV-Vis, infrared (ATR-FTIR) and electron paramagnetic resonance (EPR). Compounds **1** and **2** were successfully applied as catalysts for the microwave-assisted peroxidative oxidation of 1-phenylethanol with *tert*-butyl hydroperoxide (*t*-BuOOH), giving ketone yields up to ca. 70%, in the absence of any added solvent (Scheme 1).

In order to attempt to increase the activity of the catalytic system, we have investigated the influence of different additives such as TEMPO (2,2,6,6-tetramethyl-piperidinyloxy) radical or the presence of acids and it was demonstrated that the presence of such additives results, in some cases, in a significant decay in the catalytic performance.



Scheme 1.

Acknowledgements

Thanks are due to FCT/MEC for the financial support to CQE (FCT UID/QUI/0100/2013) and QOPNA (FCT UID/QUI/00062/2013) research units, through national funds and where appropriate cofinanced by FEDER under the PT2020 Partnership Agreement.

References

- [1] M.N. Kopylovich, A.P.C. Ribeiro, E.C.B.A. Alegria, N.M.R. Martins, L.M.D.R.S. Martins, A.J.L. Pombeiro, *Adv. Organometal. Chem.* 63 (2015) 91.
- [2] K. Castro, J. Rodrigues, R. Mendes, M. Neves, M. Simões, J. Cavaleiro, F. Paz, J. Tomé, S. Nakagaki, *J. Catal.* 344 (2016) 303.
- [3] M. Gomes, S. Woranovicz-Barreira, M. Faustino, R. Fernandes, M. Neves, A. Tomé, N. Gomes, A. Almeida, J. Cavaleiro, A. Cunha, J. Tomé, *Photochem. Photobiol. Sci.* 10 (2011) 1735.

Self-assembled Molecular Conducting Bilayers

Ana Cristina Gonçalves, Sandra Rabaça, Manuel Almeida, José António Paixão

C²TN – Campus Tecnológico e Nuclear, Estrada Nacional 10, 2695-066 Loures, Portugal

Organic conductors were initially proposed as possible high temperature superconductivity materials. While that was not achieved a new class of materials emerged with a very rich diversity of ground states, ranging from antiferromagnets, insulators, to 2D metals, superconductors and physical phenomena that are very sensitive to magnetic field, pressure and temperature. Since the first family of organic superconductors, the quasi-one dimensional Bechgaard salts (TMTSF)₂X (X = ClO₄, PF₆, AsF₆, etc), and after the quasi-two dimensional compounds (BEDT-TTF)₂X there has been a remarkable development of bidimensional molecular conducting systems in particular with other derivatives of the electron donor BEDT-TTF.¹ Systems based on double layered structures, potentially more interesting, have however never been explored.

This project aims at exploring bilayer conducting systems based on a new BEDT-TTF derivative, recently prepared in the C²TN group,² and different inorganic anions. This new organic donor was recently found to self-assemble in double layered structures in charge transfer salts with small anions.³ However a large number of different anions have not yet been explored, namely paramagnetic anions which can lead to conducting magnetic materials where anomalous magneto resistance, quantum interference effects⁴ and even superconductivity induced by magnetic fields can take place.⁵ There is a variety of mechanisms for magnetoresistance (the change of the electrical resistance by a magnetic field) which reflects the electronic structure and may be applied in different devices. Besides the common positive magnetoresistance of metals, there is a negative magnetoresistance⁶ in ferromagnets and since 1980's large magneto-resistive in multilayer systems gained importance.

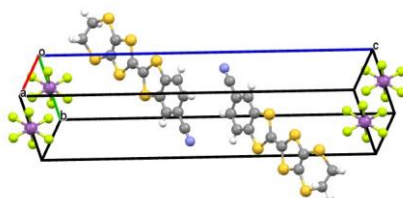


Figure 1. Crystal structure of a new bilayer salt.

Acknowledgements

Work partially supported by FCT through contracts UID/MULTI/04349/2013 and RECI/QEQ-QIN/0189/2012 and grants SFRH/BPD/113344/2015 and SFRH/PD/BD/127804/2016, to S. Rabaça and A.C. Gonçalves, respectively.

References

- [1] a) E. Coronado, P. Day, Chem. Rev. 104 (2004) 5419-5448; b) T. Mori, Chem. Rev. 104 (2004) 4947-4969.
- [2] S. Oliveira, D. Belo, I.C. Santos, M. Almeida, S. Rabaça, Beilstein J. Org. Chemistry 11 (2015) 951-956.
- [3] S. Oliveira, J.J. Ministro, I.C. Santos, D. Belo, E.B. Lopes, S. Rabaça, E. Canadell, M. Almeida, Inorg. Chem. 54 (2015) 6677-6679.
- [4] K. Clark, A. Hassanien, S. Khan, K.F. Braun, H. Tanaka, S.W. Hla, Nature Nanotechnology 5 (2010) 261-265.
- [5] a) S. Uji, H. Kobayashi *et al.*, Nature (London) 410 (2001) 908; b) L. Balicas *et al.*, Phys. Rev. Lett. 87(6) (2001) 067002.
- [6] D. Graf, J.S. Brooks, E.S. Choi, M. Almeida, R.T. Henriques, J.C. Dias, S. Uji, Phys. Rev. B 80 (2009) 155104-1551108.

Mesoporous Silica Nanoparticles with pH-responsive Polymeric Shell for Controlled Drug Release

José Gonçalves, C. I. C. Crucho, C. M. Baleizão, J. P. S. Farinha

*CQFM, Centro de Química-Física Molecular, IN—Institute of Nanosciences and Nanotechnology,
Instituto Superior Técnico, 1049-001 Lisboa, Portugal*

Email: joseluis@tecnico.ulisboa.pt

Recent progress in material chemistry and drug delivery led to the possibility to develop stimuli-responsive devices that deliver a drug with spatial, temporal and dosage control. Implementation of such devices requires the use of biocompatible materials that are susceptible to specific physical stimuli. Nanoparticles have received much attention precisely because they comprise these characteristics. In addition to improving the pharmacokinetics of the loaded poorly soluble hydrophobic drugs by solubilizing them in the hydrophobic compartments, coated with stimuli-responsive polymers, nanoparticles allow the control of drug release in response to disease-specific physiological conditions.¹ Among a variety of inorganic-based nanomaterials, mesoporous silica particles (MSNs) have several attractive features for application as a drug delivery system due to their high surface areas, large pore volumes, high payload, uniform and tunable pore sizes, and a great diversity of surface functionalization options (Figure 1).² In this work, we developed core-shell MSNs, coated with a pH-responsive polymer. In addition, by incorporating a high quantum yield fluorescent perylene diimide (PDI) dye in the MSNs pore structure, we could combine diagnostic and therapeutic properties.

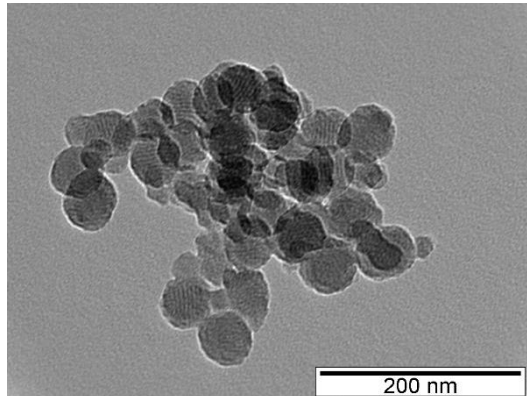


Figure 4. Transmission electron microscope image of MSN-PDI showing morphology and mesostructure. Scale bar: 200 nm.

Acknowledgements

This work was partially supported by Fundação para a Ciência e a Tecnologia (FCT-Portugal) and COMPETE (FEDER), UID/NAN/50024/2013 and PTDC/CTM-POL/3698/2014.

References

- [1] S. Mura, J. Nicolas, P. Couvreur, *Nature Materials* 12 (2013) 991-1003.
- [2] C.M. Baleizão, J.P.S. Farinha, *Nanomedicine* 10 (2015) 2311-14.

Polymorphism in Hydroxybenzoyl Compounds

Cátia S. D. Lopes¹, Ricardo G. Simões¹, Carlos E. S. Bernardes¹,

M. Fátima M. Piedade^{1,2}, Hermínio P. Diogo² and Manuel E. Minas da Piedade¹

¹ Centro de Química e Bioquímica e Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal

² Centro de Química Estrutural, Complexo Interdisciplinar, Instituto Superior Técnico, 1049-001 Lisboa, Portugal

Polymorphism, the ability of a compound to crystallize in more than one solid form, is a phenomenon that can considerably affect the properties of materials (e.g. melting point, solubility, colour). As such, different polymorphic forms should be regarded as different materials, although formed by the same molecular unit.

Studies of polymorphism involving families of structurally related molecules are particularly interesting to understand how the interplay of molecular size, shape and intermolecular interactions may affect the packing architectures and relative stability of different crystal forms. One such family is that of 4-hydroxybenzoyl compounds, $\text{HOC}_6\text{H}_4\text{C(O)R}$ ($\text{R} = \text{H}$, alkyl; Figure 1), differing only in the length of the alkyl chain bonded to the carbonyl group. Based on these materials it is, for example, possible to investigate how the hydrogen bond pattern sustaining the packing is affected by changes in the alkyl chain length and how these changes are eventually reflected by thermal events detected by calorimetric methods.

In this work, a comparative structural and energetic study of the 4-hydroxybenzoyl family of compounds will be presented. Polymorphism was identified for $\text{R} = n\text{-C}_4\text{H}_9$, $n\text{-C}_6\text{H}_{13}$, and the single crystal X-ray diffraction structures for $\text{R} = \text{C}_2\text{H}_5$, $n\text{-C}_4\text{H}_9$, $n\text{-C}_5\text{H}_{11}$, and $n\text{-C}_6\text{H}_{13}$ were determined for the first time. Although significant differences between the crystal structures are noted along the $\text{HOC}_6\text{H}_4\text{C(O)R}$, calorimetric measurements showed that the cohesive energies are approximately additive.

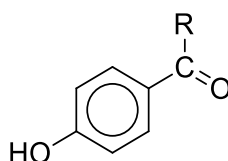


Figure 1. Molecular structure of 4-hydroxybenzoyl compounds ($\text{R} = \text{H}$, CH_3 , C_2H_5 , $n\text{-C}_4\text{H}_9$, $n\text{-C}_5\text{H}_{11}$ and $n\text{-C}_6\text{H}_{13}$)

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and UID/QUI/00100/2013. Post-Doctoral grants from FCT are also gratefully acknowledged by C.E.S. Bernardes (SFRH/BPD/101505/2014) and R.G. Simões (SFRH/BPD/118771/2016).

Py-GC/MS: a tool for the characterization of biomass

Ana Lourenço¹, Jorge Gominho¹, António Velez Marques^{1,2}, Helena Pereira¹

¹*Centro de Estudos Florestais, Instituto Superior de Agronomia, Universidade de Lisboa, Tapada da Ajuda, 1349-017 Lisboa, Portugal*

²*Instituto Superior de Engenharia de Lisboa, Instituto Politécnico de Lisboa, Rua Conselheiro Emídio Navarro 1, 1959-007 Lisboa, Portugal*

Analytical pyrolysis linked to GC mass spectrometry (Py-GC/MS) is a powerful technique for the chemical characterization of complex materials such as biomass, and also for textiles, glues, synthetic polymers among others. The principle of analytical pyrolysis is to heat the sample (80-100 µg) at temperatures ranging from 400°C to 1000°C in the absence of oxygen, for a short period of time (~ 10 s) and to separate and identify the molecular fragments that are volatilized.

The pyrolysis of biomass produces a mixture of volatile compounds derived from its three macromolecular constituents: cellulose, hemicelluloses and lignin. Pyrolysis is a particularly interesting technique to characterize the lignin monomeric composition into the so-called phenolic precursor monomers: syringyl (S), guaiacyl (G) and hydroxyphenyl (H) units. The ratio between monomers is given in the form of H:G:S or, more frequently, only as the S/G ratio.

The S/G ratio differs with the raw material: in eucalypt wood it varies from 1.9 to 5.4,¹ in cardoon from 0.8 to 1.4,²⁻³ and for cork oak wood it is 1.7⁴. Other biomasses are richer in G-units, e.g. rice straw and cork have a S/G ratio of 0.1.⁴⁻⁵

The lignin composition influences the chemical performance of biomass and the S/G ratio is often used for quality evaluation. For instance, a biomass richer in syringyl units with S/G values from 2 to 4 is mostly appreciated for the pulp and paper industries, due to an easier delignification owing to the higher reactivity of the S-units.⁶ This is the case of eucalypt wood. On the contrary, a biomass with more guaiacyl units is more interesting for energy purposes.

Acknowledgements

Support for this work was provided by FCT through UID/AGR/00239/2013. A. Lourenço acknowledges financial support from FCT through the post-doctoral grant SFRH/BPD/95385/2013.

References

- [1] A. Lourenço, J. Gominho, A.V. Marques, H. Pereira, J. Wood Chem. Technol. 33 (2013) 1-18.
- [2] A. Lourenço, J. Rencoret, C. Chemetova, J. Gominho, A. Gutiérrez, H. Pereira, J.C. del Río, Bioenerg. Res. 8 (2015) 1946-1955.
- [3] A. Lourenço, J. Gominho, M.D. Curt, E. Revilla, J.C. Villar, H. Pereira, Ind. Eng. Chem. Res. 56 (2017) 424-433.
- [4] A. Lourenço, J. Rencoret, C. Chemetova, J. Gominho, A. Gutiérrez, J.C. del Río, H. Pereira, Frontiers Plant Sci. 7 (2016) 1612.
- [5] F. Pinto, J. Gominho, R.N. André, D. Gonçalves, M. Miranda, F. Varela, D. Neves, J. Santos, A. Lourenço, H. Pereira, Energy Fuels 31 (2017) 5183-5192.
- [6] A. Lourenço, J. Gominho, A.V. Marques, H. Pereira, Biores. Technol. 123 (2012) 296-302.

Slow magnetic relaxation in a mononuclear Mn(III) complex with tridentate Schiff-base ligands

Paulo N. Martinho^a, Sara Realista^a, Liliana P. Ferreira^{b,c}, Sónia Barroso^d,
Gonçalo Santos^a, Laura C. J. Pereira^e, Maria José Calhorda^a

^a Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal

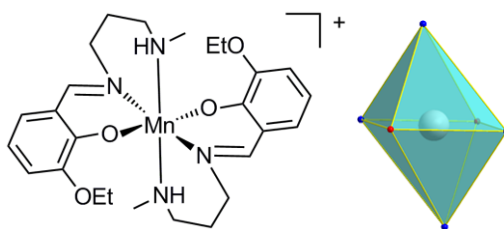
^b BioISI, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

^c Departamento de Física, Faculdade de Ciências e Tecnologia, Universidade de Coimbra,
3004-516 Coimbra, Portugal

^d Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais,
1049-001 Lisboa, Portugal

^e Solid State Group, UCQR, IST/C2TN, Universidade de Lisboa, Instituto Superior Técnico,
2695-066 Bobadela, Loures, Portugal

Single ion magnets (SIMs) are a class of materials with potential application as high-density magnetic memories and quantum-computing devices in spintronic field.¹ The size of the barrier of the reversal magnetization (U_{eff}) is the determining factor to the suitability of a single ion magnet to be applied in data storage devices. Efforts aiming at maximizing the anisotropy by an appropriate ligand field have been made to achieve high barriers.² Manganese(III) is a d^4 metal ion displaying a Jahn-Teller distortion when in an octahedral coordination environment. This feature turns Mn(III) into a promising ion to study its magnetic properties, namely spin crossover³ and single ion magnet.² We report the synthesis of Mn(III) Schiff base cationic complexes using different counter anions (Figure). SQUID magnetometry showed that all compounds are in the high-spin state with one pair of bond lengths ($\text{Mn-N}_{\text{amine}}$) considerably longer than the others (Figure). AC susceptibility measurements carried out using a MagLab2000 system showed that one of the new compounds displays single ion magnet behaviour, thus making it a good candidate for further investigation and possible application in data storage.



Acknowledgements

Support for this work was provided by Fundação para a Ciência e a Tecnologia (UID/MULTI/00612/2013, PTDC/QEQ-QIN/3414/2014).

P.N. Martinho (SFRH/BPD/73345/2010) and S. Realista (PD/BD/52368/2013) thank FCT for financial support.

References

- [1] J. Vallejo, A. Pascual-Álvarez, J. Cano, I. Castro, M. Julve, F. Lloret, J. Krzystek, G. De Munno, D. Armentano, W. Wernsdorfer, R. Ruiz-García, E. Pardo, *Angew. Chemie Int. Ed.* 52 (2013) 14075.
- [2] G.A. Craig, M. Murrie, *Chem. Soc. Rev.* 44 (2015) 2135.
- [3] P.N. Martinho, B. Gildea, M.M. Harris, T. Lemma, A.D. Naik, H. Müller-Bunz, T.E. Keyes, Y. Garcia, G.G. Morgan, *Angew. Chemie Int. Ed.* 51 (2012) 12597.

Halogen modified spin crossover in Fe(III) complexes with tridentate Schiff-base ligands

Frederico F. Martins^a, Ana I. Vicente^a, Liliana P. Ferreira^{b,c}, Maria de Deus Carvalho^a,
Vitor H. N. Rodrigues^c, Maria José Calhorda^a, Paulo N. Martinho^a

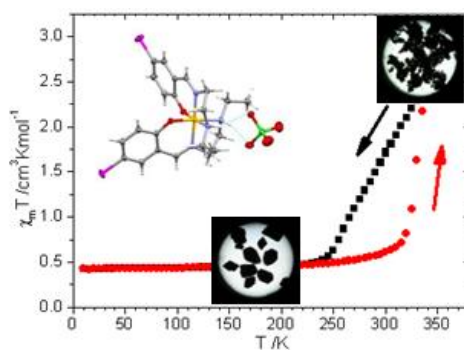
^a Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande,
1749-016 Lisboa, Portugal

^b BioISI, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

^c Department of Physics, University of Coimbra, 3004-516 Coimbra, Portugal

Technological advances have been pushing the limits of chemistry for the last few years towards creating more efficient and multifunctional molecules and materials. A phenomenon that shows great promise in molecular electronics is spin crossover (SCO).¹ This switching can be harnessed to develop materials with a wide range of possible applications such as memory or sensing nano-devices.² Halogen derivatized SCO molecules are of great interest as they can interact with neighboring molecules through either halogen or hydrogen bonds and additionally they can be modified through substitution or coupling reactions conferring additional properties and high versatility to the SCO molecules.^{3,4}

Here we report the synthesis and characterization of halogen derivatized SCO compounds with an Fe(III) metallic center coordinated to tridentate (N2O) Schiff-base ligands. We have found that all compounds exhibit SCO with profiles ranging from gradual to abrupt with hysteresis. Detailed studies on the halogen influence on these are complemented with DFT calculations using recently developed spin state specific functionals.



Acknowledgements

The authors thank Fundação para a Ciência e Tecnologia for financial support UID/MULTI/00612/2013, PTDC/QEQ-QIN/3414/2014 and COST Action CM1305. P.N. Martinho thanks FCT for financial support (SFRH/BPD/73345/2010).

References

- [1] P. Gamez, J.S. Costa, M. Quesada, G. Aromí, Dalton Trans. 38 (2009) 7845.
- [2] J. Létard, J. Mater. Chem. 16 (2006) 2550.
- [3] E.J. Devid, P.N. Martinho, M.V. Kamalakar, I. Šalitroš, Ú. Prendergast, J.F. Dayen, V. Meded, T. Lemma, R. González-Prieto, F. Evers, T.E. Keyes, M. Ruben, B. Doudin, S.J. van der Molen, ACS Nano 9 (2015) 4496.
- [4] A.B. Gaspar, V. Ksenofontov, M. Seredyuk, P. Gülich, Coord. Chem. Rev. 249 (2005) 2661.

Synthesis of Monodisperse Hybrid Nanoparticles for Structural Color

Laurinda R. P. Areias, Tiago D. Martins, José Paulo S. Farinha
CQFM-Centro de Química-Física Molecular, IN-Institute of Nanosciences and Nanotechnology,
Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal

Structural colour can be observed from the interaction of light with periodically arranged structures and can be found in nature from the feathers of peacocks, humming birds, pheasant or even in small bugs like beetles. In contrast to pigmentary colour, structural colour does not work through light absorption mechanism and therefore it does not photodegrade. Besides, it presents properties that can be used in many applications, such as low-cost non-toxic coloured pigments, full-colour paper-like displays, cosmetics and many others, replacing the use of dyes or pigments.¹⁻³ Here we describe the synthesis of several monodisperse polymer nanoparticles of different sizes that will serve as building blocks for photonic crystals exhibiting structural colour. Hybrid monodisperse polymer nanoparticles were successfully prepared by emulsion polymerization, adapting a method previously described in the literature.⁴ Styrene, methyl methacrylate and acrylic acid were used as comonomers, potassium persulfate as initiator, sodium dodecyl sulphate as surfactant and sodium hydrogen carbonate to stabilize the pH. The nanoparticles were analysed by dynamic light scattering (DLS), nanoparticle tracking analysis (NTA) and transmission electron microscopy (TEM), confirming sizes between ≈ 100 to 300 nm with low polydispersity index (PDI < 0.1)⁵ as observed on Figure 1.

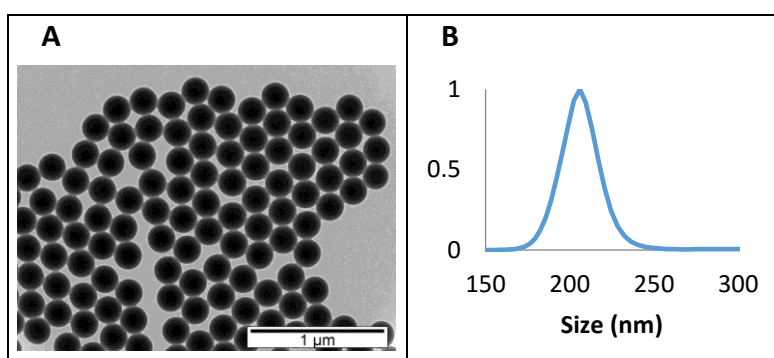


Figure 1. A) TEM images of nanoparticles with 200 nm of diameter; B) Size distribution obtained by NTA, with PDI of 0.01.

Acknowledgements

This work was partially supported by Fundação para a Ciência e a Tecnologia (FCT-Portugal) and COMPETE (FEDER), projects UID/NAN/50024/2013 and PTDC/CTM-POL/3698/2014.

References

- [1] Y. Zhao, Z. Xie, H. Gu, C. Zhu, Z. Gu, *Chem. Soc. Rev.* 41 (2012) 3297-3317.
- [2] J.G. Park, S.H. Kim, S. Magkiriadou, T.M. Choi, Y.S. Kim, V.N. Manoharan, *Angew. Chemie Int. Ed.* 53 (2014) 2899-2903.
- [3] C.E. Reese, C.D. Guerrero, J.M. Weissman, K. Lee, S.A. Asher, *J. Colloid Interface Sci.* 232 (2000) 76-80.
- [4] H. Cong, W. Cao, *Langmuir* 20 (2004) 8049-8053.
- [5] J. Wang, Y. Hu, R. Deng, W. Xu, S. Liu, R. Liang, Z. Nie, J. Zhu, *Lab Chip*. 12 (2012) 2795-2798.

Polymorphism Studies in Niflumic Acid, Phenylbutazone and Erlotinib Hydrochloride

P. Tomaz Melo, J. S. Rodrigues Alves, C. Teixeira António, C. E. S. Bernardes,
M. E. Minas da Piedade

*Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande,
1749-016 Lisboa, Portugal*

Polymorphism, the ability of a substance to crystallize in more than one lattice arrangement, is currently a major concern for the pharmaceutical industry, because it can strongly affect the design, clinical timelines, manufacturing, shelf-life, bioavailability, and patenting of solid dosage forms. Albeit the molecule does not change, different packing architectures can originate significant differences in physicochemical properties, such as fusion temperature, compressibility, and solubility/dissolution rate, which play a key role in the production and performance of active pharmaceutical ingredients (API). The lack of control over polymorphism, therefore, creates serious problems for the production and safe use of medicines. There is also interest in controlling the morphology of crystals for processing reasons: cubic crystals will, for example, filter and wash easier than plate-like crystals.

The control of polymorphism and morphology of crystals is intimately related with crystallization since this is by far the most widely used method to obtain crystalline forms.

Here we describe studies of crystallization and polymorphism (structural and energetics) for three APIs namely, niflumic acid, phenylbutazone, and erlotinib hydrochloride (Figure 1). The first two are currently used for the treatment of rheumatoid arthritis and the third one is applied in cancer therapy. Despite being marketed, all these compounds have problems of ill-defined polymorphism. The investigation relied on a variety of techniques, such as X-ray diffraction (XRD), microscopy, diffuse reflectance infrared Fourier transform spectroscopy (DRIFT), differential scanning calorimetry (DSC), and solution calorimetry.

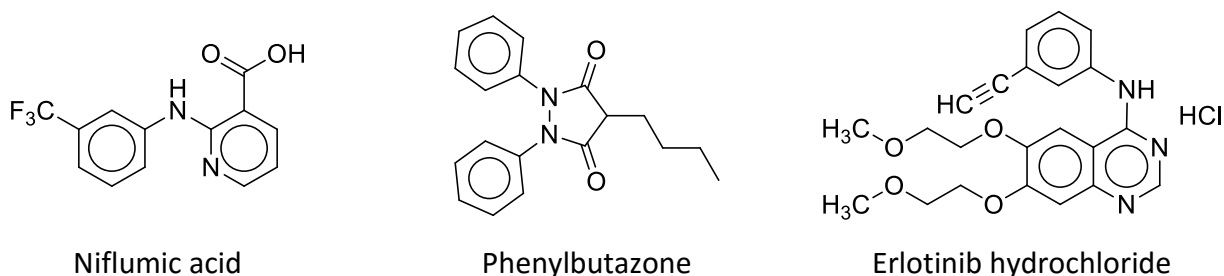


Figure 1. Molecular structures of niflumic acid, phenylbutazone, and erlotinib hydrochloride.

Acknowledgements

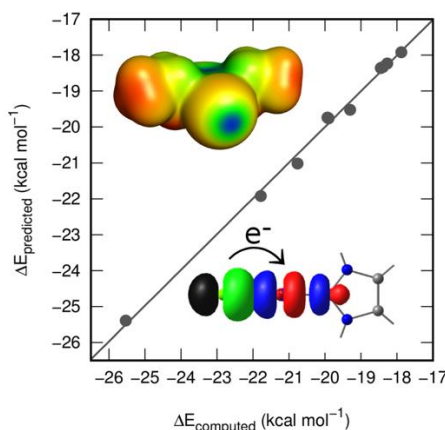
This work was supported by Fundação para a Ciência e a Tecnologia, Portugal (Projects UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013). A post-doctoral grant from FCT is gratefully acknowledged by C.E.S. Bernardes (SFRH/BPD/101505/2014).

Tuning ion-pair halogen bonds towards efficient anion receptors in solution

Rafael Nunes, Paulo J. Costa

*Centro de Química e Bioquímica, DQB, Faculdade de Ciências da Universidade de Lisboa,
1749-016 Lisboa, Portugal*

Halogen bonds (XB) are highly directional, attractive interactions involving a halogen atom (X) and a Lewis base (B), in a complex type $R-X\cdots B$ ($X = \text{Cl}, \text{Br}$ or I). The nature of this specific type of non-covalent interaction has been predominantly explained by the existence of a localized electrophilic region at X, named σ -hole, while evidence for significant contributions from charge-transfer have been the subject of intense discussion recently. XBs have found widespread application, amongst other fields, in anion recognition in solution.¹⁻² In particular, the charged haloimidazolium or halotriazolium motifs are shown to establish very strong XBs with anions in competitive aqueous media. In this communication, we investigate this class of ion-pair systems by quantum mechanical methods discussing the key roles of solvent and substituents on the XB nature and strength, and their implications for the design of efficient anion receptors working in solution.³

**Acknowledgements**

The authors thank Fundação para a Ciência e a Tecnologia (FCT), Fundo Social Europeu, and Programa Operacional Potencial Humano for the Investigador FCT contract and project IF/00069/2014. FCT is also acknowledged for financial support through projects UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. R. Nunes acknowledges financial support from doctoral grant SFRH/BD/116614/2016.

References

- [1] T.M. Beale, M.G. Chudzinski, M.G. Sarwar, M.S. Taylor, *Chem. Soc. Rev.* 42 (2013) 1667-1680.
- [2] A. Brown, P.D. Beer, *Chem. Comm.* 52 (2016) 8645-8658.
- [3] R. Nunes, P.J. Costa, *Chem. Asian J.* 12 (2017) 586-594.

New Water Soluble PDIs for Bioimaging

Tânia S. M. Oliveira, Tiago J. L. Silva, Inês F. A. Mariz, Ermelinda M. S. Maçôas,
Carlos Baleizão

CQFM, Centro de Química-Física Molecular, Instituto Superior Técnico, 1049-001 Lisboa, Portugal

Due to its extraordinary properties, several perylene-3,4,9,10-tetracarboxylic diimides (PDIs) have found their way into industrial-scale production, especially in fiber applications and in high-grade industrial paints. In 2009 a new method for the functionalization of the ortho-positions (2,5,8,11-positions) of perylene-3,4,9,10-tetracarboxylic diimides was discovered.¹ The opportunity to selectively alkylate the perylene core was demonstrated across the Murai alkylation protocol via a one-step metal catalyzed reaction, resulting in an incredible influence on the solubility, intermolecular packing and solid-state fluorescence compared to the parent unsubstituted PDIs. The excellent optical properties of PDIs, such as near-unity fluorescence quantum yield, excitation in the visible region, strong and reversible electron-accepting character, high photochemical stability and high electron mobility, lead to a burst in the development of high performance optical molecular probes based on the PDI core for Near-InfraRed (NIR) imaging techniques. Despite the fact that NIR organic probes usually suffer from poor hydrophilicity and low quantum yields, recent progress in strategies and synthetic methods for the development of water soluble PDI have been made.

In our group, we have developed several visible and NIR PDIs with different imide and bay substituents.² The synthesis of PDIs derivatives, starting from the commercially available perylene-3,4,9,10-tetracarboxylic acid dianhydride, allows the introduction of substituents in the imide group (affecting the aggregation, solubility or immobilization), in the bay region (substituents affect electronic and optical properties) or in the ortho position (affecting the solubility) (Figure 1).

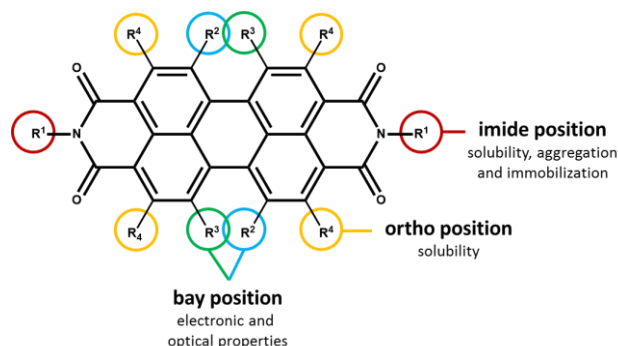


Figure 1. General structure of PDIs and influence of the different substituents position.

Acknowledgements

This work was partially supported by Fundação para a Ciência e a Tecnologia (FCT-Portugal) and COMPETE (FEDER), project UID/NAN/50024/2013 and project PTDC/CTMNAN/6249/2014.

References

- [1] S. Nakazono, Y. Imazaki, H. Yoo, J. Yang, T. Sasamori, N. Tokitoh, T. Cedric, H. Kageyama, D. Kim, H. Shinokubo, A. Osuka, *Chem. Eur. J.* 15 (2009) 7530-7533.
- [2] a) T. Ribeiro, S. Raja, A.S. Rodrigues, F. Fernandes, J.P.S. Farinha, C. Baleizão, *RSC Adv* 3 (2013) 9171-9174.
b) T. Ribeiro, S. Raja, A.S. Rodrigues, F. Fernandes, C. Baleizão, J.P.S. Farinha, *Dyes and Pigments* 110 (2014) 227-234. c) R.M. Pinto, E.M.S. Maçôas, A.I.S. Neves, S. Raja, C. Baleizão, I.C. Santos, H. Alves, *J. Am. Chem. Soc.* 137 (2015) 7104-7110. d) R.M. Pinto, W. Gouveia, E.M.S. Maçôas, I.C. Santos, S. Raja, C. Baleizão, H. Alves, *ACS Appl. Mater. Inter.* 7 (2015) 27720-27729.

In situ dithiocarbamate chemistry: a simple strategy to immobilize biological molecules for biosensing purposes

Telmo O. Paiva¹, Inês Almeida¹, Maria D. Carvalho¹, Wei Liu², Yu Niu², Gang Jin², J. P. Correia¹, Ana S. Viana¹

¹Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

²NML, Institute of Mechanics, Chinese Academy of Sciences, Beijing, 100190, China

The development of innovative and effective strategies to chemically modify metal surfaces with biological molecules, targeting catalytic and sensing applications, has faced tremendous advances in the last decades. Self-assembled monolayers (SAM) on metal surfaces, containing thiols as anchor groups and amines, or carboxylic acids as terminal functions have been widely used due to its simplicity and versatility. However, their use to covalently bind biomolecules commonly involves multi-step procedures.¹ *In situ* formation of dithiocarbamates presents a simpler and even more versatile alternative to SAM to immobilise biomolecules, consisting on the reaction between carbon disulphide and amine groups, and their prompt adsorption on metal surfaces. The resonance structure between the nitrogen, carbon and sulphur atoms is responsible for their superior attachment to the surface.² In our previous work, we have applied this methodology, as a proof of concept, to small compounds: a secondary amine (epinephrine) and an aminoacid (tryptophan), and also in the preparation of biosensing interfaces (e.g. Glucose oxidase³ and immunoglobulin G (IgG)⁴).

Hereby, we extend the applicability of this methodology to prepare nanostructured biosensing interfaces to be used in the development of enzymatic and immunosensing platforms with improved electrochemical and/or optical detection. Two examples will be described to illustrate the success of this methodology: i) Laccase/iron oxide nanoparticle assemblies have been immobilized using dithiocarbamate chemistry and their catalytic activity have been evaluated by electrochemical methods⁵; and ii) gold surface modification with dithiocarbamate nanoconjugates of protein A for the oriented immobilization of antibodies, to optimize their further specific interaction with antigen. This surface reveals a unique ability to prevent protein nonspecific adsorption, as demonstrated by real-time surface plasmon resonance spectroscopy and ellipsometry.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013, PhD scholarship (SFRH/BD/70673/2010), IF/00808/2013 (POPH, UE-FSE), 7th Sino-Portugal Scientific and Technological Cooperation 2013-2015 and PTDC/CTM-NAN/0994/2014.

References

- [1] Z.-H. Wang, A.S. Viana, G. Jin, L.M. Abrantes, *Bioelectrochemistry* 69 (2006) 180-186.
- [2] I. Almeida, A.C. Cascalheira, A.S. Viana, *Electrochim. Acta* 55 (2010) 8686-8695.
- [3] I. Almeida, V.C. Ferreira, M.F. Montemor, L.M. Abrantes, A.S. Viana, *Electrochim. Acta* 83 (2012) 311-320.
- [4] Y. Niu, A.I. Matos, L.M. Abrantes, A.S. Viana, G. Jin, *Langmuir* 28 (2012) 17718-17725.
- [5] I. Almeida, F. Henriques, M.D. Carvalho, A.S. Viana, *J. Colloid Interface Sci.* 485 (2017) 242-250.

Nanoporous materials for storage and release therapeutic doses of nitric oxide

Rosana V. Pinto^{1,2}, Ana C. Fernandes², Fernando Antunes², Moisés L. Pinto¹
and João Pires²

¹ CERENA, Departamento de Engenharia Química, Instituto Superior Técnico, Universidade de Lisboa,
Av. Rovisco Pais, nº1, 1049-001 Lisboa, Portugal

² Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal

Nitric oxide (NO) is one of the few gaseous signalling molecules known to act as a transcellular messenger in many key physiological and pathological processes, being an attractive alternative for therapy of several diseases.¹ Conventional homogeneous NO donors are limited due to its systemic action, which compromises selectivity and may cause undesirable side effects.² This problem has boosted the development of new NO donors with the ability to release controlled doses of NO in a local biological target for a specific application.

In this context, porous materials with proven potential for gas adsorption have gathered particular interest for the delivery of exogenous NO. In this work, we present some of our recent advancements in this topic. The research was concentrated in three different types of materials: titanosilicates, clays and metal organic frameworks (MOFs). These materials have been synthesized and characterized to evaluate the appropriate porosity to store NO and, at the same time, to their biocompatibility.

Kinetic studies of NO adsorption and release were performed in both gas and liquid phases, using a microbalance associated with a high-vacuum system and using the oxyhemoglobin assay, respectively. Materials biocompatibility was evaluated through toxicity assays with and without NO-loaded using HeLa cells and primary human epidermal keratinocytes (HEKn). Moreover, the control of the biological processes in the presence of the different NO donors was evaluated through the inhibition of mitochondrial respiration and the acceleration of the cell migration that simulate a wound healing process.

According to the kinetic adsorption profiles, the materials feature good gas storage properties, loading between 3.5 to 7 % (w/w) of NO. Gas release studies showed that at least 60 % of the NO previously adsorbed was after released from titanosilicates and clays, indicating a partial irreversible adsorption, whereas in MOFs total release was observed. Liquid phase studies revealed a controlled release over time.

Toxicology results are very encouraging for titanosilicates and MOFs, even when using a high concentration (toxicity \approx 20 % at 24 h, 450 $\mu\text{g}/\text{mL}$). Some materials also show the ability to inhibit mitochondrial respiration at high concentrations (450 $\mu\text{g}/\text{mL}$), demonstrating the controlled release. Cell migration studies showed a migration acceleration up to 15 % for ETS-4 with NO loaded, comparing to the control (material without NO).

Acknowledgements

Support for this work was provided by FCT through PEST UID/MULTI/00612/2013 (CQB), UID/ECI/04028/2013 (CERENA) and Investigador FCT project IF/0093/2012/CP0172/CT0013.

References

- [1] D.G. Hirst, T. Robson, in: H.O. McCarthy, J.A. Coulter JA (Eds.), Nitric Oxide Methods Protoc., Humana Press, Totowa, NJ, 2011, pp. 1-13.
- [2] L.K. Keefer, Nat. Mater. 2 (2003) 357-358.

Design of new Fe(II) coordination compounds with 1,2,4-triazole derivatives

Priscila Ramgi¹, Ana I. Vicente¹, Sara Realista¹, Liliana P. Ferreira²,
Maria José Calhorda¹, Paulo N. Martinho¹

¹Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande,
1749-016 Lisboa, Portugal

²BioISI, Faculdade de Ciências, Universidade de Lisboa, Campo Grande 1749-016 Lisboa, Portugal

There is a great interest in engineering electronic systems integrated with molecular switches, thus reducing considerably the size of such molecular devices. The spin crossover (SCO) compounds have emerged 20 years ago as promising materials for molecular electronics. This phenomenon is characterised by bistability at a molecular level, and a compound can switch between two distinct magnet states, the low spin (LS) and the high spin (HS). This switching can be triggered by external stimuli such as temperature, pressure and irradiation. The 1,2,4-triazole unit and derivatives have been quite successful in promoting highly cooperative SCO systems when coordinated to iron(II) metal centres.¹⁻³

We synthesized new 4-amino-1,2,4-triazole (Figure 1) derivatives where this ligand was coordinated to iron(II) to obtain new SCO complexes. Their characterization was made by FTIR spectroscopy, elemental analysis, and ¹H NMR measurements, and their magnetic behaviour was investigated by SQUID magnetometry. The redox properties of the compounds were studied by cyclic voltammetry and films of the complexes were prepared by drop casting onto GC electrodes. The performance of the modified electrodes with the Fe(II) magnetic films for energy storage was also investigated.

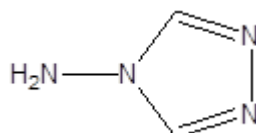


Figure 5. 4-amino-4H-1,2,4-triazole.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. P.N. Martinho (SFRH/BPD/73345/2010) and S. Realista (PD/BD/52368/2013) thank FCT for financial support.

References

- [1] O. Roubeau, Chem. Chem. Eur. J. 18 (2012) 15230-15244.
- [2] W. Wang, B. Ji, C. Zhang, X. Cao, Inorg. Chem. Commun. 67 (2016) 55-59.
- [3] M.M. Dirtu, A.D. Naik, A. Rotaru, L. Spinu, D. Poelman, Y. Garcia, Inorg. Chem. 55 (2016) 4278-4295.

Photoactive MOFs based in Diphenylanthracene Derivatives and obtained by Mechanochemistry for Energy Applications

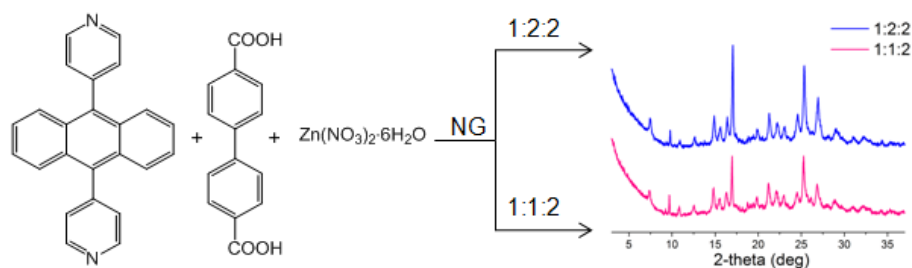
Márcia A. Ribeiro^{a,b,c}, Hermenegildo Garcia^b, Teresa Duarte^c and Carlos Baleizão^a

^a Centro de Química-Física Molecular and Institute of Nanoscience and Nanotechnology, Instituto Superior Técnico, Universidade de Lisboa, Portugal

^b Instituto de Tecnologia Química/CSIC, Universidade Politecnica de Valência, Spain

^c Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Portugal

The goal of this work is the conversion of solar energy into electrical energy through photoactive metal-organic frameworks (MOFs), taking advantage of the exciting properties of this class of nanomaterials. Since the discovery of MOF-5 electronic properties¹, more MOFs have shown semiconductor behavior and have been used with success in photovoltaic devices and in other clean energy applications². In our project, two main topics will be addressed: photon capture and host-guest interactions. The strategy to absorb high amount of photons will be focused on the electronic structure of the organic linker, namely diphenylanthracene (DPA) derivatives (dipyridyl anthracene and 4,4'-(9,10-anthracenediyl)dibenzoic acid). DPA and its derivatives exhibit a planar structure and upon incorporation in the MOF structure is expected to lead to long range π - π interactions. In addition, these molecules have already revealed electroluminescent (EL) properties and application in organic light-emitting diodes (OLEDs)³. We expect good charge mobility in the new DPA-MOFs nanomaterials. Mechanochemistry will be used to prepare the DPA-MOFs, affording a greener behavior to the synthesis approach, with solvent free and room temperature conditions. A comparative study will be developed using the solvothermal approach to correlate and identify new crystalline 3-D structures by powder X-ray diffraction (PXRD) or single crystal. Scheme 1 presents a first synthetic approach for the new DPA-MOFs by mechanochemistry.



Scheme 1. Schematic representation of the first reactions by neat grinding to obtain the DPA-MOFs.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. We thank the Fundação para a Ciência e Tecnologia for financial support within the Materials Chemistry PhD program (PD/BD/127983/2016). This work was partially supported by Fundação para a Ciência e a Tecnologia (FCT-Portugal) and COMPETE (FEDER), projects PTDC/CTM-NAN/6249/2014, RECI/QEQ-QIN/0189/2012, UID/QUI/00100/2013 and UID/NAN/50024/2013.

References

- [1] M. Alvaro, E. Carbonell, B. Ferrer, F.X. Llabrés I Xamena, H. Garcia, Chem. Eur. J. 13(18) (2007) 5106-5112.
- [2] S.-L. Li, Q. Xu, Energy Environ. Sci. 6(6) (2013) 1656-1683.
- [3] D. Chen, H. Xing, Z. Su, C. Wang, Chem. Commun. 2(L) (2016) 2-5.

The heavy atom effect in iminopyrrolyl boron complexes: synthesis and photoluminescence properties

A. I. Rodrigues¹, P. Krishnamoorthy¹, B. Ferreira¹, C. S. B. Gomes¹, R. D. Paolo¹,
A. Maçanita¹, J. Pina², J. S. S. Melo², P. T. Gomes¹

¹Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Portugal

²Chemistry Department, University of Coimbra, Portugal

Light-emitting diodes (LEDs) prepared with tetracoordinate boron compounds containing bidentate *N,N*-ligand chromophores exhibit good properties.¹ Since the steric and electronic characteristics of the 2-iminopyrrolyl ligand core can be varied, the colour tuning becomes wider.² Thus, these ligands have been employed in the synthesis of a family of 2-(*N*-arylformimino)pyrrolyl diphenylboron compounds with interesting luminescence properties.³ Aiming to explore different photoluminescence properties by using the internal heavy atom effect, we report in this communication the synthesis of new halogen substituted 2-iminopyrrolyl-BPh₂ chromophores (Figure 1) and their structural and photophysical characterisation.

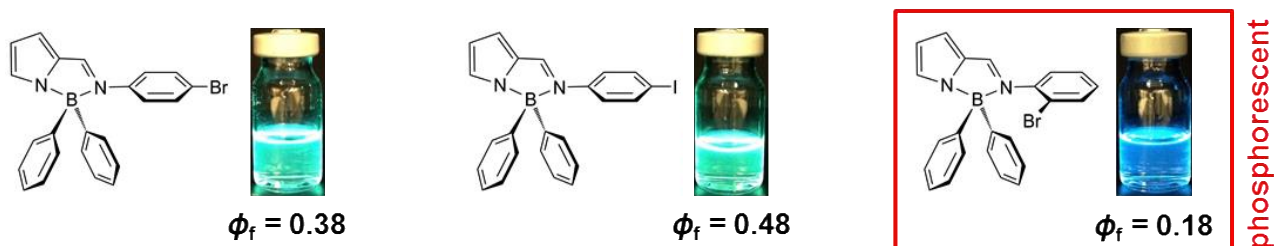


Figure 1. Some of the synthesized 2-iminopyrrolyl-BPh₂ complexes, their emission color and respective quantum yields.

Acknowledgements

We thank the Fundação para a Ciência e Tecnologia, Portugal, for financial support (Projects UID/QUI/00100/2013) and for a ChemMat fellowship PD/BD/113535/2015 (A.I. Rodrigues).

References

- [1] (a) D. Li *et al.*, Chem. Soc. Rev. 42 (2013) 8416.
- [2] P.T. Gomes *et al.* (IST), World Patent WO2013039413 (2013).
- [3] (a) D. Suresh *et al.*, Chem. Eur. J. 20 (2014) 4126; (b) D. Suresh *et al.*, Chem. Eur. J. 21 (2015) 9133; (c) P. Krishnamoorthy *et al.*, Dyes Pigm. 140 (2017) 520-532.

Zinc(II) and Copper(II) Metal–Organic Frameworks Constructed from a Terphenyl-4,4''-Dicarboxylic Acid Derivative: Synthesis, Structure and Catalytic Application in the Cyanosilylation of Aldehydes

Guilherme M. D. M. Rúbio, Anirban Karmakar, Anup Paul, M. Fátima C. Guedes da Silva and Armando J. L. Pombeiro

Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisbon, Portugal

The design and synthesis of microporous metal–organic frameworks (MOFs) have become the subject of extensive interest due to their intriguing architectures and functional properties, such as gas storage, separation, catalysis, etc.¹ The application of such materials largely depends on the nature of metal ions and linkers.^{2,3}

In this context, a rigid dicarboxylate pro-ligand – 3,3''-dipropoxy-[1,1':4',1''-terphenyl]-4,4''-dicarboxylic acid (**H₂L**) (Figure 1A) – was synthesized and utilized for the construction of various 1D and 2D MOFs. The solvothermal reaction between zinc(II) and copper(II) salts with **H₂L** in presence or absence of an auxiliary ligand gives rise to four new MOFs which were characterized by single crystal and powder X-ray diffraction, elemental microanalysis, IR spectroscopy and thermogravimetric analysis. These MOFs act as efficient heterogeneous catalysts for the cyanosilylation of aldehydes with trimethylsilyl cyanide at room temperature. The catalysts can be easily recovered from reaction mixture and reusable at least for five consecutive cycles without losing activity.

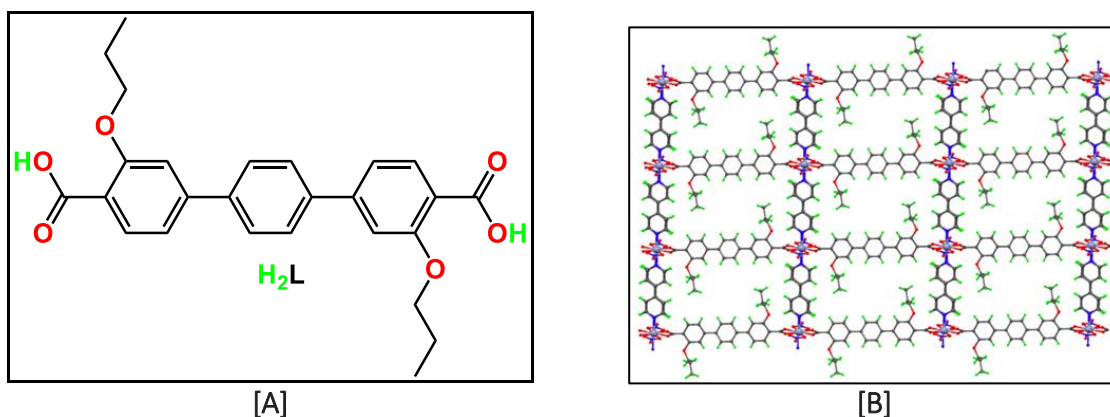


Figure 6. [A] Schematic diagram of pro-ligand **H₂L**; [B] The rectangular grid-type layer of one of the MOF catalysts.

Acknowledgements

This work was supported by the Foundation for Science and Technology (FCT) (project UID/QUI/00100/2013), Portugal. A. Karmakar and A. Paul express their gratitude to the FCT for postdoctoral fellowships (SFRH/BPD/76192/2011 and SFRH/BPD/88450/2012).

References

- [1] Z. Zhang, M.J. Zaworotko, *Chem. Soc. Rev.* 43 (2014) 5444-5455.
- [2] F.A. Almeida Paz, J. Klinowski, S.M.F. Vilela, J.P.C. Tomé, J.A.S. Cavaleiro, J. Rocha, *Chem. Soc. Rev.* 41 (2012) 1088-1110.
- [3] A. Karmakar, M.F.C. Guedes da Silva, S. Hazra, A.J.L. Pombeiro, *New J. Chem.* 39 (2015) 3004-3014.

Smart Polymer Fibers for Stem Cell Cultivation

Ana C. Santos^{a,b}, C. Baleizão^a, M. H. Godinho^b, J. P. S. Farinha^a

^a Centro de Química-Física Molecular and IN-Institute of Nanoscience and Nanotechnology, Instituto Superior Técnico, 1049-001 Lisboa, Portugal; E-mail: ana.c.santos@tecnico.ulisboa.pt

^b CENIMAT/13N, Departamento de Ciência dos Materiais, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal

Stem cell (SC) therapies are frequently compromised due to problems related to cell recovery from cultivation substrates. The main goal of this work is to produce stimuli-responsive networks designed from fibers with nano/micro diameters that match the dimensions of the natural niche fibrous proteins where SC inhabit.¹ Electrospinning is a simple and highly versatile method for generating fibers. This technique has attracted tremendous recent interest in both academia and industry, owing to its unique ability to produce ultrafine fibers of different materials in various fibrous assemblies.² The desirable smart behavior of this new material is achieved by the presence of copolymer chains of 2-(2'-methoxyethoxy)ethyl methacrylate (MEO2MA) and oligo(ethylene glycol) methacrylate (OEGMA), that are thermoresponsive and especially suitable for biomedical applications.³

Here we present a bottle brush like copolymer based in a cellulose acetate (CA) backbone grafted with thermo-responsive polymer chains (P(MEO2MA-co-OEGMA-b-AHMA)). This polymer presents a LCST behavior, resulting in a conformational coil-to-globule transition (CGT) on the polymer chains, thus affecting the solubility upon a temperature stimulus. The thermo-responsive polymer was synthesized by reversible addition fragmentation transfer (RAFT) methodology and was grafted to previously propargylated CA, by a “click-chemistry” reaction (Figure 1). The final product was characterized, by NMR, FTIR and DSC, and turned into fibers (Figure 2), through electrospinning technique, to produce a thermo-responsive fibrous membrane. The membranes are being characterized by SEM, AFM and submitted to mechanical characterization.

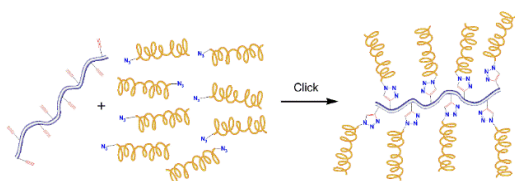


Figure 1. Schematic representation of click-chemistry reaction between azide and propargyl groups

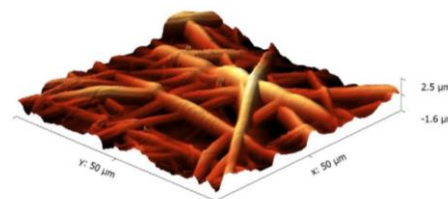


Figure 2. AFM image of fiber morphology.

Acknowledgements

This work was partially supported by Fundação para a Ciência e a Tecnologia (FCT-Portugal) and COMPETE (FEDER), project UID/NAN/50024/2013 and PTDC/CTM-POL/3698/2014. A.C. Santos also thanks FCT for an AdvAMTech Doctoral Program PhD grant PD/BD/52628/2014.

References

- [1] T. Liang, S. Mahalingam, M. Edirisinghe, Mater. Sci. Eng. C. Mater. Biol. Appl. 33(7) (2013) 4384-91.
- [2] J.P. Canejo, J.P. Borges, M.H. Godinho, P. Brogueira, P.I.C. Teixeira, E.M. Terentjev, Adv. Mater. 20(24) (2008) 4821-4825.
- [3] A.M. Santiago, T. Ribeiro, A.S. Rodrigues, B. Ribeiro, R.F.M. Frade, C. Baleizão, J.P.S. Farinha, Eur. J. Inorg. Chem. 2015(27) (2015) 4579-4587.

Wet chemical determination of the summative composition of corks from different species

Ali Sen, Isabel Miranda, Helena Pereira

Centro de Estudos Florestais, Instituto Superior de Agronomia, Universidade de Lisboa, Portugal

Cork is a cellular material with an interesting set of properties that makes it the raw-material of an industrial chain producing cork bottle sealants, insulation and surfacing products. Cork is obtained mainly from the cork oak (*Quercus suber*) but other tree species produce also significant amounts of cork in their barks such as *Quercus cerris* and *Beaucarnea recurvata*. Cork content, structural features and chemical composition vary between these species but it is the structure, chemical composition and properties of *Quercus suber* cork that establish the benchmark for this potential raw-material.

The chemical composition of cork, especially its suberin, lignin and extractive contents determine its utilization routes. Often, higher suberin and lower lignin contents are desired by the cork stoppers industry, while bioactive cork extractives such as polyphenols and triterpenoids show potential for pharmaceutical industry.

The chemical compositions of corks from the cork oak (*Q. suber*), Turkey oak (*Q. cerris*) and elephant's foot (*B. recurvata*) were determined using wet chemical methods for summative composition analysis. Cork samples were first extracted successively with dichloromethane, ethanol and water to determine the extractive contents. Suberin contents were determined afterwards on the extracted corks using methanolysis with 3% NaOCH₃ for depolymerization. Acid insoluble and soluble lignin contents were determined by acid hydrolysis and UV spectroscopy methods.

The results show that the overall chemical composition of cork depends on the tree species. *Q. suber* cork contains higher suberin and lesser lignin, while *B. recurvata* cork contains higher lignin and lower suberin contents. *Q. cerris* cork showed intermediate values for these components. The results suggest that non-conventional corks such as *Q. cerris* and *B. recurvata* corks may be used in agglomerates in the cork industry.

Chemical composition of cork from *Beaucarnea recurvata*
analyzed by FTIR-ATR and Py-GC-MS

Ali Sen, Isabel Miranda, Ana Lourenço, Helena Pereira

Centro de Estudos Florestais, Instituto Superior de Agronomia, Universidade de Lisboa, Portugal

Fourier-transform infrared spectroscopy (FTIR-ATR) and pyrolysis coupled to gas chromatography mass spectroscopy (Py-GC-MS) methods are powerful tools to characterize biomass since they are much faster than wet chemical methods and require smaller amounts of biomass. More important, they give structural chemical information that wet chemical summative analysis does not provide. Tree barks may contain significant amounts of cork, of which the cork oak (*Quercus suber*) is the iconic example with a thick and homogeneous cork layer that is the basis of an industrial chain and one pillar for the national economy. Search for other species with cork-rich barks is an undergoing research line. Fast chemical characterizations of such cork-enriched barks using FTIR-ATR or Py-GC-MS methods may provide an insight into their chemical suitability as complementary cork raw materials.

In the present study, the outer bark of elephant's foot (*Beaucarnea recurvata*) was separated manually from the inner bark. The outer bark was constituted by a thick layer of cork tissue, as checked microscopically using scanning electron microscopy. The cork layer was dried and grinded to 40-60 mesh. The resulting fraction was further ball-milled for the subsequent FTIR-ATR and PY-GC-MS analyses.

The results of FTIR showed that the outer bark has chemical composition similar to cork as indicated by the peaks at 1742, 2927 and 2859 cm^{-1} , that indicate the presence of suberin. Suberin is a macromolecule made up of esterified glycerol to long chain fatty acids and alcohols that is specific to cork. The Py-GC-MS results showed that cork has G-type of lignin i.e. a lignin made up by guaiacyl monomer units. Taken together these results confirmed the cork structure of the elephant's foot outer bark and showed its chemical similarity to the commercial cork from *Quercus suber*.

Carbon dots for copper (I,II) and iron (II,III) detection

Marta D. Silva^{a,b}, Teresa S. C. Rosa^{a,b}, Ana Paula C. Ribeiro^{a,*},

Elisabete C. B. A. Alegria^{a,b}, Rui P. Oliveira-Silva^c and Armando J. L. Pombeiro^a

^a Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal

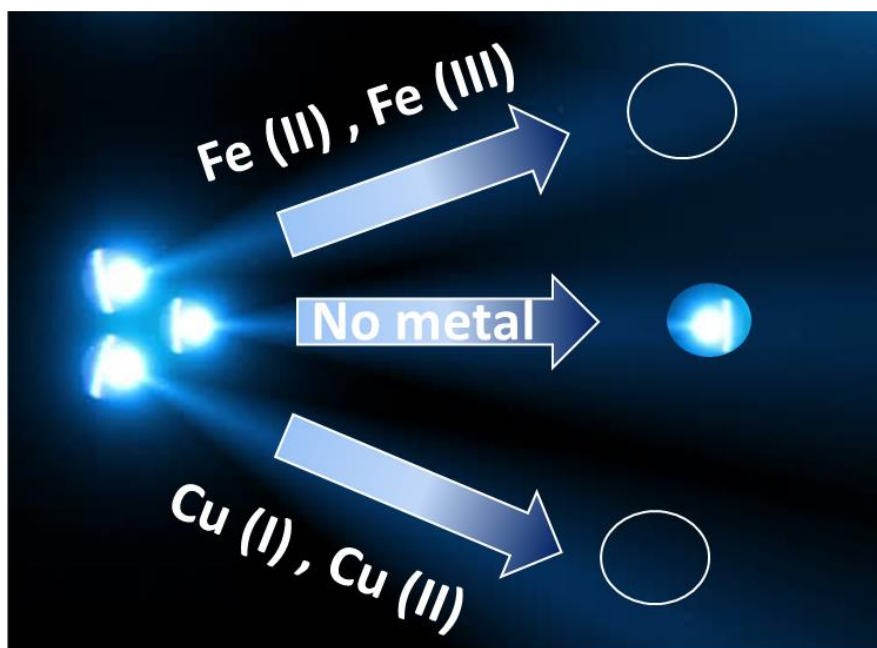
^b Chemical Engineering Department, Instituto Superior de Engenharia de Lisboa, Instituto Politécnico de Lisboa, Rua Conselheiro Emídio Navarro, 1959-007 Lisboa, Portugal

^c IBB, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal

E-mail: apribeiro@tecnico.ulisboa.pt

The aim of this work is to demonstrate the potential of carbon dots¹ in the determination and quantification of Cu(I,II) and Fe(II,III) metal ions in solution.

Carbon quantum dots are a type of nanoparticles of less than 10 nm in size. Due to their unique properties, like size-dependent fluorescence, non-toxicity and biocompatibility, carbon quantum dots possess a potential in fields such as chemical sensing (Scheme 1) or catalysis and drug delivery. The tests performed using pre-defined samples are presented and the influence of the size of the carbon dots in the concentration of the metal detection will be discussed.



Scheme 1. Schematic representation of the detection behaviour.

Acknowledgements

Funding from FCT (Fundação para a Ciência e a Tecnologia, Portugal) (UID/QUI/00100/2013, PTDC/QEQ-ERQ/1648/2014 and PTDC/QEQ-QIN/3967/2014 projects). A.P.C. Ribeiro also acknowledges FCT for the SFRH/BPD/90883/2012 grant.

References

[1] X. Gao, C. Du, Z. Zhuang, W. Chen, J. Mater. Chem. C 4 (2016) 6927.

Suzuki-Miyaura C-C coupling reaction catalyzed by carbon-metal composites

Mohamed Soliman^a, Elisabete C. B. A. Alegria^{a,b}, Ana P. C. Ribeiro^a, Marta S. Saraiva^c,
 Maria José Calhorda^c and Armando J. L. Pombeiro^a

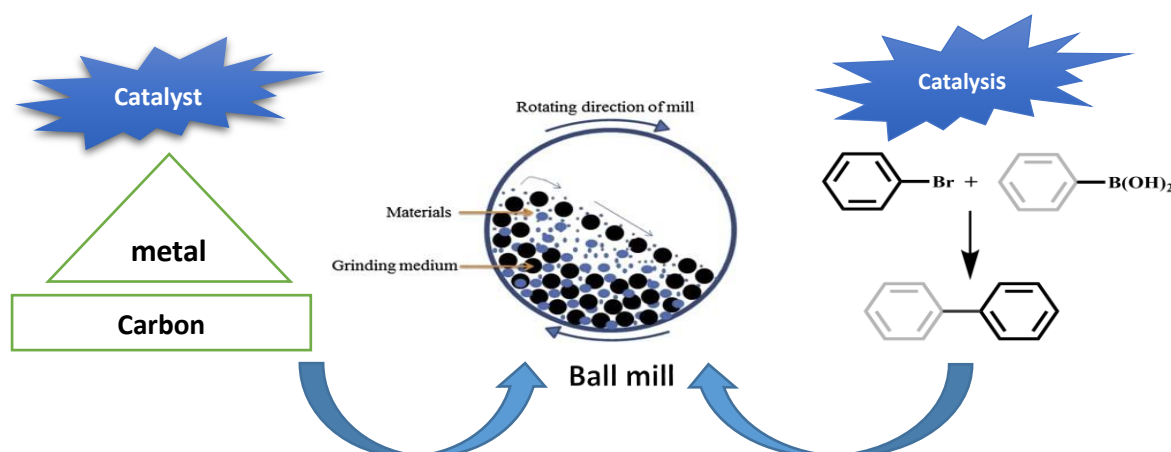
^a Centro de Química Estrutural, Complexo I, IST, Universidade de Lisboa, 1049-001 Lisboa, Portugal

^b Chemical Engineering Department, ISEL, Instituto Politécnico de Lisboa, 1959-007 Lisboa, Portugal

^c Centro de Química e Bioquímica (CQB), Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal

The sustainable production of expensive catalysts represents an appealing procedure to obtain a large variety of catalysts (with Pd and Pt, for example) that can be effectively used. We produced mixtures of an expensive metal (Pt or Pd) with carbon nanomaterials (activated carbon or multiwalled carbon nanotubes) and test them in metal-catalyzed bond forming reactions namely in the Suzuki-Miyaura cross-coupling.

Characterization of the stability of the catalysts, in terms of TGA, will be evaluated and a comparison and discussion of the yield of the reaction in terms of time and type of catalytic mixture will be addressed.



Acknowledgements

We thank the Fundação para a Ciência e Tecnologia (fellowships SFRH/BPD/90883/2012, SFRH/BPD/88082/2012 and PD/BD/114400/2016 to A.P.C. Ribeiro, M.S. Saraiva and M. Soliman, respectively, and the UID/QUI/00100/2013, UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013 projects) and the Instituto Politécnico de Lisboa (IPL/2016/MechSynCat_ISEL project) for financial support.

References

- [1] A.P.C. Ribeiro, E. Fontolan, E.C.B.A. Alegria, M.N. Kopylovich, R. Bertani, A.J.L. Pombeiro, *J. Mol. Catal. A Chem.* 426 (2017) 557.
- [2] E. Fontolan, E.C.B.A. Alegria, A.P.C. Ribeiro, M.N. Kopylovich, R. Bertani, A.J.L. Pombeiro, *Inorg. Chim. Acta* 455 (2017) 653.

Structural, optical and photocatalytic properties of titanate nanotubes modified by Cu, Mn and Ni incorporation

Sara C. A. Sousa, O. C. Monteiro

Centro de Química e Bioquímica, Faculdade de Ciências, ULisboa, 1749-016 Lisboa, Portugal

Over the last years, the use of pharmaceuticals and personal care products (PPCPs), which include pharmaceutical drugs, cosmetics, food supplements and other personal care products, has been increasing and, consequently, their release to the environment. However, their disposal after use has become very problematic as they are extremely resistant to conventional treatments and even at very low concentrations they may impose toxicity at all biological hierarchy levels. Many attempts have been made to overcome this dramatic environmental problem, but unfortunately haven't been very successful.

The application of nanocrystalline semiconductors as photocatalysts, on the treatment of wastewaters, has been shown to be effective. Among the many candidates of photocatalysts, TiO₂ is the most widely studied material as it presents high photocatalytic activity and therefore has been investigated for the treatment of wastewaters.¹ However, TiO₂ has a major drawback in processes associated with solar photocatalysis due to its wide bandgap (3.2 eV) and high recombination rate of photo-generated carriers. Therefore, the synthesis of TiO₂-based materials, e.g. titanate nanotubes (TNT), with a broader range of light absorption and a lower charge recombination rate would be an important achievement towards the development of successful photoactive materials.

To help overcome this problem, the present work reports the synthesis of nanocrystalline TNT-based materials modified by selected transition metals, such as Cu, Mn and Ni, by using ion-exchange (TNT/M) and doping (M-TNT) processes.² These materials were characterized by XRD, DRS, TEM and B.E.T. aiming to study the influence of the transition metal position in the TNT structure and on the TNT optical properties. The photocatalytic activity of the modified metal-titanate nanotubes was investigated using terephthalic acid (TA) as probe molecule to study the catalytic production of hydroxyl radical (\bullet OH). The results were very promising and show that either M-TNT or TNT/M modified samples are better catalysts than the pristine TNT, being the photocatalytic performance dependent on the transition metal used and on its position in the TNT crystalline structure. Therefore, these materials show that they are excellent candidates for photocatalytic degradation of PPCPs.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013, PEst-OE/QUI/UI0612/2013 and IF/01210/2014 projects.

References

- [1] M. Kaneko, I. Okura (Eds.), Photocatalysis: Science and Technology, Biological and Medical Physics Series, Springer, Berlin, 2010.
- [2] B. Barrocas, A.J. Silvestre, A.G. Rolo, O.C. Monteiro, Phys. Chem. Chem. Phys. 18 (2016) 18081-18093.

Strategies to improve the cooperativity in iron(III) spin crossover complexes

Ingrid Suzana^{†,‡}, Ana I. Vicente[‡], Paulo N. Martinho[‡], Liliana P. Ferreira^{‡,||},
 Maria José Calhorda[‡]

[†]Département de Chimie, Université Pierre et Marie Curie, Paris 75005, France

[‡]Centro de Química e Bioquímica, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

^{||}BioISI, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

The construction of complex hybrid materials which combine different properties, i.e. multifunctional materials, has been at the heart of research in recent years. Among these, our interest is focused upon polymeric complexes that have the potential of featuring switching magnetic properties combined with electrical conductivity, with the goal of using the latter by applying an external electric field to control the bistability in magnetic molecules and materials. For that, we wish to approach the fabrication of multifunctional materials using a common strategy for electrochemical synthesis thus preparing electropolymerised magnetic films with conducting polymers attached onto spin crossover cations.

As a polymerisable unit, 3'-bromo-2,2':5',2''-terthiophene is particularly attractive because of its electrochemical stability and its high conductivity, both properties indispensable for preparing conducting polymers.¹ As a magnetic switching unit, the $[\text{Fe}(\text{salEen})_2]^+$ has been selected due to its known spin crossover (SCO) behaviour.² Here we report the synthesis of both ligand and Fe(III) complexes that are used to materials development through electropolymerization of the thiophene unit. The magnetic properties of both complexes and polymer are also investigated.

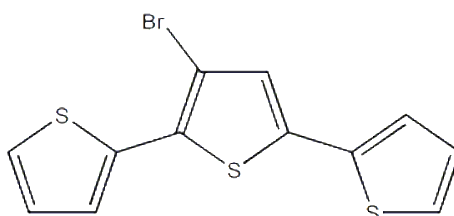


Figure 1. Electropolymerizable unit.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013, PEst-OE/QUI/UI0612/2013 and PTDC/QEQ-QIN/3414/2014. P.N. Martinho thanks FCT for financial support (SFRH/BPD/73345/2010).

I. Suzana acknowledges financial support from Erasmus+ and from l'État managed by the Agence Nationale de la Recherche in accordance with l'Idex Sorbonne Universités, in the context of the program "Investissement d'avenir/Bourse de mobilité internationale" of Sorbonne Universités.

References

- [1] B. Djukic, M.T. Lemaire, *Inorg. Chem.* 48(22) (2009) 10489-10491.
- [2] A.I. Vicente, A. Joseph, L.P. Ferreira, M.D. Carvalho, V.H.N. Rodrigues, M. Duttine, H.P. Diogo, M.E. Minas da Piedade, M.J. Calhorda, P.N. Martinho, *Chemical Science* 7 (2016) 4251-4258.

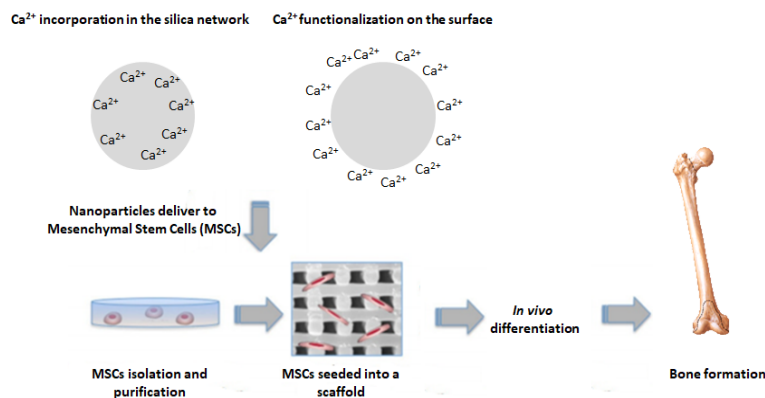
Calcium and Phosphorous Incorporation in Silica Nanoparticles for Stem Cell Differentiation in Bone Regeneration

Márcia Tavares^{a,b}, João Mano^b, José Paulo Farinha^a, Carlos Baleizão^a

^a CQFM, Centro de Química-Física Molecular, IN—Institute of Nanosciences and Nanotechnology, Instituto Superior Técnico, Universidade de Lisboa, Lisboa, Portugal

^b CICECO e Departamento de Química, Universidade de Aveiro, Aveiro, Portugal

The application of adult stem cells in regenerative medicine requires the spatiotemporal control of their differentiation and of new tissue production. The differentiation is usually performed *in vitro*, by exposing the stem cells to specific factors. Alternatively, one can use carriers containing such factors, that can be internalized by the cells. In this case, the cells can be immediately implanted or further manipulated without the need for incubation in a culture media containing the factors. Calcium and phosphorous ions, once released inside adult stem cells induce bone cell proliferation and differentiation, and also stimulate the expression of growth factors.¹ The goal of this work is to develop silica nanoparticles (SiNPs) containing calcium and phosphorous ions, by incorporating it in the silica network during the synthesis or at the particle surface in a post-synthetic procedure (Scheme 1). We have tested different calcium precursors: calcium hydroxide, calcium oxide, calcium acetate and calcium methoxyethoxide. In the case of phosphate, we used triethyl phosphate (TEP) or ammonium phosphate dibasic. The nanoparticles were characterized by TEM and DLS, and the ion incorporation degree and releases kinetics were accessed by ICP. The influence of the precursor and functionalization on the particle morphology, degree of functionalization and releases kinetics profiles will be discussed.



Scheme 1. Representation of bone regeneration approach (Adapted from [2]).

Acknowledgements

This work was partially supported by Fundação para a Ciência e a Tecnologia (FCT-Portugal) and COMPETE (FEDER), project UID/NAN/50024/2013 and PhD grant PD/BD/114019/2015.

References

- [1] Y. C. Chai *et al.*, *Acta Biomaterialia* 8(11) (2012) 3876-3887.
- [2] F. Viti, S. Scaglione, A. Orro, L. Milanesi, *BMC Bioinformatics* 15(1) (2014) S14.

Strategies for Thin Films of Hybrid Mesoporous Silica Nanoparticles

Guido Valentini^{a,b}, Tânia Ribeiro^a, José Paulo S. Farinha^a and Carlos Baleizão^a

^a CQFM-Centro de Química-Física Molecular, IN-Institute of Nanosciences and Nanotechnology, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal

^b Faculty of Nanomaterials and Nanotechnology Engineering, Politecnico di Milano, Milan, Italy

Mesoporous Silica Nanoparticles (MSNs) are very promising structured materials because of their high pore volume and surface area, defined geometric mesostructure and functionalization versatility.¹ Due to their low density and high pore volume, MSNs could accommodate large quantities of conjugate polymers on the pore volume. Additionally, it is possible to incorporate electron acceptor molecules on the silica structure. This way, hybrid MSNs can be used as an ordered scaffold for donor acceptor pairs, providing new opportunities to the organization of the active layer layout in organic photovoltaics devices. The bottleneck of this new approach is the organization of the hybrid MSNs in thin films (below 150 nm).

Our goal is to develop a deposition strategy of hybrid MSN in different surfaces (glass, hydrophobic or hydrophilic) to obtain a homogeneous and compact layer. We tested different deposition techniques (dip coating, drop casting and spin coating) and tuned different parameters (solvent, nanoparticles concentrations and drying environment).

The dip coating and drop casting approaches have shown problems in homogeneity of the final layer, while spin coating exhibit good results in terms of thickness and homogeneity (Figure 1).

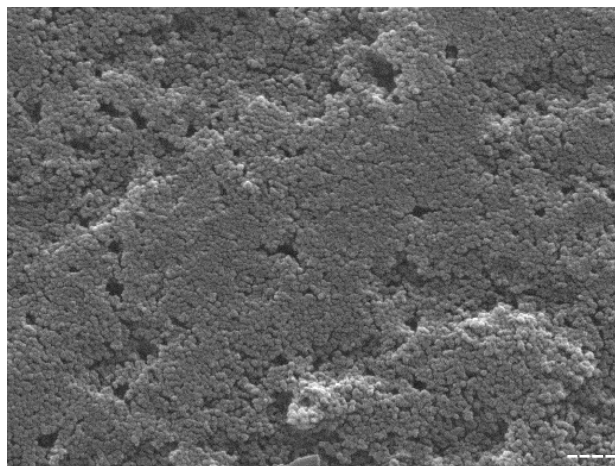


Figure 1. SEM image of hybrid MSNs spin coated onto a glass slide (scale bar: 400 nm).

Acknowledgements

This work was partially supported by Fundação para a Ciência e a Tecnologia (FCT-Portugal) and COMPETE (FEDER) within projects, UID/NAN/50024/2013 and PTDC/CTM-NAN/6249/2014.

References

[1] a) K.C.W. Wu et al., *J. Mater. Chem.* 22(4) (2012) 1251-1256; b) F. Silencieux et al., *Langmuir* 31(47) (2015) 13011-13021.

Spin Crossover in solution: overcoming the solid state hurdles

Xinwey Wu^a, Ana I. Vicente^a, Yannick Ortin^b, Liliana P. Ferreira^{c,d},
 Maria de Deus Carvalho^a, Andrew Barker^b, Grace G. Morgan^b, Maria José Calhorda^a,
 Paulo N. Martinho^a

^a Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande,
 1749-016 Lisboa, Portugal

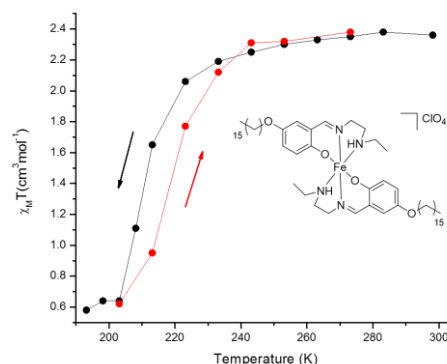
^b Centre for Synthesis and Chemical Biology and School of Chemistry and Chemical Biology,
 University College Dublin, Belfield, Dublin 4, Ireland

^c BioISI, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

^d Department of Physics, University of Coimbra, 3004-516 Coimbra, Portugal

The ability of certain first row transition metal ions to switch electronic state with thermal or optical stimulus has long been cited as having excellent potential for data storage, and in recent years the emphasis has moved from synthesis of new examples towards suitable engineering of existing complexes into polymeric or amphiphilic environments.¹ Amphiphilic compounds have proved to promote self-assembly in solution with some few examples displaying hysteresis. This opens new opportunities for solution processing magnetic materials.²

Here we present the preparation of an alkyl functionalised iron(III) compound [Fe(LOC16)₂]ClO₄ (Figure 1). The magnetic profile of the compound was analysed both in solid state and solution with the latter showing the formation of a cooperative system proved by the spin crossover with a hysteresis window of 15 K around 220 K. The nature of both the spin crossover and hysteresis was further investigated using different techniques such as NMR, SQUID, EPR, UV-visible spectroscopy and Mössbauer spectroscopy.



Acknowledgements

The authors thank Fundação para a Ciência e Tecnologia for financial support UID/MULTI/00612/2013 and PTDC/QEQ-QIN/3414/2014. P.N. Martinho thanks FCT for financial support (SFRH/BPD/73345/2010).

References

- [1] M.A. Halcrow (Ed.), Spin-Crossover Materials: Properties and Applications, John Wiley & Sons Ltd., Chichester, 2013.
- [2] P.N. Martinho, Y. Ortin, B. Gildea, C. Gandolfi, G. McKerr, B. O'Hagan, M. Albrecht, G.G. Morgan, Dalton Trans. 41 (2012) 7461.

Iron(III) Spin Crossover Compound with two step spin transition:
Structural and magnetic characterization

Bruno J. C. Vieira, Laura C. J. Pereira, Vasco da Gama, Isabel C. Santos,

Joana T. Coutinho and João C. Waerenborgh

*Centro de Ciências e Tecnologias Nucleares (C2TN), Instituto Superior Técnico,
Universidade de Lisboa, E.N. 10 ao km 139.7, 2695-066 Bobadela, Loures, Portugal*

The spin crossover (SCO) phenomenon can be found in a variety of $3d^4$ – $3d^7$ transition metal complexes and has been extensively studied in past decades.^{1,2} In these complexes, the spin state of the transition metal can be reversibly switched between the low-spin (LS) and high-spin (HS) states by the application of an external perturbation (such as temperature, pressure, magnetic field, light irradiation). The bistability between the HS and LS states is quite promising for the application as molecular memories and switches, as it is associated with changes in the physical properties (crystal structure, magnetism, color, etc.) and its progress can be monitored using a variety of techniques.¹⁻³ Here, we report the first example of a two-step SCO mononuclear Fe(III) complex, [Fe(nsal2trien)]SCN, with structural symmetry breaking in the intermediate phase (with the doubling of the unit cell) and a “re-entrant” behavior as the LS crystal structure is isostructural to the one in the HS phase. The hexadentate nsal2trien ligand (see Figure 1) was obtained by condensation of triethylenetetramine with 2-hydroxy-1-naphthaldehyde.

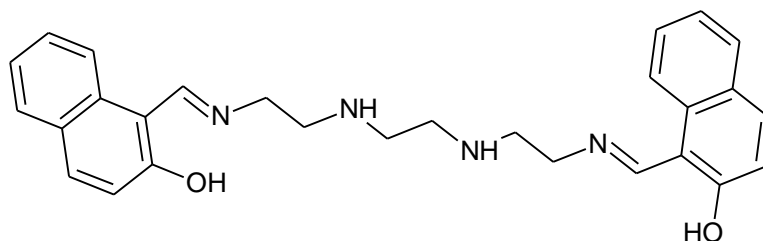


Figure 1. nsal2trienH₂.

Acknowledgements

Authors gratefully acknowledge the FCT support through the UID/Multi/04349/2013 project and SFRH/BD/65237/2009 grant.

References

- [1] O. Kahn, *Molecular Magnetism*, Wiley-VCH, New York, 1993.
- [2] A. Bousseksou, G. Molnar, G. Matouzenko, *Eur. J. Inorg. Chem.* (2004) 4353.
- [3] A.B. Gaspar, M.C. Muñoz, J.A.J. Real, *Mater. Chem.* 16 (2006) 2522.

Technology & Industry

T&I.InvitedLecturer

Leading Cork Business Through R&D and Innovation

Miguel Cabral

Amorim & Irmãos, S. A.

R&D and innovation has been the engine of the new era of A&I. A company with great attention to the quality of the products, the control of the processes and the knowledge of the interaction between the products and the beverages for which they are intended.

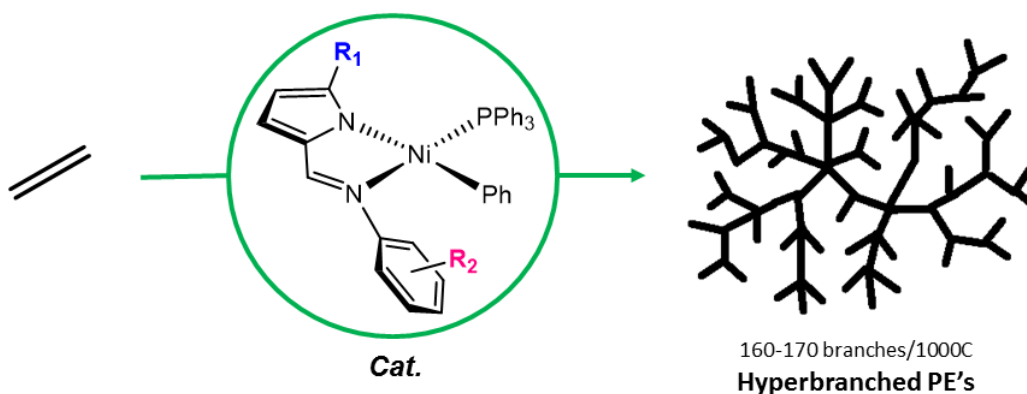
This strategy led the company to beat all records of number of corks sold and profits.

In this presentation we intend to show how A&I faces a challenge, showing a recent example of great success, and at the same time we will present the challenges that still lie ahead.

Iminopyrrolyl Nickel(II) catalysts for the production of hyperbranched polyethylene

Cláudia A. Figueira¹, Patrícia S. Lopes¹, Clara S. B. Gomes¹,
 Joselaine S. Gomes¹, Francisco Lemos², Pedro T. Gomes¹
¹ Centro de Química Estrutural, ² CERENA;
 Instituto Superior Técnico, Lisboa, Portugal

The developments in the area of olefin polymerization catalyzed by late transition metal complexes as homogeneous catalytic systems led to new polyolefin materials with novel characteristics.¹ In this context, hyperbranched polyethylenes have unique chain architectures that confer distinctive physical properties (*e.g.* low viscosity, good solubility), which could be used in specialty applications such as lubricants.² We have been developing Ni(II) complexes with bulky 2-iminopyrrolyl ligands to be applied as aluminium-free catalysts in the polymerization of ethylene. The catalytic tests performed revealed the PE products obtained are highly branched, exhibiting up to 160-170 branches/1000C, which are values higher than the ones reported for similar systems.³



e.g. $R_1 = C_6H_5$; 3,5-Me₂C₆H₃; 3,5-(CF₃)₂C₆H₃; 2,4,6-*i*Pr₃C₆H₂; CH(C₆H₅)₂; C₃H₇ $R_2 = 2,6-Me_2$; 2,6-*i*Pr₂

Acknowledgements

Support for this work was provided by FCT through UID/QUI/00100/2013 and RECI/QEQ-QIN70189/2012. C.A. Figueira acknowledges financial support from SFRH/BPD/112340/2015, P.S. Lopes acknowledges financial support from SFRH/BD/88639/2012 and C.S.B. Gomes acknowledges financial support from SFRH/BPD/107834/2015.

References

- [1] H. Mu, L. Pan, D. Song, Y. Li, *Chem. Rev.* 115 (2015) 12091.
- [2] Z. Dong, Z. Ye, *Polym. Chem.* 3 (2012) 286.
- [3] (a) D. Zhang, E.T. Nadres, M. Brookhart, O. Daugulis, *Organometallics* 32 (2013) 5136; (b) T.J. Marks, *ACS Catal.* 4 (2014) 999.

Polymer-based sensors for detecting explosives vapours

Liliana M. Martelo^{1,2*}, Tiago Neves², Lino Marques², Joana Farinhas³, Ana Charas³,
Mário N. Berberan-Santos¹ and Hugh D. Burrows²

¹ *Centro de Química-Física Molecular (CQFM) and the Institute of Nanotechnology (IN), Instituto Superior Técnico, University of Lisbon, 1049-001 Lisbon, Portugal*

² *Department of Chemistry and Institute of Systems and Robotics (IRS), University of Coimbra, 3004-535 Coimbra, Portugal*

³ *Instituto de Telecomunicações (IT), Instituto Superior Técnico, University of Lisbon, 1049-001 Lisbon, Portugal*

* Corresponding author. E-mail: liliana.martelo@ist.utl.pt

Current security and environmental concerns have forced the development of new devices capable of rapid and cost-effective detection of explosives. These sensors must fulfill a number of criteria, namely sensitivity, reversibility and capability for real-time signal processing. For nitroaromatic explosives, sensing of a few parts per billion or less of the analyte vapour is required, with rapid and ideally reversible changes in the sensor. For in-field applications, a portable system would be advantageous. Conjugated polymers (CP) have emerged as a promising chemosensory material for detecting nitroaromatic explosive vapours, as they readily transform a chemical interaction into an easily measured optical output with high sensitivity. The explosive vapour analyte consist of nitrated molecules which are strongly electron-deficient, while the conjugated polymer sensing materials are electron-rich. As a result, photoexcitation of the conjugated polymer is followed by electron transfer to the explosive vapour, leading to quenching of the light-emission from the conjugated polymer.

The best conjugated polymer in our studies was found to be poly[(9,9-dioctylfluorene-2,7-diyl)-co-bithiophene] (PF2T). This is stable, has a good absorption between 400 and 450 nm, a strong and structured fluorescence around 550 nm, and up to 96 % quenching of fluorescence, accompanied by decrease in fluorescence lifetimes, is seen on exposure of films of PF2T in ethylcellulose to nitrobenzene (NB) or 1,3-dinitrobenzene (DNB) vapours. The effect of matrix, plasticizer and temperature has been studied, and the morphology of films determined by scanning electron microscopy (SEM) and confocal fluorescence microscopy. We also used the ink jetting technology to design this sensor. In addition, a high dynamic range, intensity-based fluorometer, using a laser diode and a filtered photodiode has been developed for use with this system.

Recently we have been working on insoluble patterns of cross-linkable poly[(9,9-dioctyl)-alt-bithiophene] (PF8T2). The columnar, spike and porous structures obtained leads to a significantly improvement in the TNT-like compounds detection.

Acknowledgements

L. Martelo acknowledges financial support from FCT through SFRH/BPD/121728/2016.

Green synthesis of nuclear heterocyclic cores by oxidative coupling using laccases as biocatalysts

Ana Catarina Sousa^{a,b}, Lígia O. Martins^c, Maria Paula Robalo^{a,b}

^a *Área Departamental de Engenharia Química, Instituto Superior de Engenharia de Lisboa, Instituto Politécnico de Lisboa, 1959-007 Lisboa, Portugal*

^b *Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal*

^c *Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, 2780-15 Oeiras, Portugal*

E-mail: acsousa@deq.isel.ipl.pt

Nowadays is widely accepted that the development of strategies to enhance the greenness in chemical synthesis is an imperative way to follow in order to face the current environmental challenges. Different chemical industries, including pharmaceutical, have heavily invested in the design of new pathways and technologies towards the development of green catalytic protocols to produce more safety compounds with both environmental and economic benefits. Over the past decade, an increasing number of organic synthetic chemists have used biocatalytic steps in their synthetic schemes in order to overcome the use of more toxic solvents and reagents.¹ Biocatalysis have been highlighted as an important alternative to the conventional chemical synthetic routes. Enzymes are biological catalysts that have emerged in green chemistry due to their ability to catalyse reactions with high efficiency and specificity, operating in milder reaction conditions and using water as solvent. Within the various classes of available enzymes, laccases (EC 1.10.3.2) promote the oxidation of a wide range of substituted phenols and anilines derivatives, leading to the formation of value-added heterocyclic cores presented in several scaffolds of biological active molecules. Herein we report the biotransformation of different substituted aromatic amines, conducting to the formation of nuclear heterocyclic cores such as phenazines, phenoxazinones, acridines and naphotoquinones mediated by laccases.^{2,3} The target products were produce in good to moderated yields and short reaction times in a process that uses molecular oxygen as the oxidizing agent and produces water as the only by-product, showing clearly environmental advantages.

Acknowledgements

Support for this work was provided by FCT through Projects PTDC/BBB-EBB/0122/2014, IUD/QUI/00100/2013 and REM2013. Authors also thank to the IST-UTL NMR and MS networks for facilities.

References

- [1] F. Hollmann, I.W.C.E. Arends, K. Buehler, A. Schallmeyer, B. Buhler, *Green Chem.* 13 (2011) 226-265.
- [2] A.C. Sousa, M.C. Oliveira, L.O. Martins, M.P. Robalo, *Green Chem.* 16 (2014) 4127-4136.
- [3] A.C. Sousa, M.F.M. Piedade, L.O. Martins, M.P. Robalo, *Green Chem.* 17 (2015) 1429-1433.

Stability Scope of the Boronic Acid Salicylidene Hydrazone (BASHY) Fluorescent Dye Platform

Cátia Parente Carvalho, Fábio M. F. Santos, Pedro M. P. Gois

iMed.UL, Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal

The quest for flexible and modular approaches that enable the construction of electronically tunable and environmentally responsive fluorophore platforms is vital for the development of functional dyes for bioimaging, sensing, and probing applications.^{1,2} Very recently, our group disclosed a new family of modular photostable fluorescent dyes [boronic acid salicylidene hydrazone (BASHY)], obtained by the assembly of structurally diverse boronic acids with Schiff base ligands.³ As a result, BASHY fluorescent dyes already emerged as a powerful tool for site-selective live cell bioimaging.⁴ Herein our interest focus a dye synthetic scope in order to unveil the best structural core for biological conditions (Figure 1). By varying the BASHY core we expect to obtain distinct stability properties that will be discussed in detail.

$X = \text{H}, \text{CH}_3, \text{CH}_2\text{CH}_3, \text{CH}(\text{CH}_3)_2, \text{C}(\text{CH}_3)_3, \text{C}_6\text{H}_6$

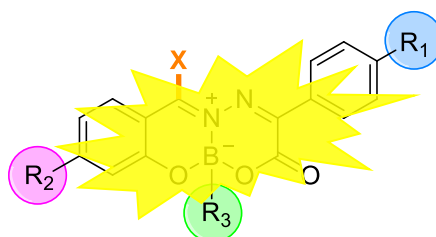


Figure 1. Chemical Structure of the BASHY Platform.

Acknowledgements

Support for this work was provided by FCT through PTDC/QEQMED/5512/2014, PTDC/QEQ-QOR/1434/2014, UID/DTP/04138/2013, SAICTPAC/0019/2015 and SFRH/BPD/115442/2016.

References

- [1] J. Yin, Y. Hu, J. Yoon, *Chem. Soc. Rev.* 44 (2015) 4619.
- [2] L.D. Lavis, R.T. Raines, *ACS Chem. Biol.* 9 (2014) 855.
- [3] F.M.F. Santos, J.N. Rosa, N.R. Candeias, C.P. Carvalho, A.I. Matos, A.E. Ventura, H.F. Florindo, L. Silva, U. Pischel, P.M.P. Gois, *Chem. Eur. J.* 22 (2016) 1631.
- [4] P.M.S.D. Cal, F. Sieglitz, F.M.F. Santos, C.P. Carvalho, A. Guerreiro, J.B. Bertoldo, U. Pischel, P.M.P. Gois, G.J.L. Bernardes, *Chem. Commun.* 53 (2017) 368.

Cationic indenyl-nickel complexes bearing a 1,5-cyclooctadiene ligand: Synthesis and characterization

Clara S. B. Gomes, Sandra I. Costa, Luís F. Veiros, Pedro T. Gomes

*Centro de Química Estrutural, Departamento de Engenharia Química,
Instituto Superior Técnico, Universidade de Lisboa, Portugal*

The synthesis of neutral and cationic nickel(II) complexes bearing alkene, N-, O-, and P-ligands and their application in catalysis, especially in the oligomerization and polymerization of olefins has been a focus of great interest in the last decades, both in academia and industry.¹

Recently, we described a novel methodology for the synthesis of new neutral $[(\eta\text{-R-Ind})\text{Ni}(\text{EPh}_3)\text{X}]$ and cationic $[(\eta\text{-R-Ind})\text{Ni}(\text{EPh}_3)_2]\text{BF}_4$ indenyl nickel complexes, containing neutral AsPh_3 or SbPh_3 donor ligands, the resulting complexes acting as very efficient catalysts for the oligomerization of styrene.²

The results obtained prompted us to investigate the versatility of this new synthetic method and, consequently, the possibility of its extension to the preparation of new indenyl-nickel derivatives containing other type of ligands. One of such ligands is the neutral 1,5-cyclooctadiene (COD), which coordinates to metals in a bidentate fashion via both alkene groups. Metal-COD complexes are attractive because they are sufficiently stable to be isolated, and are often more robust than the related ethylene complexes, their stability being attributed to the chelate effect.

Herein, we report the synthesis and full characterization of the new cationic 1-R-indenyl-nickel complexes (R = H, Me), containing 1,5-cyclooctadiene as donor ligand and BF_4^- as counterion (Figure 1). DFT studies were also performed in order to investigate the dynamic behavior observed by ^1H NMR spectroscopy.

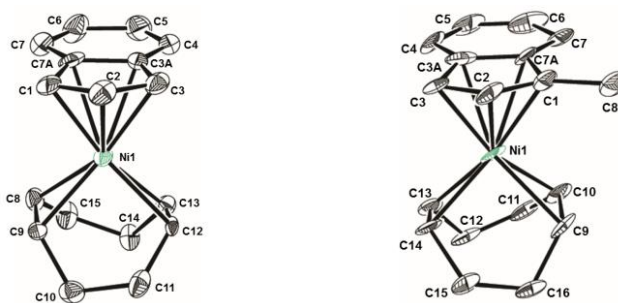


Figure 1. Molecular structures of cationic 1-R-indenyl-nickel complexes (a) **1** and (b) **2**. All hydrogen atoms and the counteranions were omitted for clarity.

Acknowledgements

Support for this work was provided by FCT through UID/QUI/00100/2013. C.S.B. Gomes acknowledges financial support from FCT (SFRH/BPD/107834/2015).

References

- [1] For example: R. Gao, W.-H. Sun, C. Redshaw, *Catal. Sci. Technol.* **3** (2013) 1172-1179.
- [2] C.S.B. Gomes, P. Krishnamoorthy, L.C. Silva, S.I. Costa, P.T. Gomes, M. Jiménez-Tenorio, P. Valerga, M.C. Puerta, *Dalton Trans.* **44** (2015) 17015-17019.

Search for Green Solvents for Cyclohexane Oxidation

Ana P. C. Ribeiro, Manas Sutradhar, M. Fátima C. Guedes da Silva, António M. F. Palavra
and Armando J. L. Pombeiro

Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa,
Av. Rovisco Pais, 1049-001 Lisboa, Portugal

E-mail: apribeiro@tecnico.ulisboa.pt

The catalytic activities of three *cis*-dioxidomolybdenum(VI) complexes with aroylhydrazone Schiff bases were examined towards cyclohexane (CyH) oxidation¹ and compared in CH₃CN, ionic liquid (1-butyl-3-methylimidazolium hexafluorophosphate, [bmim][PF₆]), supercritical carbon dioxide (scCO₂), and scCO₂/[bmim][PF₆] mixed solvent. Comparison in yields, selectivity and recyclability (Figure 1) for the three complexes will be discussed and the effects of solvents compared. Discussion of the previous application of the same media to cyclohexane oxidation in Industry will also be addressed.

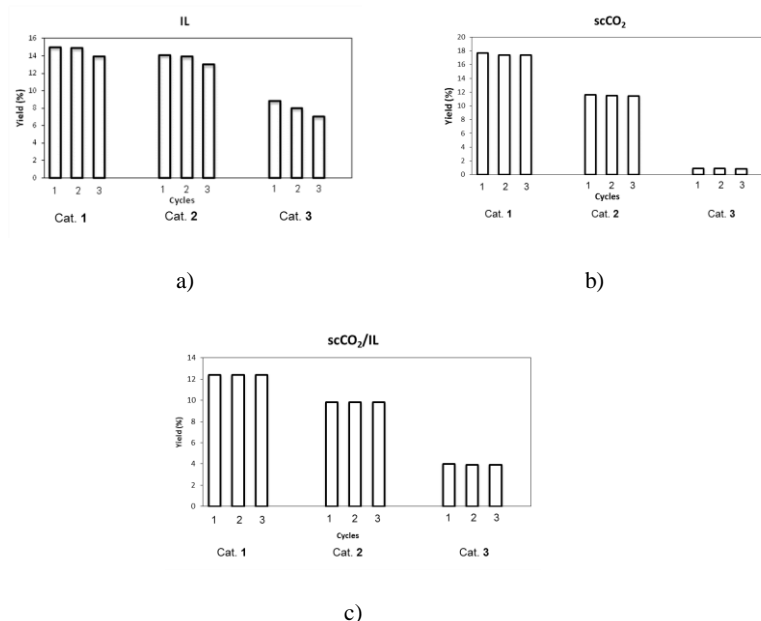


Figure 1. Product yield upon catalyst recycling in: **a)** ionic liquid (IL) [reaction time: 10 h]; **b)** scCO₂ [$p(\text{CO}_2)=110$ bar and 10 h of reaction time] and **c)** scCO₂/IL [$p(\text{CO}_2)=110$ bar and 9 h of reaction time].

Acknowledgements

Financial support from FCT, Portugal, for fellowships SFRH/BPD/86067/2012 to M. Sutradhar and SFRH/BPD/90883/2012 to A.P.C. Ribeiro, and for the UID/QUI/00100/2013 and PTDC/QEQ-QIN/3967/2014 projects are gratefully acknowledged.

References

[1] S. Hazra, A.P.C. Ribeiro, M.F.C. Guedes da Silva, C.A. Nieto de Castro, A.J.L. Pombeiro, Dalton Trans. 45 (2016) 13957-13968.

Novel Magnetic Scorpionate Ligands: A Sustainability Improvement

Marta R. Alexandre^a, Inês Matias^a, Ana P. C. Ribeiro^a, Elisabete C. B. Alegria^{a,b},
A. J. L. Pombeiro^a, Luísa M. D. R. S. Martins^{a,b}

^a Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal

^b Chemical Engineering Department, Instituto Superior de Engenharia de Lisboa, Instituto Politécnico de Lisboa, Rua Conselheiro Emídio Navarro, 1959-007 Lisboa, Portugal

E-mail: lmartins@deq.isel.ipl.pt

Despite the sustainability improvement of industrial oxidation processes remains a challenge, some catalytical systems, such as the C-scorpionate complexes, had showed a good performance on C-H bond activation.¹ An important requirement for a suitable catalyst is its recyclability, enabling its use in consecutive cycles.²

Herein we report the synthesis of novel magnetic scorpionate ligands (MScorp) which are easily removed from the reaction medium with a magnet. The MScorp are prepared by a microwave-assisted method, providing a sustainable alternative method for producing magnetic ferrite based materials. This method has significant advantages over the conventional current impregnation processes in terms of safety, simplicity, energy saving, time consuming and economical and environmental concerns.³ Experimental parameters, such as temperature, time and irradiation power were optimized. The as-prepared MScorp were characterized by elemental analysis, magnetic susceptibility, SEM and TEM.

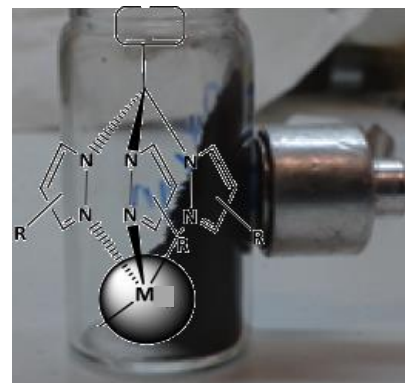


Figure 1. MScorp ligands.

Acknowledgements

Funding from FCT (Fundação para a Ciência e a Tecnologia), Portugal (UID/QUI/00100/2013, PTDC/QEQ-ERQ/1648/2014 and PTDC/QEQ-QIN/3967/2014 projects). A.P.C. Ribeiro also acknowledges FCT for the SFRH/BPD/90883/2012 grant.

References

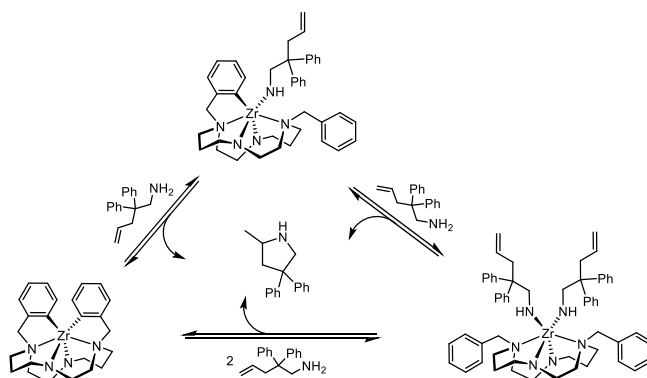
- [1] L.M.D.R.S. Martins, A.J.L. Pombeiro, *Eur. J. Inorg. Chem.* (2016) 2236-2252.
- [2] A.P.C. Ribeiro, L.M.D.R.S. Martins, M.L. Kuznetsov, A.J.L. Pombeiro, *Organometallics* 36 (2017) 192-198.
- [3] a) M.M. Cruz, R.P. Borges, M. Godinho, C.S. Marques, E. Langa, A.P.C. Ribeiro, M.J.V. Lourenço, F.J.V. Santos, C.A. Nieto de Castro, M. Macatrão, M. Tariq, J.M.S.S. Esperança, J.N. Canongia Lopes, C.A.M. Afonso, L.P.N. Rebelo, *Fluid Phase Equilibria* 350 (2013) 43-50; b) L.M.D.R.S. Martins, A.J.L. Pombeiro, *Coord. Chem. Rev.* 265 (2014) 74-88.

Synthesis of biologically relevant azarings by intramolecular hydroamination catalysis

Luis G. Alves, Filipe Madeira, Luis F. Veiros, Ana M. Martins

Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Portugal

Hydroamination is an atom-efficient procedure for the formation of carbon-nitrogen bonds through inter- or intramolecular addition of an amine to a carbon-carbon unsaturated bond. This process may be particularly useful and important as a single step procedure for the synthesis of nitrogen heterocycles, which are the main cores of important natural and/or synthetic alkaloid substructures. Although enthalpically favoured, the negative entropy balance of the reaction requires that a catalyst activates the carbon-carbon bond and/or the amine for the coupling process. Cationic Zr and Ti complexes were found to catalyze the hydroamination of secondary aminoalkenes, while neutral Group 4 metal compounds were used for primary aminoalkenes.¹ In this communication, we present the intramolecular hydroamination of aminoalkenes using a new class of zirconium catalyst precursors supported by dianionic *trans*-disubstituted cyclams. The ancillary ligand evidenced hemilabile behaviour² and ability to activate C-H bonds³. Both properties play a prominent role in catalysis.⁴ The synthesis of 2-methyl-4,4-diphenylpyrrolidine shown in Scheme 1 is a proof of concept that will be further explored.



Scheme 1

Acknowledgements

Support for this work was provided by FCT through UID/QUI/00100/2013.

L.G. Alves and F. Madeira acknowledge financial support from SFRH/BPD/86815/2012 and SFRH/BD/87679/2012, respectively.

References

- [1] T.E. Müller, K.C. Hultsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* 108 (2008) 3795-3892.
- [2] L.G. Alves, F. Madeira, R.F. Munhá, S. Barroso, L.F. Veiros, A.M. Martins, *Dalton Trans.* 44 (2015) 1441-1455.
- [3] R.F. Munhá, M.A. Antunes, L.G. Alves, L.F. Veiros, M.D. Fryzuk, A.M. Martins, *Organometallics* 29 (2010) 3753-3764.
- [4] a) L.G. Alves, F. Madeira, L.F. Veiros, A.M. Martins, *unpublished results*. b) M.A. Antunes, R.F. Munhá, L.G. Alves, L.L. Schafer, A.M. Martins, *J. Organomet. Chem.* 696 (2011) 2-6.

Synthetic transformations of oleuropein

Lídia A. S. Cavaca^{a,b}, Catarina A. B. Rodrigues^a, Svilen P. Simeonov^c,
Carlos A. M. Afonso^a

^a Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, Universidade de Lisboa,
Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal

^b Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa,
2829-516 Caparica, Portugal

^c Institute of Organic Chemistry with Centre of Phytochemistry Bulgarian Academy of Sciences,
Acad. G. Bonchev str., bl. 9, 1113 Sofia, Bulgaria

Olive tree (*O. europaea*) is a natural source of oleuropein (Figure 1), a secoiridoid present only in plants from *Oleaceae* family. Although it can be found in fruits and small branches, oleuropein is present in higher amounts in olive leaves, which are considered a cheap and easily available source of oleuropein, since are industrial by-products with no practical applications.¹ Oleuropein has potent biological and pharmaceutical properties: anticancer, cardioprotective, neuroprotective, gastroprotective, anti-diabetes and anti-obesity, in large part attributed to its antioxidant and anti-inflammatory effects.²

Extraction and analytical methods have been developed and widely reported for qualitative and quantitative studies of olive polyphenols, including oleuropein. Published transformations of oleuropein are generally related to the removal of hydroxytyrosol and glucoside moieties. Since few research has been done at this level ³, we will describe the synthesis of new scaffolds from oleuropein at the level of elenolic acid unit, through semi-synthetic transformations.

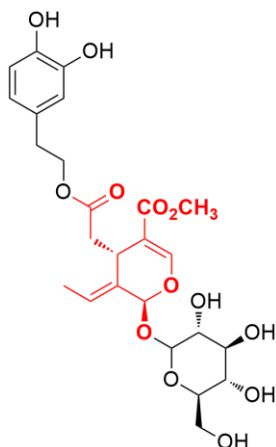


Figure 1. Molecular structure of oleuropein. Elenolic acid unit highlighted (red).

Acknowledgements

The authors acknowledge the Fundação para a Ciência e a Tecnologia (FCT) (ref. SFRH/BPD/109476/2015 and UID/DTP/04138/2013), and the European Research Area Network; ERANet LAC (ref. ELAC2014/BEE-0341) for financial support.

References

- [1] M.L. de Castro, R. Japón-Luján, *Trend. Anal. Chem.* 25 (2006) 501-510.
- [2] I. Hassen, H. Casabianca, K. Hosni, *J. Funct. Foods.* 18 (2015) 926-940.
- [3] L. Abaza, A. Taamalli, H. Nsir, M. Zarrouk, *Antioxidants* 4 (2015) 682-698.

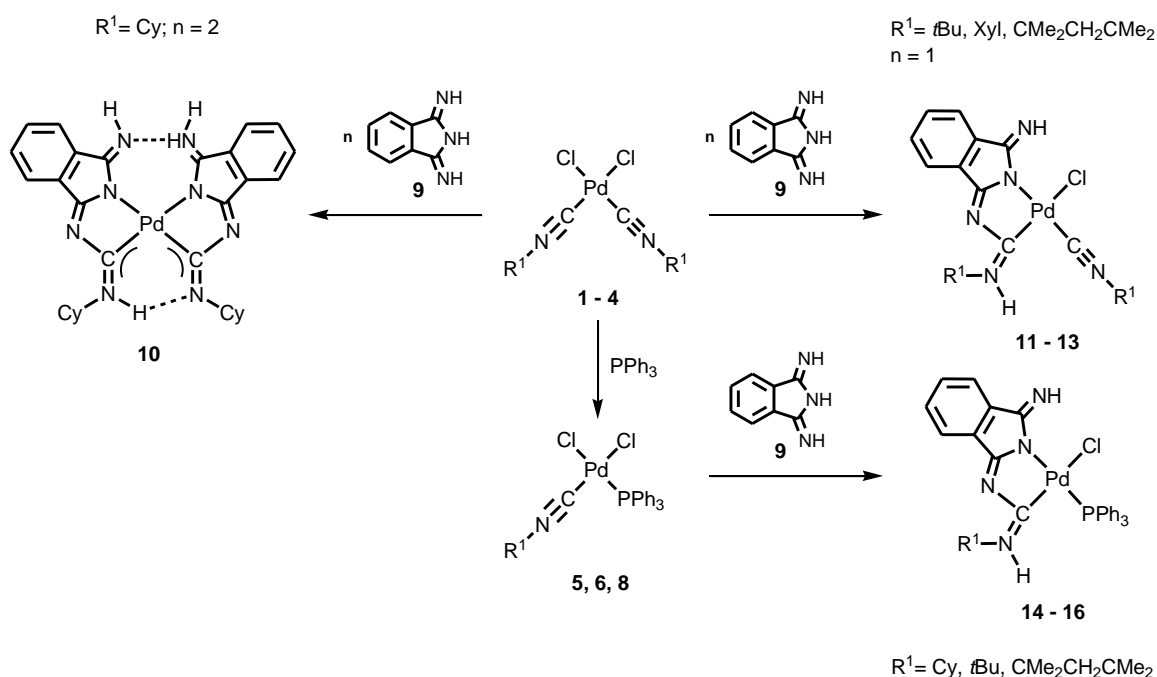
Novel palladium-aminocarbene species derived from
metal-mediated coupling of isonitriles and 1,3-diiminoisoindoline

Rogério S. Chay^a, Konstantin V. Luzyanin^b, Armando J. L. Pombeiro^a

^a Centro de Química Estrutural, Complexo I, Instituto Superior Técnico, Universidade de Lisboa,
Av. Rovisco Pais, 1049-001 Lisbon, Portugal

^b Department of Chemistry, University of Liverpool, Crown Street, Liverpool L69 7ZD, United Kingdom

Metal-mediated coupling of isonitrile in cis-[PdCl₂(C≡NR¹)₂] [R¹ = Cy **1**, Bu^t **2**, Xyl **3**, CMe₂CH₂CMe₂ **4**] with one or two equivalents of 1,3-diiminoisoindolinone, HN=CC₆H₄C=NHNH **9**, accomplish aminocarbene species [Pd{C(N=C(C₆H₄CNHN))=N(H)Cy}₂] (**10**) and [PdCl{C(N=C(C₆H₄CNHN))=N(H)R¹}(CNR¹)] (**11-13**). Reaction of formulae of **5,6,8** with **9** provides [PdCl{C(N=C(C₆H₄CNHN))=N(H)R¹}(PPh₃)] (**14-16**) (Scheme 1)¹.



Scheme 1.

These novel type of carbene ligands (**10-16**) were isolated in good yields (80-90%) and characterized by elemental analyses (C, H, N), ESI⁺-MS, IR, 1D (¹H, ¹³C{¹H}) and 2D (¹H,¹H-COSY, ¹H,¹³C-HMQC/¹H,¹³C-HSQC, ¹H,¹³C-HMBC) NMR spectroscopies.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. R.S. Chay acknowledges financial support from SFRH/BD/90280/2012. The authors are grateful to Portuguese NMR (grant NRNNM2013) and MS (IST Node, grant REM 2013 da FCT) networks.

References

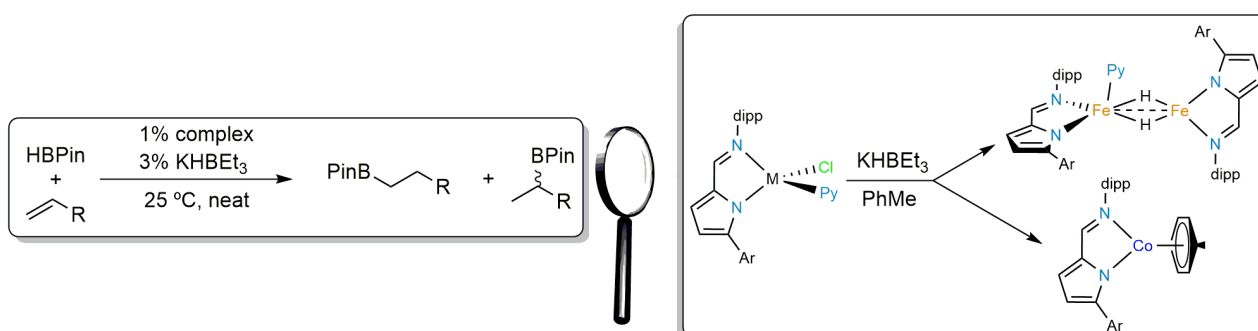
- [1] R.S. Chay, K.V. Luzyanin, V.Y. Kukushkin, M.F.C. Guedes da Silva, A.J.L. Pombeiro, *Organometallics* 31 (2012) 2379-2387.

Iron and cobalt complexes of 5-aryl-2-iminopyrrolyl relevant to the catalytic hydroboration of terminal alkenes

Tiago F. C. Cruz, Pedro T. Gomes

Centro de Química Estrutural, Instituto Superior Técnico, Lisbon, Portugal

Hydroboration is a viable route to organoboron compounds that are widely used in organic synthesis.¹ The development of hydroboration catalysts of cheap and abundant metals is still a relatively unexplored area.² As such, families of Fe(II) and Co(II) complexes of 5-aryl-2-iminopyrrolyl ligands have been prepared and characterized, which have been applied as precatalysts for the hydroboration of terminal alkenes with pinacolborane, upon activation by KHBET_3 . A set of stoichiometric experiments of the precursor complexes with KHBET_3 revealed that the Co system generates a low valent arene complex, whereas the Fe system forms a hydride species.



Acknowledgements

Support for this work was provided by FCT through UID/QUI/00100/2013.

T.F.C. Cruz acknowledges financial support from PD/BD/52372/2013 (CATSUS PhD program).

References

- [1] V.P. Ananikov, M. Tanaka, *Hydrofunctionalization*, Vol. 43, Springer, 2013.
- [2] J.V. Obligacion, P.J. Chirik, *Org. Lett.* 15 (2013) 2680-2683.

Catalytic performance of a new copper-phthalocyanine dye

Roberto Giacomantonio^{a,b}, Leandro M. O. Lourenço^c, M.F.C. Guedes da Silva^a,

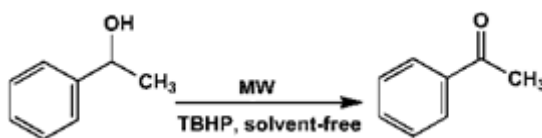
Armando J. L. Pombeiro^a, Corrado Bacchiocchi^b, Ana P. C. Ribeiro^a, João P. C. Tomé^a

^a Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa 1049-001 Lisboa, Portugal

^b School of Sciences and Technology, University of Camerino, I-62032 Camerino (MC), Italy

^c QOPNA e Departamento de Química, Universidade de Aveiro, 3810-193 Aveiro, Portugal

Multi-substituted Pc dyes have also been prepared to be used as (photo)active molecules in more complex materials, such as coordination polymers.¹ This work aims to study the catalytic performance of a new copper(II) tetra-substituted mercaptopyridine-phthalocyanine in the oxidation of alcohols. In particular, 1-phenylethanol to acetophenone (Scheme 1) was chosen as a model reaction to check and compare the catalytic activity and recyclability of the prepared catalysts in view of the generality and wide application of the alcohol oxidation reaction.² The differences in the catalytic activity, under several reaction conditions, of the new copper(II) tetra-substituted mercaptopyridine-phthalocyanine are discussed.



Scheme 1. Oxidation of 1-phenylethanol to acetophenone.

Acknowledgements

Thanks are due to FCT/MEC for the financial support to CQE (FCT UID/QUI/00100/2013, PTDC/QEQ-ERQ/1648/2014 and PTDC/QEQ-QIN/3967/2014 projects) and QOPNA (FCT UID/QUI/00062/2013) research units, through national funds and where applicable co-financed by the FEDER, within the PT2020 Partnership Agreement. L.M.O. Lourenço thanks to the project PTDC/QEQ-SUP/5355/2014. A.P.C. Ribeiro also acknowledges FCT for the SFRH/BPD/90883/2012 grant.

References

- [1] a) L. Fernández, V.I. Esteves, Â. Cunha, R.J. Schneider, J.P.C. Tomé, J. Porphyrins Phthalocyanines 20 (2016) 1; b) K.M. Kadish, K.M. Smith, R. Guilard (Eds.), Handbook of Porphyrin Science, World Scientific, volume 1; c) Q. Liang, M. Zhang, Z. Zhang, C. Liu, S. Xu, Z. Li, J. Alloys Compd. 690 (2017) 123.5336.
- [2] M.N. Kopylovich, A.P.C. Ribeiro, E.C.B.A. Alegria, N.M.R. Martins, L.M.D.R.S. Martins, A.J.L. Pombeiro, Adv. Organomet. Chem. 63 (2015) 91.

Exploring Ionic Liquid-based Materials

I. M. Marrucho, L. C. Tomé, D. J. S. Patinha, C. Florindo, F. Lima, M. Marchel,
A. Gouveia

*Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Avenida Rovisco Pais,
1049-001 Lisboa, Portugal*

The challenge of today's chemical engineers is to continuously meet society's demands for new high performing products that have increased benefit and fewer detrimental effects on environment, at an acceptable cost. Green Chemistry has stepped up as the new, simple and intuitive tool that enables the development of sustainable solutions that meet these criteria. Triggered by increased regulations on pollution and environmental performance and rolled-out between the constant struggle attain different criteria, such as waste generation, cost effectiveness, high performance and the use of materials from renewable resources, Green Chemistry has been viewed by many as the modern chemical engineering.

Separation processes have a great importance in a wide variety of industries. Although the reactor is the heart of the chemical plant, in most cases, 60-80% of the total cost is taken up by the separation/purification steps. These steps usually involve one or more separation processes such as distillation, extraction, absorption, crystallization, adsorption, membrane processes, etc., which are used to obtain the products at the required purity. It is, therefore, necessary to provide alternative smart solvents or other task specific materials that might afford economically optimized processes, in sum better products at lower prices. Ionic liquid (IL)-based materials have been gaining relevance in the field of separation through their application in the re-design of the technological basis of variety of approaches, showing remarkable versatility.

In this work, the use of IL-based materials in the development of better separation processes will be highlighted through the presentation of two distinct separation processes, liquid-liquid extractions and gas separation using membranes. The choice of these two applications intends to illustrate how versatile ionic liquid-based materials can be, providing innovative separation schemes through the full use of their tunability, either in terms of their chemical functionalities or even in terms of their mechanical properties through the use of polymeric ILs.

Acknowledgements

L.C. Tomé, D.J.S. Patinha, C. Florindo, M. Marchel, F. Lima and A. Gouveia are grateful to FCT for the research grants SFRH/BPD/101793/2014, SFRH/BD/97042/2013, SFRH/BD/102313/2014, PD/BD/114041/2015, PD/BDE/114355/2016 and SFRH/BD/116600/2016, respectively.

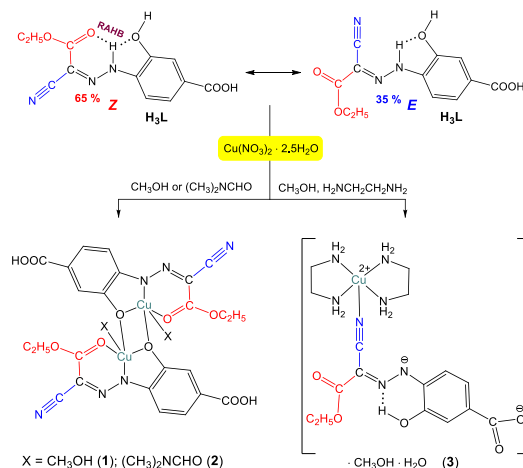
Copper(II) complexes bearing arylhydrazone ligands: cooperative coordination/ionic interactions and catalysts for cyclohexane oxidation
 Nuno M. R. Martins^a, Kamran T. Mahmudov^{a,b}, Luísa M. D. R. S. Martins^{a,c},
 M. Fátima C. Guedes da Silva^a, Armando J. L. Pombeiro^a

^a Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisbon, Portugal

^b Department of Chemistry, Baku State University, Z. Xalilov Str. 23, Az 1148 Baku, Azerbaijan

^c Chemical Engineering Department, ISEL, R. Conselheiro Emídio Navarro, 1959-007 Lisboa, Portugal

The aquasoluble $[\text{Cu}(\text{1}\kappa\text{N}, \text{O}^2\text{:2}\kappa\text{O-HL}^1)(\text{S})_2]$ [$\text{S} = \text{CH}_3\text{OH}$ (**1**), $(\text{CH}_3)_2\text{NCHO}$ (**2**)] and $[\text{Cu}(\kappa\text{N-HL}^1)(\text{en})_2]\cdot\text{CH}_3\text{OH}\cdot\text{H}_2\text{O}$ (**3**) Cu^{II} complexes were prepared by reaction of Cu^{II} nitrate hydrate with the new (*E/Z*)-4-(2-(1-cyano-2-ethoxy-2-oxoethylidene)hydrazinyl)-3-hydroxybenzoic acid (**H₃L**), in the absence (for **1** and **2**) or presence (for **3**) of ethylenediamine (en). Complexes **1–3** were fully characterized. Cooperative *E,Z* → *E* isomerization of **H₃L**, induced by coordination and ionic interactions, occurs upon interaction with Cu^{II} in the presence of en. Solvent-free microwave (MW) assisted production of cyclohexanone and cyclohexanol from cyclohexane using **1–3** as catalyst precursors was performed. The effects of various reaction parameters (temperature, time, influence of acid promoter) are studied allowing to achieve yields up to 17 % (TONs value of 86).



Scheme 1. *E/Z* isomerization in arylhydrazone ligand leading to a variety of Cu^{II} complexes **1–3**.

Acknowledgements

This work has been supported by the FCT, Portugal (UID/QUI/00100/2013 and PTDC/QEQ-QIN/3967/2014). N.M.R. Martins is thankful to FCT for the CATSUS PhD programme (PD/00248/2012) and his fellowship (SFRH/BD/52371/2013). The authors acknowledge the Portuguese NMR Network (IST-UTL Centre) for access to the NMR facility, and the IST Node of the Portuguese Network of mass-spectrometry for the ESI-MS measurements.

References

- [1] K.T. Mahmudov, M.N. Kopylovich, A. Sabbatini, M.G.B. Drew, L.M.D.R.S. Martins, C. Pettinari, A.J.L. Pombeiro, *Inorg. Chem.* 53 (2014) 9946-9958.
- [2] K.T. Mahmudov, M.F.C. Guedes da Silva, M. Sutradhar, M.N. Kopylovich, F.E. Huseynov, N.T. Shamilov, A.A. Voronina, T.M. Buslaeva, A.J.L. Pombeiro, *Dalton Trans.* 44 (2015) 5602-5610.
- [3] M. Saha, K.M. Vyas, L.M.D.R.S. Martins, N.M.R. Martins, A.J.L. Pombeiro, S.M. Mobin, D. Bhattacharjee, K.P. Bhabak, S. Mukhopadhyay, *Polyhedron* 132 (2017) 53-63.

Catalytic effect of Fe(II)-scorpionate complexes towards cyclohexane oxidation in organic and ionic liquid solvents: a comparative study

Inês Matias^a, Ana P. C. Ribeiro^a, Elisabete C. B. A. Alegria^{a,b}, Tiago A. G. Duarte^a,
Armando J. L. Pombeiro^a and Luísa M. D. R. S. Martins^{a,b}

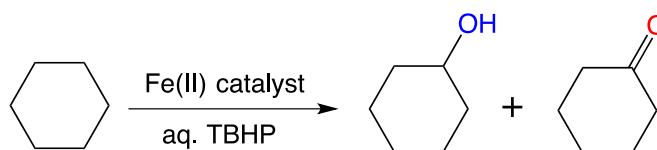
^a Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal

^b Chemical Engineering Department, Instituto Superior de Engenharia de Lisboa, Instituto Politécnico de Lisboa, Rua Conselheiro Emídio Navarro, 1959-007 Lisboa, Portugal

E-mail: lmartins@deq.isel.ipl.pt

The aim of this work was evaluating and compare the catalytic activity of the C-scorpionate iron(II) complex [FeCl₂{HC(pz)₃}] **1** (pz = pyrazol-1-yl) and of its precursor FeCl₂·2H₂O **2** towards cyclohexane oxidation with *tert*-butyl hydroperoxide (Scheme 1) in different media: acetonitrile and ionic liquids (1-butyl-3-methylimidazolium hexafluorophosphate, [bmim][PF₆], and 1-butyl-3-methylimidazolium tris(pentafluoroethyl)trifluorophosphate, [bmim][FAP]).

The use of such alternative solvents will be presented as well as how to tune the alcohol/ketone selectivity by choosing the suitable solvent.



Scheme 1. Peroxidative oxidation of cyclohexane.

Acknowledgements

Funding from FCT (Fundação para a Ciência e a Tecnologia), Portugal (UID/QUI/00100/2013, PTDC/QEQ-ERQ/1648/2014 and PTDC/QEQ-QIN/3967/2014 projects). A.P.C. Ribeiro also acknowledges FCT for the SFRH/BPD/90883/2012 grant.

References

- [1] A.P.C. Ribeiro, L.M.D.R.S. Martins, S. Hazra, A.J.L. Pombeiro, C. R. Chim. 18 (2015) 758.
- [2] L.M.D.R.S. Martins, A.P.C. Ribeiro, A.J.L. Pombeiro, Lett. Org. Chem 14 (2017).
- [3] A.P.C. Ribeiro, L.M.D.R.S. Martins, M.L. Kuznetsov, A.J.L. Pombeiro, Organomet. 36 (2017) 192.
- [4] M. Cruz, R.P. Borges, M. Godinho, C. Marques, E. Langa, A.P.C. Ribeiro, M.J. Lourenço, F. Santos, C. Nieto de Castro, M. Macatrão, M. Tariq, J. Esperança, J.N. Canongia Lopes, C. Afonso, L.P. Rebelo, Fluid Phase Equilibria 350 (2013) 43.

Integrating virgin cork chemical features in provenance selection

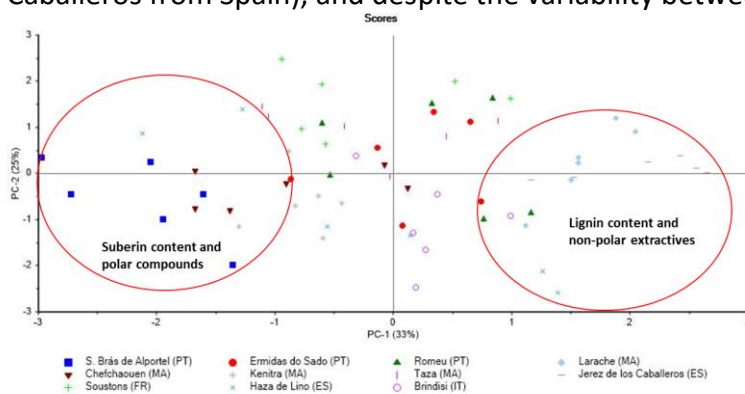
Vanda Oliveira, Isabel Miranda, Helena Pereira

Centro de Estudos Florestais, Instituto Superior de Agronomia, Universidade de Lisboa, Lisboa, Portugal

Cork, one of the main non-wood forest products in the world, is a major forest product in Portugal and the basis of an industrial cluster where the country has the world leading role. Cork is a cellular material known worldwide for “corking” wine bottles, with applications for vibrational and sound absorption, and as a thermal insulator.

The features of cork cellular structure and cell wall chemical composition are the basis of many of the material’s physical properties e.g. very low permeability, hydrophobic behaviour, large elastic compression and dimensional recovery.¹⁻² The distinctive features of cork are the presence of suberin as the main cell wall structural component, amounting on average to 43%, and of lignin with 22%.²⁻³ It is believed that the cell wall chemical composition plays a role in cork’s properties which should be related mostly to the combined presence of these two polymers.⁴ It is therefore of strategic importance, and was established in 3i9 Agenda, that the cork oak breeding and gene conservation strategies should integrate the evaluation of cork quality at young ages.

The study was conducted in using virgin cork samples from provenances trials that are part of a multi-locality provenance test belonging to a Euforgen Network, where 35 cork oak provenances (population of trees that come from a particular location) covering all the natural distribution range are represented.⁵ The samples were selected from 11 provenances from Portugal, Morocco, Spain, Italy and France. The cork samples were ground in a Retsch SK cutting mill, sieved and the 40-60 mesh fraction was kept for chemical analysis. Chemical summative analyses included determination of extractives, suberin, kason and acid soluble lignin. A principal component analysis was performed allowing to identify the provenances with higher suberin content (S. Brás de Alportel from Portugal and Chefchaouen from Morocco) in opposite to the provenances with higher lignin content (Jerez de los Caballeros from Spain), and despite the variability between trees.



Acknowledgements

Support for this work was provided by CEF, a research unit funded by FCT through UID/AGR/00239/2013. V. Oliveira acknowledges financial support from SFRH/BPD/118037/2016. The authors acknowledge Professor M. Helena Almeida for the cork material availability and as provenance trial coordinator.

References

- [1] H. Pereira, *Cork: Biology, Production and Uses*, Elsevier B.V. (Eds.), Amsterdam, 2007.
- [2] H. Pereira, *Bioresources* 10 (2015) 6207-6229.
- [3] H. Pereira, C. Baptista, *Holz Roh Werkst.* 51 (1993) 301-308.
- [4] H. Pereira, *BioResources* 8 (2013) 2246-2256.
- [5] M.C. Varela, *European network for the evaluation of genetic resources of cork oak for appropriate use in breeding and gene conservation strategies*, Handbook, Lisboa, 2000.

V(IV), Fe(II), Ni(II) and Cu(II) scorpionate complexes:
application as catalysts for the cyclooctane oxidation

Bruno G. M. Rocha^{a*}, Telma F. S. Silva^{a,b}, M. Fátima C. Guedes da Silva^a,
Luísa M. D. R. S. Martins^{a,c}, Armando J. L. Pombeiro^a

^a Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais,
1049-001, Lisboa, Portugal; *E-mail: bruno.g.m.rocha@tecnico.ulisboa.pt

^b Área Departamental de Física, Instituto Superior de Engenharia de Lisboa,
R. Conselheiro Emídio Navarro, 1959-007 Lisboa, Portugal

^c Área Departamental de Engenharia Química, Instituto Superior de Engenharia de Lisboa,
R. Conselheiro Emídio Navarro, 1959-007 Lisboa, Portugal

Water-soluble compounds $[\text{VOCl}_2\{\text{CH}_3\text{SO}_2\text{OCH}_2\text{C}(\text{pz})_3\}]$ (pz= pyrazol-1-yl) **1**, $[\text{FeCl}_2\{\text{CH}_3\text{SO}_2\text{OCH}_2\text{C}(\text{pz})_3\}]$ **2**, $[\text{NiCl}_2\{\text{CH}_3\text{SO}_2\text{OCH}_2\text{C}(\text{pz})_3\}]$ **3** and $[\text{Cu}\{\text{CH}_3\text{SO}_2\text{OCH}_2\text{C}(\text{pz})_3\}_2](\text{OTf})_2$ **4** were obtained by reactions between the corresponding metal salts and 2,2,2-tris(pyrazol-1-yl)ethyl methanesulfonate, $\text{CH}_3\text{SO}_2\text{OCH}_2\text{C}(\text{pz})_3$, thus contributing towards the expansion of the still scarcely explored coordination chemistry of such a type of C-functionalized scorpionate. In all, half- (**1–3**) or full-sandwich (**4**), compounds shows the tri-hapto N,N,N-coordinated mode of 2,2,2-tris(pyrazol-1-yl)ethyl methanesulfonate. **3** and **4** were the first examples of a Ni(II) and a full-sandwich Cu(II) compound respectively, bearing that scorpionate ligand.

Compounds **1–4** exhibit catalytic activity in the single-pot homogeneous cyclooctane oxidation, under mild conditions and with an environmentally friendly oxidant (H_2O_2), to the corresponding alcohol and ketone. The effect of the presence of additives, such as nitric acid or pyridine, was studied. The reactions proceed via radical mechanisms with involvement of both C-centred and O-centred radicals. While **3** is the first Ni(II) tris(pyrazol-1yl)methane type complex to be applied as catalyst for the oxidation of alkanes, **4** provides the best activity which is promoted in acidic medium reaching remarkable yields (based on the cyclooctane) up to *ca.* 27%.

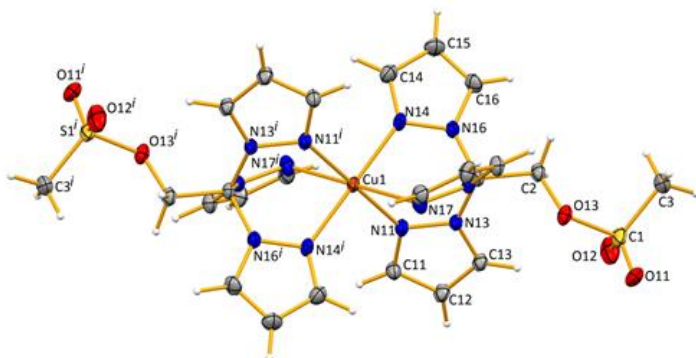


Figure 1. Thermal ellipsoid diagrams of complex **4** with atomic numbering schemes. Ellipsoids are drawn at 30% probability and the sulfonate counterions are omitted

Acknowledgements

This work has been supported by the Fundação para a Ciência e a Tecnologia (FCT), Portugal (FCT projects PEst-OE/QUI/UI0100/2013, UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013). B.G.M. Rocha is grateful to FCT for the PhD fellowship (SFRH/BD/52370/2013) of the CATSUS PhD program.

References

- [1] B.G.M. Rocha, T.F.S. Silva, M.F.C. Guedes da Silva, L.M.D.R.S. Martins, A.J.L. Pombeiro, *New J. Chem.* **40** (2016) 528-537.

**Life
&
Health**

Therapeutic delivery of CO: state-of-the-art

Carlos Romão

Alfama

The development of methods adequate to the *in vivo* and *in vitro* delivery of therapeutic amounts of Carbon Monoxide (CO) started with the use of metal carbonyls selected through educated guesses.

In spite of the remarkable utility of several of them, the need to improve the selectivity of CO delivery to target tissues under temporal-spatial control led to the development of a broad variety of CO releasing molecules and devices.

This highly imaginative evolution will be discussed in this presentation.

Polyurea Dendrimers as Nanocarriers for Ovarian Cancer Therapeutics

Vasco D. B. Bonifácio¹, Lawrence B. Mensah^{2,3}, Mohiuddin A. Quadir^{2,4}, Rita F. Pires¹, Aysen K. Richison², Paula T. Hammond²

¹Centro de Química-Física Molecular and Institute of Nanoscience and Nanotechnology, Instituto Superior Técnico, Universidade de Lisboa, Portugal

²The Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, USA

³Department of Chemical Engineering, Massachusetts Institute of Technology, USA

⁴Department of Coatings and Polymeric Materials, North Dakota State University, USA

Polyurea (PURE) dendrimers¹ are a new class of intrinsically fluorescent, biocompatible, pH responsive and biodegradable² polymers. PURE dendrimers have been used in a wide range of applications, both as sensors³ and drug⁴ and gene⁵ nanocarriers. To comprehensively evaluate the use of PURE dendrimers in ovarian cancer chemotherapy, we investigated the biological interaction of polyurea dendrimer PURE_{G4} and new generations PURE_{G5} and PURE_{G6} in the ovarian cancer cell line COV362 and in the normal fibroblast cell line NIH/3T3. We systematically conducted a panel of cell biological assays to explore the generation-dependent effects of PURE-type dendrimers on cell morphology, viability, proliferation, metabolic generation of reactive oxygen species, and modulation of key therapeutic biomarkers. For therapeutic applications, we show that through surface modification it is possible to render these dendritic structures to encapsulate and release *cis*-platin in a time-dependent manner and with high therapeutic efficacy.

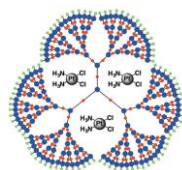


Figure 1. Schematic representation of a *cis*-platin encapsulated generation 6 polyurea dendrimer.

Acknowledgements

We thank the financial support from Fundação para a Ciência e a Tecnologia (FC&T, Portugal) through project PTDC/CTM/099452/2008 and from DoD OCRP TEAL grant. M.A. Quadir would like to thank a Misrock Foundation Fellowship.

References

- [1] R.B. Restani, P.I. Morgado, M.P. Ribeiro, I.J. Correia, A. Aguiar-Ricardo, V.D.B. Bonifácio, *Angew. Chem. Int. Ed.* 51 (2012) 5152-5155.
- [2] R.F. Pires, A. Moro, A. Lourenço, J.C. Lima, T. Casimiro, V.D.B. Bonifácio, *ChemistrySelect* 1 (2016) 6818-6822.
- [3] A. Bragança, M. Araújo, V.D.B. Bonifácio, *Part. Part. Syst. Charact.* 32 (2015) 98-103.
- [4] a) R.B. Restani, J. Conde, R.F. Pires, P. Martins, A.R. Fernandes, P.V. Baptista, V.D.B. Bonifácio, A. Aguiar-Ricardo, *Macromol. Biosci.* 15 (2015) 1045-1051; b) R.B. Restani, A.S. Silva, R.F. Pires, R. Cabral, I.J. Correia, T. Casimiro, V.D.B. Bonifácio, A. Aguiar-Ricardo, *Part. Part. Syst. Charact.* 33 (2016) 851-858.
- [5] R.B. Restani, J. Conde, P.V. Baptista, M.T. Cidade, A.M. Bragança, J. Morgado, I.J. Correia, A. Aguiar-Ricardo, V.D.B. Bonifácio, *RSC Adv.* 4 (2014) 54872-54878.

Liposomes as drug delivery system of fibrinolytic agents to blood clots

Marco M. Domingues¹, Patrícia M. Carvalho¹, Diogo Sequeira^{1,2}, Nuno C. Santos¹¹ Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Av. Prof. Egas Moniz, 1649-028, Lisboa, Portugal² Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Quinta da Torre, Campus Universitário, 2829-516, Caparica, Portugal

Cardiovascular diseases (CVDs) are the major cause of death worldwide, accounting for nearly one-third of deaths (World Health Organization data). Statistics indicate that CVDs are responsible for 45% of all deaths in Europe and 37% in the European Union (EU). There is increasing evidence for a consistent association between denser fibrin clot structure, and more resistant to degradation (fibrinolysis), with CVD and (athero)thrombotic disorders. Current therapy on fibrin clot degradation (fibrinolysis) has an increased bleeding risk, mainly cerebral haemorrhage. The aim of this project is to develop an encapsulated fibrinolytic therapeutic strategy with decreased bleeding risk, to be incorporated into the clot structure, and understand its impact on blood clot formation and lysis. Liposome nanoparticles have drawn significant interest as pharmaceutical drug carriers, due to their stability and content release in a controlled manner. To evaluate the impact of the drug delivery system on fibrin clot structure, without affecting its haemostasis properties, it is necessary to record clot polymerization and lysis kinetics in its absence and presence. Empty and undecorated liposome nanoparticles with two different PEGylated lipids do not interfere significantly in both fibrin polymerization and degradation with lipid increasing concentrations (Figure 1A-B). Furthermore, the liposome nanoparticles do not aggregate over time or change their surface charge for up to 30 days (Figure 1C-D). These results demonstrate that the liposome nanoparticles composition is adequate and functions as a stable formulation for thrombolytic encapsulation. Future work will focus on the optimization of the encapsulation of thrombolytic agent and surface decoration in the used lipid formulations, testing, respectively, the thrombolytic agent release kinetics and specific fibrin binding.

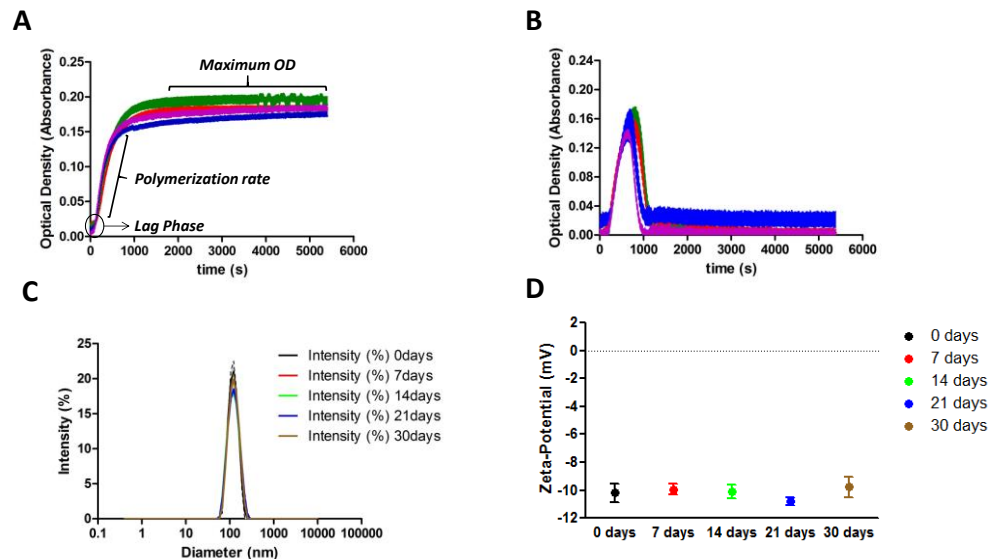


Figure 1. Liposome nanoparticle (POPC:Chol:DSPE-PEG-COOH (65:35:5)) effect on fibrin clot polymerization and lysis, and its stability measured by Dynamic Light Scattering and Zeta-Potential. **(A)** Turbidity curves of 1 experiment (representative of at least 3 independent experiments) at fibrinogen concentration of 0.5 mg/mL, 2.5 mM CaCl₂, and 0.1 U/mL thrombin in the presence of liposome nanoparticle concentration: 0 mM (red), 0.5 mM (green), 1 mM (blue) and 2 mM (purple); **(B)** Lysis curves of 1 experiment (representative of at least 3 independent experiments) at different liposome nanoparticle concentration (the same color scheme as above); **(C)** The liposome nanoparticle did not aggregate for 30 days; **(D)** The liposome nanoparticle did not modify surface charge for 30 days. The data represents one experiment from a triplicate. Similar results were obtained with empty and undecorated liposome nanoparticles of POPC:Chol:DSPE-PEG-Maleimide at the same lipid concentrations.

Acknowledgements

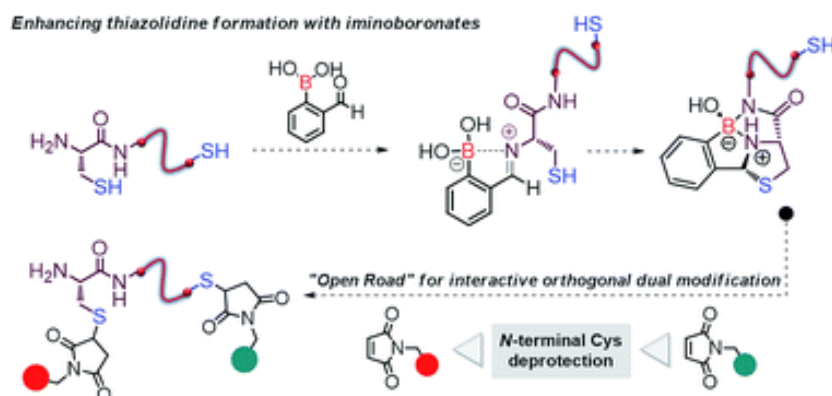
M.M. Domingues and P.M. Carvalho acknowledge financial support from FCT Individual Fellowships SFRH/BPD/122779/2016 and SFRH/BD/108077/2015, respectively.

Fast and dynamic *N*-Terminal Cysteine Functionalization with 2-Formylbenzeneboronic acids (2FBBA)

H. Faustino, M. J. S. A. Silva and P. M. P. Gois

Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal; E-mail: heliogaustino@ff.ul.pt

In recent years several methods for facile and selective modification of peptides and proteins were disclosed and become a powerful strategy to study fundamental biological processes, to construct therapeutics and functional hybrid materials without the need for more specialized techniques.^{1a} However, among these methods, those that can reversible on command are scarce.^{1b} Recently our group showed that 2-acetylbenzenoboronic acids (2ABBA) reversible functionalize protein exposed lysine residues *via* the formation of iminoboronates.² We envisioned that the condensation reaction of aldehydes with *N*-terminal Cys residues could also be significantly improved by generating a transient iminoboronate *en route* to the cyclization (Scheme 1).³ Herein we will demonstrate that this process is fast, selective for *N*-terminal Cys and results in the formation of thiazolidine constructs under mild aqueous conditions. These constructs can be easily reversed in the presence of benzyl hydroxylamine, leading to the deprotection of the *N*-terminal Cys. The dynamic nature of this system can be used to differentiate between in chain and *N*-terminal Cys residues allowing their selective modification with different maleimide probes (Scheme 1).



Scheme 2. Selective for *N*-terminal Cys modification with 2FBBA, allowing an interactive installation of two different maleimides.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. We thank the Fundação para a Ciência e Tecnologia for financial support through grants SFRH/BPD/102296/2014, PTDC/QEQMED/5512/2014, PTDC/QEQ-QOR/1434/2014, UID/DTP/04138/2013 and SAICTPAC/0019/2015.

References

- [1] a) O. Konievab, A. Wagner, Chem. Soc. Rev. 44 (2015) 5495; b) A. Wilson, G. Gasparini, S. Matile, Chem. Soc. Rev. 43 (2014) 1948.
- [2] a) P.M.S.D. Cal, J.B. Vicente, E. Pires, A.V. Coelho, L.F. Veiros, C. Cordeiro, P.M.P. Gois, J. Am. Chem. Soc. 134 (2012) 10299; b) P.M.S.D. Cal, R.F.M. Frade, V. Chudasama, C. Cordeiro, S. Caddick, P.M.P. Gois, Chem. Commun. 50 (2014) 5261; c) P.M.S.D. Cal, R.F.M. Frade, C. Cordeiro, P.M.P. Gois, Chem. Eur. J. 21 (2015) 8182.
- [3] H. Faustino, M.J.S.A. Silva, L.F. Veiros, G.J.L. Bernardes, P.M.P. Gois, Chem. Sci. 7 (2016) 5052.

Looking inside bark

Joana Ferreira, Isabel Miranda, Helena Pereira

Centro de Estudos Florestais, Instituto Superior de Agronomia, Universidade de Lisboa, Portugal

Optimum utilization of bark residues demands appreciation of the complexity of bark and the extreme variation in chemical and physical properties between barks of different tree species.¹

The chemical composition of bark exhibits great diversity, so that analytical data on bark samples are difficult to obtain. Numerous differences in the nature and amounts of countless chemical components and of several extraneous materials contained within the bark can be found within even a single species, depending on the age and growth site of the trees sampled, the fraction of bark examined, climate and geographical conditions, and so on.²⁻⁴

Bark has useful by-products waiting for the right economic conditions or the development of satisfactory commercial processes. The rich and complex bark (including cork) contain bioactive molecules with potential applications in medicines, cosmetics, industrial chemicals and plant protection products.⁵

Our main goal focus on finding high-value products from these renewable, naturally occurring raw materials, knowing that this will probably enhance rural-based economies and promote a sustainable forestry management.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. J. Ferreira acknowledges financial support from UID/AGR/002397/2013.

References

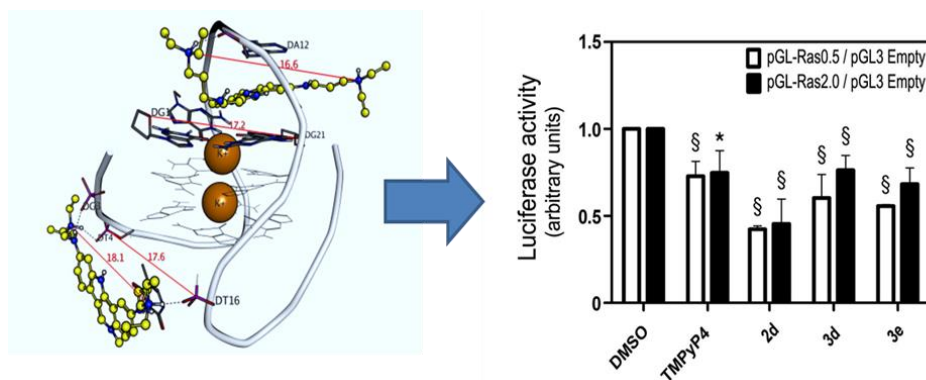
- [1] S. Feng, S. Cheng, Z. Yuan, M. Leitch, C. Xu, *Renew. Sust. Energ. Rev.* 26 (2013) 560-578.
- [2] I. Miranda, J. Gominho, I. Mirra, H. Pereira, *Ind. Crops Prod.* 41 (2013) 299-305.
- [3] A. Keller, M. Leupin, V. Mediavilla, E. Wintermantel, *Ind. Crops Prod.* 1 (2001) 35-48.
- [4] A. Berrocal, J. Baeza, J. Rodríguez, M. Espinosa, J. Freer, *J. Chil. Chem. Soc.* 49 (2004) 251-256.
- [5] G. M. Cragg, D. J. Newman, *Biochimica et Biophysica Acta*, 1830 (2013) 3670.

Targeting Oncogene Expression with Small Molecules

Alexandra Paulo, João Lavrado, Ana Paula Francisco, Eduarda Mendes,
Cecília M. P. Rodrigues

iMed.Ulisboa, Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal

Nucleic acids are prone to structural polymorphism and a number of structures may be formed in addition to the well-known DNA double helix. Among these is a family of nucleic acid four-stranded structures known as G-quadruplexes (G4). These quadruplex structures can be formed by sequences containing repetitive guanine-rich tracks and computational human genome analysis indicate an enrichment of these sequences in genomic regions controlling cellular proliferation, such as for example in the promoter regions of *c-MYC*, *k-RAS*, *c-KIT*, *HSP90* and *VEGF* among others. The broad concept of G4 targeting with small molecules is now generally accepted as a promising novel approach to anticancer therapy.¹ We have used this information to design focused regioisomeric small libraries of indoloquinolines^{2,3} and to inquire into the druggability of *k-RAS* oncogene. Our studies show that selective G4-ligands can reduce *k-RAS* oncogene expression, as well to induce cancer cell apoptosis at similar or lower concentrations than a standard anticancer drug. Moreover, these designed indoloquinolines are 5-10 fold selective to *k-RAS*-dependent cancer cell lines (pancreatic, colon and lung) compared to other cancer cells or normal human lung fibroblasts. In the next years, besides new and innovative G4-interactive lead molecules, we will also need to fully understand the targets and the biological effects of the existing G4-interactive small molecules, in order to efficiently optimize their structures and push them forward into the clinic.



Acknowledgements

Support for this work was provided by FCT through EXPL/QEQ-MED/0502/2012 and PEst-OE/SAU/UI4013/2014. J. Lavrado acknowledges financial support from SFRH/BPD/72903/2010.

References

- [1] A.P. Francisco, A. Paulo, *Curr. Med. Chem.* (2016). DOI: [10.2174/0929867323666160829145055](https://doi.org/10.2174/0929867323666160829145055)
- [2] Brito *et al.*, *Plos One* 10 (2015) e0126891.
- [3] J. Lavrado *et al.*, *Scientific Reports* 5 (2015) 9696.

Molecular and Nanosized Probes for Nuclear Medicine Imaging and Theranostics

António Paulo

*Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa,
Estrada Nacional 10, 2695-066 Bobadela LRS, Portugal*

Nuclear imaging modalities (Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT)) have an unsurpassable potential for the non-invasive imaging of cellular/molecular events in living subjects, offering the possibility of an accurate and early diagnosis of diseases, to predict the treatment responsiveness and the follow-up of therapies. These imaging modalities also play an important role in real time assessment of metabolism and pharmacokinetics in drug development studies. Furthermore, nuclear imaging also offers an inestimable contribution to theranostics, as many radionuclides or matched-pair of radionuclides can be explored simultaneously for imaging or therapy.

This research area has a valuable translational potential in the diagnostic and treatment of oncological, cardiovascular or neurodegenerative diseases, and might contribute for the rise of molecular and personalized medicine, which depends primarily on the availability of innovative, more sensitive and specific nuclear probes. To tackle this goal, the Radiopharmaceutical Science Group (RSG) from C²TN/IST has been involved, during the past few years, in the study of novel molecular/nanosized tools for nuclear imaging and theranostics, based on PET (e.g. ⁶⁴Cu, ⁶⁸Ga) and SPECT (e.g. ^{99m}Tc, ⁶⁷Ga, ¹¹¹In) radiometals and on beta- (e.g. ¹⁸⁸Re) or Auger-emitting (¹²⁵I) therapeutic radionuclides. In this communication, it will be concisely reviewed the most relevant contributions of the RSG from IST/C²TN to this field, with an emphasis on metal-based compounds for cardiac imaging and cancer theranostics.¹⁻⁵

Acknowledgements

Support for this work was provided by FCT through UID/Multi/04349/2013 and EXCL/QEQ-MED/0233/2012.

References

- [1] F. Silva, C. Fernandes, M.P.C. Campello, A. Paulo, *Polyhedron* 125 (2017) 186-205.
- [2] A. Paulo, G.R. Morais, I. Santos, "Organometallic Chemistry of Rhenium and Technetium Complexes fuelled by biomedical applications" (Chapter 44) in: *Advances in Organometallic Chemistry, The Silver/Gold Jubilee ICOMC Celebratory Book*, John Wiley & Sons, Inc. (2014), pp. 589-604.
- [3] M. Morais, A. Paulo, L. Gano, I. Santos, J.D.G. Correia, *J. Organomet. Chem.* 744 (2013), 125-139.
- [4] G.R. Morais, A. Paulo, I. Santos, *Organometallics* 31 (2012), 5693-5714.

Sugar Chemistry at the FCUL Consortium of the European Innovation Partnership on Active and Healthy Ageing – A3 Group on disease prevention and treatment:
Achievements and challenges

Amélia Pilar Rauter

*Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa
Ed C8, piso 5, 1749-016 Lisboa, Portugal*

The goals of the European Innovation Partnership on Active and Healthy Ageing (EIP-AHA) A3 group cover innovation on early diagnosis, disease prevention and treatment. Within its consortia approved on the basis of commitment application, we highlight the FCUL consortium, presently with more than 30 members from industry, academy and reference laboratories, from Portugal, Spain, Italy, France, UK, Germany and Poland.

The *Centro de Química e Bioquímica* (CQB) is one of the founder members of this consortium and in this presentation we disclose our achievements and discuss future challenges towards new multitarget leads acting on infection or other diseases, given a particular emphasis to anthrax, Alzheimer's disease and diabetes. The role of sugar chemistry by tuning bioactivity and selectivity will be discussed, and demonstrated its importance towards the prevention or treatment of these diseases, presently threatening our society.

Acknowledgements

Support for this work was given by the European Union through the project "Diagnostic and Drug Discovery Initiative for Alzheimer's Disease" (D3i4AD), FP7-PEOPLE-2013-IAPP, GA 612347, and for the approval and renewal of the commitment INOVAFUNAGEING. FCT is also acknowledged for the support of the project UID/MULTI/00612/2013.

A new combined approach of *Plectranthus* diterpenoids as anticancer and antitubercular drugs

Catarina Garcia^{a,#}, Joana Marçalo^{a,#}, Marisa Nicolai^a, Epole Ntungwe^a, Catarina Silva^a, Milica Pesic^b, Tijana Stankovic^b, Célia Faustino^d, Catarina Reis^d, Gian Maria Fimia^c, Carlos A. M. Afonso^d, Patrícia Rijo^{a,d,*}

#shared authorship

^a CBIOS, ULHT, Campo Grande 376, 1749-024 Lisbon, Portugal

^b Institute for Biological Research, "Siniša Stanković", University of Belgrade, Belgrade, Serbia

^c National Institute for the Infectious Disease Lazzaro Spallanzani – Laboratorio di Biologia Cellulare e Microscopia Elettronica, Rome, Italy

^d iMed.ULisboa, FFUL, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal

*E-mail: patricia.rijo@ulusofona.pt

Plectranthus spp. are cited as important sources of lead natural products. Previously, the cytotoxic agent 6,7-dehydroroyleanone (DHR) was isolated from *P. madagascariensis* Benth., and some halimane derivatives isolated from *P. ornatus* Benth., structurally similar to Rv3377c and Rv3378c targets (important to *Mycobacterium tuberculosis* survival and virulence), were prepared.

Immunosuppression and aggressive chemotherapy can promote the coexistence of tuberculosis (TB) and lung cancer (LC). Thus, this work aims to study the possible synergic effect of these diterpenoids as a potential combined system.

DHR was evaluated for its preliminary toxicity using the *Artemia salina* L. brine shrimp method. In addition, its cytotoxicity was also determined resorting to a model system of sensitive and multidrug resistant cell line (NCI-H460, NCI-H460/R) along with normal bronchial epithelial cells (MRC-5). Moreover, a colony-forming units assay was used to evaluate the halimane derivatives (non-cytotoxic) in primary macrophages infected with *M. tuberculosis* H37Rv.

The diterpenoid DHR showed moderate cytotoxicity and selectivity. Furthermore, a formulation of polymeric coated gold nanoparticles enhanced its anticancer properties by tenfold factor. Regarding the anti-tubercular activity, a diol halimane derivative showed low CFU/mL similar to ethambutol, a clinical drug for TB treatment.

The results revealed a promising approach system with anti-LC and anti-TB activities that support further studies on this synergic effect, for a new forthcoming combined therapy against this major public health problem.

Acknowledgements

This work was supported by PADDIC 2016 (ALIES-COFAC) as part of the PhD Program in Health Sciences from Universidad de Alcalá and ULHT, and also by a STSM Grant from COST Action CM1407.

References

- [1] S. Cicenas *et al.*, World J. Surg. Oncol. 5(22) (2007).
- [2] P. Rijo *et al.*, The Natural Products Journal 1 (2011) 57-64.
- [3] P. Rijo *et al.*, Biochemical Systematics and Ecology 35 (2007) 215-221.
- [4] H.C. Chan *et al.*, J. Am. Chem. Soc. 136 (2014) 2892-2896.
- [5] C. Silva, National patent number 20151000093093 (Portugal), 2015.

Mutations in the KatG heme pocket modulate local electrostatics and impair INH activation

Bruno L. Victor^a, Diogo Vila-Viçosa^a, Filomena Martins^a, Peter Loewen^b, Miguel Machuqueiro^a

^a *Centro de Química e Bioquímica, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Lisboa, Portugal*

^b *Department of Microbiology, University of Manitoba, Winnipeg, Canada*

Although tuberculosis (TB) is a treatable and curable disease, it is still one of the top ten causes of death worldwide.¹ The reason for these epidemics comes from reported multidrug and extensively drug-resistant forms of TB, non-responsive to first and second-line antitubercular drugs. Despite the known problems associated with isoniazid (INH) resistance, it is unquestionable that this drug is still one of the most powerful first-line anti-TB medicines available on the market. INH mechanism of action is still unclear, but the most accepted theory reports an initial activation of this pro-drug by the catalase peroxidase enzyme (KatG). During its catalytic cycle, KatG is able to receive electrons from INH, forming the isonicotinoyl radical, which binds to nicotinamide adenine dinucleotide (NAD⁺) originating the IN-NAD adduct. This is the real inhibitor of InhA that blocks mycolic acid biosynthesis, and, ultimately, leads to cell death.

KatG catalytic efficiency is reported to decrease with several mutations. Although some may reflect small steric changes in the heme pocket region, others have been associated with changes in its electrostatic balance.² His108 has been identified as the only pH sensitive residue in the heme pocket.³ Since its protonation state will be drastically influenced by changes in the electrostatic potential, we have performed several pK_a calculations on KatG *wt*, S315T and S315N mutations. We used Linear Response Approximation with Poisson-Boltzmann/Monte Carlo calculations done on MD simulations snapshots to estimate the final pK_a values. We observed significant changes in the final pK_a values, indicating that small changes introduced by the mutations can affect the heme pocket electrostatics, inevitably influencing KatG activity.

Acknowledgements

We acknowledge financial support from FCT through project UID/MULTI/00612/2013.

References

- [1] [WHO, Global Tuberculosis Report 2016](#) (accessed: March 2017).
- [2] V.H. Teixeira *et al.*, *Mol. Pharm.* 12 (2015) 898.
- [3] M. Machuqueiro *et al.*, *Biochemistry* 56(17) (2017) 2271-2281.

Role of fibrinogen-erythrocyte and erythrocyte-erythrocyte adhesion on cardiovascular pathologies

Filomena A. Carvalho^{1,*}, Ana Filipa Guedes¹, Luís Sargento², J. Braz Nogueira³, Nuno Lousada², Carlos Moreira³, Nuno C. Santos¹

¹*Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal*

²*Hospital Pulido Valente, Centro Hospitalar Lisboa Norte, Lisbon, Portugal*

³*Hospital Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon, Portugal*

*E-mail: filomenacarvalho@medicina.ulisboa.pt

Cardiovascular pathologies are the major cause of death worldwide. Erythrocyte aggregation is an indicator of cardiovascular risk, which is influenced by high plasma fibrinogen levels. Our main goals were to understand how fibrinogen-erythrocyte binding influences erythrocyte aggregation and how it constitutes a cardiovascular risk factor in essential arterial hypertension (EAH) and chronic heart failure (CHF). Differences on cell stiffness, protein-cell interaction and cell-cell adhesion forces were evaluated by AFM-based force spectroscopy with cells from 31 EAH patients, 30 CHF patients and 15 healthy blood donors. The main procedures used were previously described by us.¹⁻³ Results were correlated with patients' clinical profiles.

From cell-cell adhesion studies, we concluded that, upon increasing fibrinogen concentration (from 0 to 1 mg/mL), there was an increase in the work and force necessary for erythrocyte-erythrocyte detachment on EAH patients and healthy donors. Nevertheless, higher values from both parameters were obtained for EAH patients, when comparing to healthy donors, at each fibrinogen concentration.

Fibrinogen-erythrocyte (un)binding forces were higher in EAH and in CHF patients, when compared with the control group, despite a lower binding frequency. Ischemic CHF patients showed increased binding forces compared to non-ischemic patients. A 12-month clinical follow-up shows that CHF patients with higher fibrinogen-erythrocyte binding forces, probed by AFM at the beginning of the assessment, had a significantly higher probability of being hospitalized due to cardiovascular complications, pointing out the value of AFM for clinical prognosis.⁴

Erythrocyte stiffness studies revealed differences between CHF patients and healthy donors, in terms of erythrocyte elasticity (Young's modulus) and AFM tip penetration depth into the cells. Erythrocytes from non-ischemic CHF patients presented a higher average stiffness than those from the other groups (ischemic CHF and control). Nevertheless, a significantly higher cell penetration depth at the same applied force was observed for ischemic CHF patients. In conclusion, fibrinogen promotes erythrocyte adhesion, leading to its aggregation, probably by transient simultaneous binding of the protein to two cells, bridging them. Our results may be relevant for potential future drug interventions to reduce aggregation and enhance microcirculatory flow conditions in cardiovascular patients.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. F.A. Carvalho acknowledges financial support from FCT project PTDC/BBB-BMD/6307/2014.

References

- [1] F.A. Carvalho *et al.*, ACS Nano 4 (2010) 4609-4620.
- [2] F.A. Carvalho *et al.*, Plos One 6 (2011) e18167.
- [3] A.S. Ribeiro *et al.*, Nanoscale 8 (2016) 19390-19401.
- [4] A.F. Guedes *et al.*, Nature Nanotechnology 11 (2016) 687-692.

Regulation of Bax by Bile acids. A Matter of Life and Death

T. Sousa¹, Š. Pokorná², N. Bernardes³, R. E. Castro⁴, M. Hof², S. Banerjee⁵, G. Gröbner⁶,
R. J. Youle⁵, A. Coutinho^{1,7}, C. M. P. Rodrigues⁴, M. Prieto¹, F. Fernandes^{1,8}

¹ Centro de Química-Física Molecular and Institute of Nanoscience and Nanotechnology, Instituto Superior Técnico, University of Lisbon, Lisbon, Portugal

² J. Heyrovský Institute of Physical Chemistry, Academy of Sciences of the Czech Republic, Czech Republic

³ Institute for Bioengineering and Biosciences, Department of Bioengineering, Instituto Superior Técnico, Universidade de Lisboa, Lisbon, Portugal

⁴ Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal

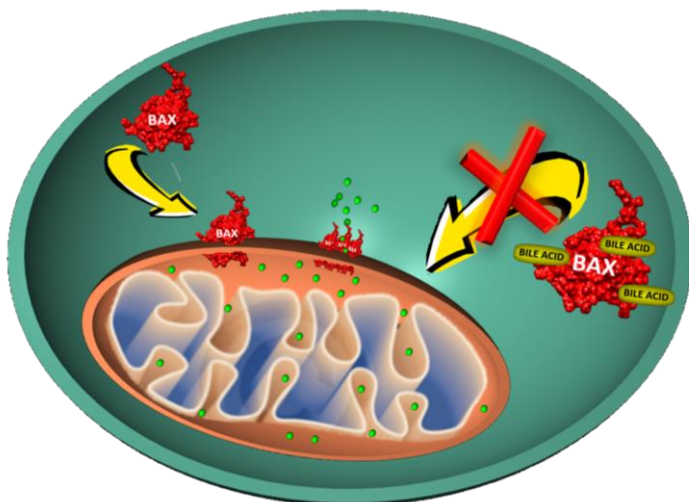
⁵ Surgical Neurology Branch, NINDS, NIH Bethesda, MD 20892, USA

⁶ Department of Chemistry, University of Umeå, SE-901 87 Umeå, Sweden

⁷ Departamento de Química e Bioquímica, Faculty of Sciences, University of Lisbon, Lisbon, Portugal

⁸ UCIBIO, REQUIMTE, Departamento de Química, FCT, Universidade Nova de Lisboa, Caparica, Portugal

Ursodeoxycholic acid (UDCA) and its taurine conjugate, tauroursodeoxycholic acid (TUDCA), are well characterized potent inhibitors of apoptosis in different cell types, although the mechanisms associated with this cytoprotection are not yet resolved. Interestingly, their structures are very similar to heavily cytotoxic bile acids, such as deoxycholic acid. Cytoprotection by bile acids has been linked to the protection of cellular membranes from damage or to the modulation of pro-apoptotic proteins, such as Bax. Here we show that while apoptotic bile acids induce permeabilization of mitochondrial membranes, cytoprotective bile acids show very limited membrane interaction, suggesting that their physiological action is not mediated by the membrane environment. In fact, both UDCA and TUDCA are shown to interact with soluble Bax and reduce significantly the membrane permeabilization through this protein, likely through inhibition of membrane interaction. Additionally, UDCA and TUDCA also inhibit the interaction of Bax with pro-apoptotic binding partners. Overall, cytoprotective bile acids are expected to contribute to the stabilization of the soluble and inactive form of Bax, decreasing both activation of the protein by pro-apoptotic partners and mitochondrial pore formation after translocation to mitochondrial membranes.



Acknowledgements

Supported by FCT/Portugal's projects FAPESP/20107/2014 and LISBOA-01-0145-FEDER-016405 and grants SFRH/BD/92398/2013 (T. Sousa) and IF/00386/2015 (F. Fernandes).

Dual-action triazene prodrugs as potent antimelanoma agents

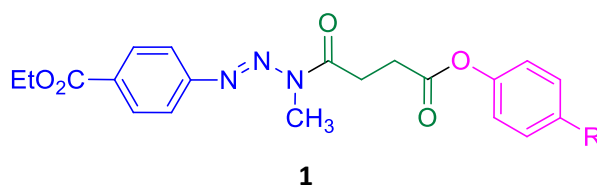
A. P. Francisco^a, Emília Carvalho^b, Jim Iley^c, Eduarda Rosa^b and Manuela Gaspar^a

^a *Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal*

^b *Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal*

^c *The Open University, School of Life, Health and Chemical Sciences, Milton Keynes, MK7 6AA, United Kingdom*

Metastatic melanoma is the most aggressive and lethal skin cancer.¹ Stage IV metastatic melanoma is also extremely resistant to all forms of therapy including chemotherapy, radiotherapy and immunotherapy.² To overcome intrinsic tumour resistance and improve survival rates of metastatic melanoma we have devised a strategy based in the development of dual-action prodrugs (**1**). Design of these molecules involved the conjugation of triazenes (blue moiety) with melanocytotoxic phenols (pink moiety) linked via succinoyl ester (green moiety). Prodrugs (**1**) were synthesized and evaluated for their anticancer activity against two (human and murine) melanoma cell lines.



Metabolic stability studies of prodrugs **1** showed that they combine chemical stability with enzymatic hydrolysis and displayed high cytotoxicity and selectivity against the MNT-1 human melanoma cell line. Compound with R = OBu, the most cytotoxic against the MNT-1 melanoma cell line, is more active than each parent drug and also than temozolomide, used as positive control. These cytotoxic studies support the design of dual-action prodrugs **1** and demonstrate that these compounds exhibit significant selectivity over the human melanoma cell line MNT-1. The dual-action prodrugs **1** are potential candidates for metastatic melanoma chemotherapy.

Acknowledgements

The authors gratefully acknowledge the Fundação para a Ciência e Tecnologia (Portugal) for financial support through funding of the research unit iMed.Ulisboa PEst-OE/SAU/UI4013/2014.

References

- [1] A.M. Matos, A.P. Francisco, *Chemmedchem*. 8 (2013) 1751-1765.
- [2] Z. Apalla, D. Nashan, R.B. Weller, X. Castellsague, *Dermatol. Ther.* 7 (2017) S5-S19.

π – Chem & Go! π – Stack on DNA and go to the best placeA. Gil*^a, S. Elleuchi^{a,b}, K. Jarraya^b, M. J. Calhorda*^a^a Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa,
1749-016 Lisboa, Portugal^b Laboratory of Inorganic Chemistry UR_{11RS73}, Faculty of Sciences of Sfax, 3000, Sfax, Tunisia
E-mail: aqmestres@fc.ul.pt; mjc@fc.ul.pt

The interaction of the [Mo(η^3 -C₃H₅)Br(CO)₂(phen)] metal complex synthesized in our group¹ with DNA has been studied at computational level by docking, semiempirical methods including dispersion, QM/MM and DFT. The [Mo(η^3 -C₃H₅)Br(CO)₂(phen)] metal complex exists as two main isomers in solution. Indeed, in one isomer phenanthroline (phen) is coordinated in the equatorial plane (Eq), whereas in the other one N of the phen is coordinated in an equatorial position and the other N in an axial one (Ax). Although the Eq structure is more stable, there is not a great difference between the energy of the isomers and we studied both systems, Eq and Ax, interacting with DNA to explain the experimentally found cytotoxicity.¹ We also took into account two different modes of interaction with DNA, that is, groove binding and intercalation, since such competition has been recently described in the bibliography for metal complexes with flat ligands interacting with DNA.²⁻⁴ PM6-DH2 hamiltonian and QM/MM methods by using M11L/6-31+G(d,p):AMBER were calibrated with the intercalated 1n37 structure of PDB and were observed to perform excellently. On the other hand, for the [Mo(η^3 -C₃H₅)Br(CO)₂(phen)] metal complex, it is observed that the system prefers the intercalation via minor groove than through the major groove. Moreover, once the bases experimented the rise movement to allocate the metal complex, the groove binding mode became unstable and the intercalation more likely.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. A. Gil acknowledges financial support from SFRH/BPD/89722/2012.

References

- [1] D. Bandarra, M. Lopes, T. Lopes, J. Almeida, M.S. Saraiva, M. Vasconcellos-Dias, C.D. Nunes, V. Félix, P. Brandão, P.D. Vaz, M. Meireles, M.J. Calhorda, *J. Inorg. Biochem.* 104 (2010) 1171-1177.
- [2] A. Mukherjee, R. Lavery, B. Bagchi, J.T. Hynes, *J. Am. Chem. Soc.* 130 (2008) 9747-9755.
- [3] W.D. Sasikala and A. Mukherjee, *Phys. Chem. Chem. Phys.* 15 (2013) 6446-6455.
- [4] D. Franco, A.V. Vargiu, A. Magistrato, *Inorg. Chem.* 53 (2014) 7999-8008.

Pa-MAP's analogues: antimicrobial peptides with anticancer activities

Mário R. Felício¹, Octávio L. Franco², Nuno C. Santos¹, Sónia Gonçalves¹

¹ Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

² Centro de Proteómica e Análise Bioquímica, Universidade Católica de Brasília, Brasília, Brazil

In recent years, the number of people suffering from cancer and multi-resistant infections has increased, such that both diseases are already seen as current and future major causes of death. The physical debility associated with cancer or with anticancer therapy itself often paves the way for opportunistic infections. Antimicrobial peptides (AMPs) are found in the innate immune system of a wide range of organisms. With similar properties, some AMPs can also act as anticancer peptides (ACPs). They are viewed as a new approach for chemotherapeutic drugs, with the advantage of low propensity to resistance, which may lead this paradigm into the pharmaceutical market.

In the present work a family of *Pa*-MAP analogues was synthesized, with two of them (*Pa*-MAP 2 and *Pa*-MAP 1.9) confirming the antimicrobial activity in lipid vesicles and *Escherichia coli* cells. In vitro assays against HeLa cells showed high toxicity at low peptide concentrations, without haemolytic effect. Here we demonstrated that even with designed peptides that are so closely similar, minor changes can affect their activity toward the target cells, and therefore, their potential application. Nonetheless, both peptides showed promising results for a future therapeutic application.

Acknowledgements

This work was funded by Fundação para a Ciência e a Tecnologia – Ministério da Ciência, Tecnologia e Ensino Superior (FCT-MCTES, Portugal), FP7-IRSES project MEMPEPACROSS (European Union), Marie Skłodowska-Curie Research and Innovation Staff Exchange (MSCA-RISE) project INPACT (call H2020-MSCA-RISE-2014, grant agreement 644167, European Union) and CNPq – Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazil). M.R. Felício also acknowledges FCT-MCTES PhD fellowship SPRH/BD/100517/2014.

CBA – cytokines applied to sports sciences

C. N. Matias^{1,2,3}, J. P. Morgado¹, C. P. Monteiro¹, F. Martins³, P. Rocha-Pereira⁴, A. M. Silva²

¹ *Physiology and Biochemistry Laboratory, CIPER, Fac Motricidade Humana, Univ Lisboa, Portugal*

² *Exercise and Health Laboratory, CIPER, Fac Motricidade Humana, Univ Lisboa, Portugal*

³ *Immunology Laboratory, National Institute of Health Dr. Ricardo Jorge, Lisboa, Portugal*

⁴ *Center for Neuroscience and Cell Biology, Universidade de Coimbra, Coimbra, Portugal*

It is widely accepted that athletes are more prone to infections than the common population. Nevertheless, scientific knowledge has not yet been conclusive regarding this believe. It seems that moderate physical activity reinforces the production of a Th1 cytokine profile (namely IL-2 and IL12) activating the innate immune response while intense physical activity seems to be more related with the production of the Th2 cytokine profile (IL-4, IL-6 and IL-10) influencing the acquired immune response. If physical activity is intense and prolonged it can induce an inflammatory response, that starts by releasing pro inflammatory cytokines (TNF- α and IL-6) and, in a second phase, anti-inflammatory and regulatory cytokines (example IL-4 and IL-10).

The gold standard method for cytokine analysis is based on flow cytometry and ELISA, named Cytometric Bead Array (CBA). This combined method employs a series of particles with different fluorescence intensities coated with capture antibodies specific for the cytokines, analogous to a conventional ELISA plate. Subsequently, standard procedures for the formation of sandwich complexes, similar to sandwich ELISA complexes, are performed. By mixing particles with different specificities that bind to specific proteins, this method allows for the detection of multiple parameters in a smaller sample volume and reducing the total time to obtain results.

Towards, flow cytometry method is applied. Flow cytometry is an analytical method that can measure the emission of fluorescence and scattered light, caused by the incidence of a laser on cells or suspended particles as they pass, one by one, through the analysis zone.

In order to verify if the cytokines profile changes due to physical activity practice, we assessed the Th1/Th2 cytokine profile in a) 2 groups of individuals: 28 active men (AM) and 29 judo high competition athletes (HCA), at rest; b) 23 swimming HCA both at rest and after an intense physical activity task.

Saliva samples were collected with standard procedure and frozen until analysis. On the analysis day, each saliva sample was unfrozen and centrifuged in order to obtain the supernatant.

Saliva cytokine profile was assessed by cytometric bead array, including IL2, IL4, IL6, IL10, IFN- γ and TNF- α , in a flow cytometer (*FACS Calibur*, da *Becton Dickinson Biosciences*).

Unpaired and paired sample T Tests were performed and statistical significance was set at $p < 0.05$.

Anthropometric characteristics and cytokine profile did not differ between compared groups (AM and Judo HCA). Concerning the cytokine profile before and after a high intensity swimming task, only IL-10 showed differences, with higher levels after the task.

Regarding the comparison between individuals practicing moderate and intense physical activity, our data does not support that high intense physical activity change the cytokine profile in athletes, at rest. Concerning the cytokine release profile during the exercise, the increase in IL-10 levels reinforce the literature suggestion, that anti-inflammatory and regulatory cytokines are displayed to control the inflammatory response produced by the physical activity stress.

Valorization of *Salvia sclareoides* - a contribution to the development
of a new dietary supplement

Luisa Abraços¹, Alice Martins¹, Amélia P. Rauter², Paula Batista², Anabela Raimundo², Isabel Sousa²

¹Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal

²LEAF – Linking Landscape, Environment, Agriculture and Food, Instituto Superior de Agronomia,
Universidade de Lisboa, Tapada da Ajuda, 1349-017 Portugal

Salvia sclareoides is a plant of the Portuguese spontaneous vegetation that has demonstrated a potent cholinergic action and the ability to prevent amyloid aggregation. Aiming at the development of new food supplements based on this plant and components, it is necessary to investigate whether this species, when planted, has the same properties as the species harvested in the field.

In this communication, we describe extracts preparation from plant provided by the company ERVITAL and, in collaboration with the Instituto Superior de Agronomia (ISA), the incorporation of the dry plant in sweet and salty cookies was investigated. The results obtained will be presented and discussed.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013.

Protein functionalization through a clickable and reversible linker

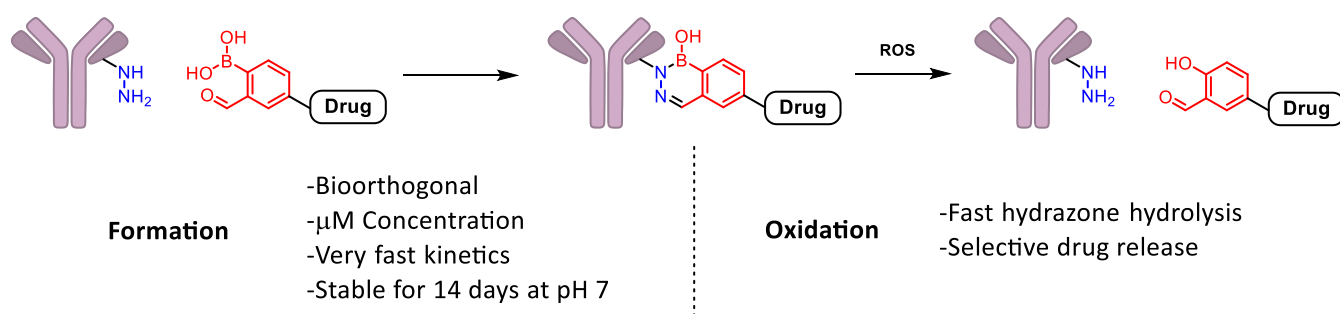
J. P. M. Antonio and P. M. P. Gois

iMed.UL, Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal

A new paradigm has been emerging in medicinal chemistry, where the focus of research has been shifting from the discovery of new chemical entities to the optimization of the current ones. Drug targeting is one of the most successful approaches and its importance has been demonstrated by the FDA's approval of Antibody-Drug Conjugates (ADCs). The biggest challenge of this approach is the development of functional linkers which are stable in physiological conditions but, at the same time, capable of releasing the payload under very selective conditions. We hereby present a bioorthogonal clickable linker which is reversible selectively under oxidative conditions.

Despite been known since early XX century, very recently Bane¹ and Gillingham² have demonstrated the formation of boron-nitrogen heterocycle in water, with exceptional kinetics through the reaction of hydrazines with o-formylphenylboronic acids. We envisioned the possibility of using these heterocycles as a clickable linker to conjugate drugs with targeting peptides. At the same time, the oxidation of boronic acids to phenols in the presence of oxidative conditions has been described several times in literature.³ We proposed that the same could happen with these compounds and provide an innovative mechanism to add reversibility.

Herein, we performed the reaction of different hydrazines with formyl and acetyl boronic acids and evaluated the kinetics and stability to select the optimal linker for bioconjugation. The selected pair formed a very stable heterocycle (over 14 days) with extraordinary kinetics (less than 5 minutes) and with close to 100% conversion. Several model peptides were easily tagged with fluorescent probes using this technology. Upon the addition of hydrogen peroxide, it was possible to observe the oxidation of the boron-nitrogen ring and sequential hydrolysis of the hydrazone, thus releasing the payload. We are presently working on conjugating a cytotoxic drug to a targeting peptide and evaluating its activity.



Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013 and the European Union UID/DTP/04138/2013, SAICTPAC/0019/2015. J.P.M. Antonio acknowledges financial support from PD/BD/128239/2016 and P.M.P. Gois from PTDC/QEQMED/5512/2014 and PTDC/QEQ-QOR/1434/2014.

References

- [1] O. Dilek, Z. Lei, K. Mukherjee, S. Bane, *Chem. Commun.* 51 (2015) 16992.
- [2] C.J. Stress, P.J. Schmidta, D.G. Gillingham, *Org. Biomol. Chem.* 14 (2016) 5529.
- [3] K.S. Webb, D. Levy, *Tetrahedron Letters* 36 (1995) 5117.

Synthesis of boronate complexes for multivalent drug-conjugates targeting

S. Baldo, Fabio M. F. Santos, Catia Parente Carvalho, Pedro M. P. Gois*

iMed.UL, Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal

E-mail: silviabaldo@ff.ulisboa.pt

Medicinal chemists incessantly face the daunting task of discovering new strategies to tackle cancer. Nowadays, the most recent strategies focus at interrupting the evolution of the neoplastic state. Since it involves a variety of biological process, multifunctional constructs that combine the lethality of a cytotoxicity drug with the targeting ability of specific biomolecules are necessary. Despite conceptually simple, the assembly of multifunctional construct is often hampered by the complexity of the synthetic steps. A promising strategy to create such compounds, known as Cancer Cell-Targeting Drug Conjugates (CCTDC) is the use of Boronic Acids (BAs). Based on work of P. Gois *et al.*¹ we conceived that CCTDC could be easily created by assemblage of simple building blocks promoted by a boron tether. Indeed, boronic acids are planar trivalent Lewis acids able to establish modular and reversible complexes due to their capacity to form negatively charged tetravalent framework with Lewis base donors.² In the vision of develop useful CCTDC, suitable propriety of stability, controlled reversibility in biological environment and fluorescence are highly desirable. Herein we present the development of multifunctional B-core complex. Starting from different building blocks, and based on a one-pot three-component reaction, boronate core complexes have been synthesized; evaluated at physiological and lysosomal pH, and in human plasma, as along as their hydrolysis resistance tested in the presence of glutathione. UV/Vis absorption and fluorescence analysis have been also carried out. The cores showing suitable stability and controlled reversibility will be selected as the components to build the multifunctional conjugates, featuring a cytotoxic drug, a polar small chain and a target unit (Figure 1). Finally, the selectivity and cytotoxicity of the synthesized B-core complexes will be evaluated against human cancer cells.

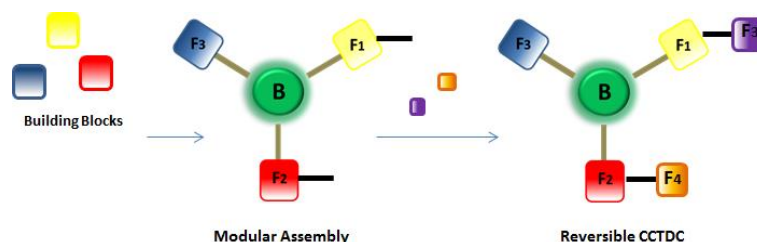


Figure 1. Modular and reversible assembly of CCTDC.

Acknowledgements

We thank the *Marie Skłodowska-Curie* Actions grant, and Fundação para a Ciência e a Tecnologia (FCT) Portugal (grants PTDC/QEQMED/5512/2014, PTDC/QEQ-QOR/1434/2014, UID/DTP/04138/2013, SAICTPAC/0019/2015) for financial support.

References

- [1] P.M.P. Gois *et al.*, Chem. Eur. J. 21 (2015) 1-8.
- [2] a) T. Flagstad, M.T. Petersen, T.E. Nielsen, Angew. Chem. Int. Ed. 54 (2015) 895-8397; b) P.M.P. Gois *et al.*, Chem. Eur. J. 21 (2015) 1-8.

Synthesis of tryptophanol-derived oxazoloisoindolinones: a scaffold with interesting anti-cancer properties

Valentina Barcherini^a, Sara Gomes^b, Margarida Espadinha^a, Joana Loureiro^b,
Alexandra M. M. Antunes^c, Lucília Saraiva^b, Maria M. M. Santos^a

^a *iMed.ULisboa, Faculdade de Farmácia da Universidade de Lisboa, Portugal*

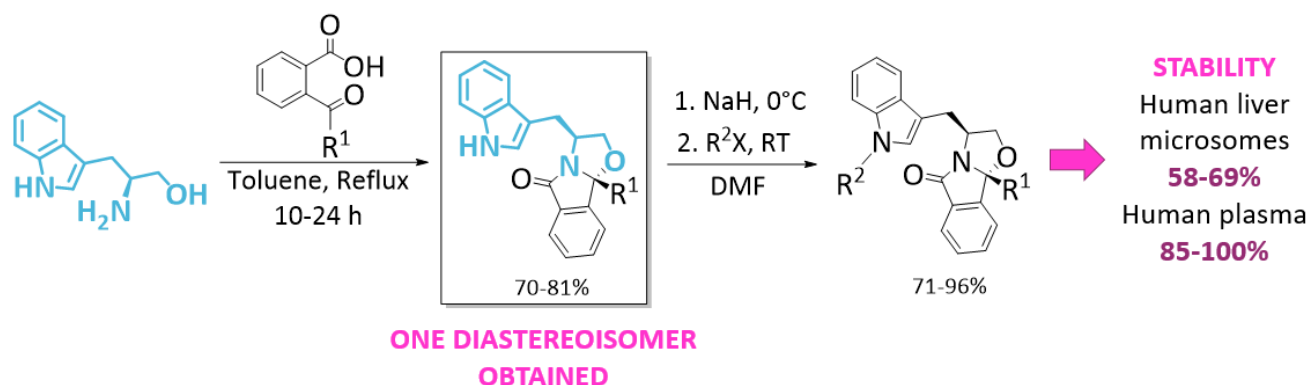
^b *UCIBIO/REQUIMTE Dep. de Ciências Biológicas, Faculdade de Farmácia da Universidade do Porto, Portugal*

^c *Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Portugal*

E-mail: vbarcherini@ff.ulisboa.pt

Synthesis of enantiopure drugs is of high importance in the field of organic synthesis, and specifically for the pharmaceutical industry. One methodology to access enantiomerically pure compounds involves the use of an enantiopure starting material, such as an amino acid/alcohol, an alkaloid or a carbohydrate, that acts as chiral inductor. Using this approach, we have developed several biologically active small molecules starting from 1,2-aminoalcohols.¹ Here we present our most recent results in the development of a chemical library of enantiopure tryptophanol-derived oxazoloisoindolinones to modulate p53 activity (a tumor suppressor protein that is inactivated in all types of cancer, thus representing a promising therapeutic target for the treatment of cancer).

The target compounds were obtained in good to excellent yields (Scheme 1) through a highly efficient/atom economic cyclocondensation reaction between the aminoalcohol tryptophanol and different oxoacids. The compounds were then screened as p53 activators using a yeast model and the validation of the molecular mechanism of action was performed in human tumor cell lines and in human xenograft mice models.² At last, the stability of the most promising hits was assessed in human liver microsomes and plasma.



Scheme 1. Synthesis of enantiopure tryptophanol-derived oxazoloisoindolinones.

Acknowledgements

This work was supported by FCT (Fundação para a Ciência e a Tecnologia) through iMed.ULisboa (UID/DTP/04138/2013), fellowship SFRH/BD/96189/2013 (S. Gomes), grant IF/00732/2013 (M.M.M. Santos), and also by the European Union and National Funds under the project PTDC/DTP-FTO/1981/2014-POCI-01-0145-FEDER-016581.

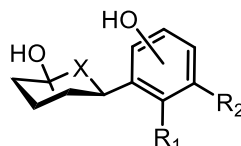
References

- [1] a) M. Espadinha, J. Dourado, R. Lajarin-Cuesta, C. Herrera-Arozamena, L. Gonçalves, M.I. Rodríguez-Franco, C. de los Rios, M.M.M. Santos, *ChemMedChem*. 21 (2017) 537-45; b) N.A.L. Pereira, A. Monteiro, M. Machado, J. Gut, E. Molins, M.J. Perry, J. Dourado, R. Moreira, P.J. Rosenthal, M. Prudêncio, M.M.M. Santos, *ChemMedChem*. 10 (2015) 2080-89; b) L. Saraiva, M.M.M. Santos, N.A.L. Pereira, C. Pereira, S. Moreira, M. Leão, A. Monteiro, J. Soares, *PCT/IB2014/062617, WO2014/207688 A1* (2014).
- [2] J. Soares, M. Espadinha, L. Raimundo, H. Ramos, A.S. Gomes, J.B. Loureiro, A. Inga, F. Reis, C. Gomes, M.M.M. Santos, L. Saraiva, *Mol. Oncol.* 11 (2017) 612-27.

Approaches to polyphenol C-glycosylation towards potential therapeutics for neurodegenerative diseases

María Teresa Blázquez Sánchez, Ana Marta Matos, Amélia Pilar Rauter
Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa,
Campo Grande 1749-016, Lisboa, Portugal
E-mail: mblazquez@fc.ul.pt

Polyphenols have shown numerous biological activities and health benefits for the treatment of neurodegenerative diseases as Alzheimer's¹ and prion diseases². Both disorders are characterized neuropathologically by extracellular deposits of A β and PrP amyloid fibrils, respectively.³ Previous work in our group has disclosed a C-glycosyl flavonoid, namely 8- β -D-glucopyranosylgenistein (8G), to interact with amyloid oligomers preventing aggregates formation.⁴ In this work, 8G scale up optimization was carried out and 8G small analog structures have been synthesised to evaluate the minimum C-glycoside building block necessary for showing therapeutic effect. In addition, we present our efforts in the synthesis of new C-glycosyl polyphenols based on structure A designed to be decorated with different saccharide units and phenol fragments obtained by proper substitution of R₁ and R₂ (Figure 1).



Structure A

Figure 1. Scaffold for the generation of C-Glycosylated polyphenols.

Acknowledgements

Support for this work was provided by the European Union's Seventh Framework Programme (FP7-PEOPLE-2013-IAPP, GA 612347).

References

- [1] K.M. Pate, M. Rogers, J.W. Reed, N. van der Munnik, S.Z. Vance, M.A. Moss, *Neurosci Ther.* 23 (2017) 135-144.
- [2] A.S. Rambold, M. Miesbauer, D. Olschewski, R. Seidel, C. Riemer, L. Smale, L. Brumm, M. Levy, E. Gazit, D. Oesterhelt, M. Baier, C.F.W. Becker, M. Engelhard, K.F. Winklhofer, J. Tatzelt, *J. Neurochem.* 107 (2008) 218-229.
- [3] P. Eikelenboom, C. Bate, W.A. van Gool, J.J. Hoozemans, J.M. Rozemuller, R. Veerhuis, A. Williams, *Glia.* 40 (2002) 232-239.
- [4] A.R. Jesus, C. Dias, A.M. Matos, R. de Almeida, A.S. Viana, F. Marcelo, R.T. Ribeiro, M.P. Macedo, C. Airoidi, F. Nicotra, A. Martins, E.J. Cabrita, J. Jiménez-Barbero, A.P. Rauter, *J. Med.Chem.* 57 (2014) 9463-9472.

How can in silico methodologies contribute to understand the molecular basis of drug efflux mediated by human P-Glycoprotein?

C. A. Bonito^a, R. J. Ferreira^a, M. J. U. Ferreira^a, D. J. V. A. dos Santos^{a,b}

^a *Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, Universidade de Lisboa, 1649-003 Lisboa, Portugal; E-mail: cambonito@ff.ul.pt*

^b *LAQV@REQUIMTE, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto, Rua do Campo Alegre, 4169-007 Porto, Portugal*

Multidrug resistance (MDR) to anticancer drugs is, currently, a major contributor in cancer treatment failures. One of the most significant mechanisms in MDR phenotypes results from the overexpression of P-glycoprotein (P-gp, *ABCB1*). Therefore, a deeper understanding on P-gp substrate recognition and efflux-related signal transmission mechanism is crucial to develop more potent and selective compounds able to reverse MDR.

From a recently published murine P-gp structure, a stable human P-gp model was obtained by our group. Following, four systems with P-gp structures (embedded in a bilayer, water solvated and charge neutralized) and containing the most common mutations experimentally linked with changes in efflux or substrate recognition (G185V, G830V, F978A and Δ F335) were built and equilibrated by means of molecular dynamics (MD) simulations.

When compared with the human homology model, each P-gp variant revealed slight differences in the helices repacking of the transmembrane domains (TMDs), leading to further studies to assess how drug binding may affect the interaction of residues between TMDs and the nucleotide binding (NBD) domains, thought to mediate signal transmission and efflux-related conformational changes. The G185V and G830V mutations are located at the substrate binding sites H and R respectively and the F978A and Δ F335 at the modulator binding site M. Molecules experimentally known to interact in each of the three sites were docked at the corresponding site and the best top-ranked docking pose were used as starting points for several short 20 ns MD runs (three replicates for each molecule).

For each docked molecule, the free energies of binding were calculated by *g_mmpbsa* with polar solvation energies corrected through an implicit membrane approach and the herein obtained results could be correlated with the experimentally determined changes in drug efflux for each specific mutation. Moreover, while in some cases the increase of drug affinity inside the pocket is the major determinant, in other cases variations in residue contacts at the NBD-TMD interface were the main reason for changes in drug efflux.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013, PEst-OE/QUI/UI0612/2013, PTDC/QEQ-MED/0905/2012 and UID/DTP/04138/2013. R.J. Ferreira acknowledges financial support from the PhD grant SFRH/BD/84285/2012.

Discovery and validation of new modulators of necroptosis using phenotypic high throughput screening of a large compound library

H. Brito, V. Marques, R. E. Castro, C. M. P. Rodrigues

Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, Universidade de Lisboa, Portugal

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in the Western world, affecting up to 30% of adult population and representing an important public health concern. NAFLD spectrum ranges from simple steatosis to more aggressive necroinflammation and non-alcoholic steatohepatitis (NASH), cirrhosis and finally hepatocellular carcinoma (HCC). Disruption of the equilibrium between cell death and proliferation may be at the origin of liver disease pathogenesis. Necroptosis, a form of regulated necrosis, plays a key role in NAFLD pathogenesis¹. As such, the discovery of novel, selective and potent inhibitors of necroptosis might represent a potential therapeutic strategy. Benefiting from a privileged research collaboration on target innovation between AstraZeneca and iMed.Ulisboa we have gained access to a high-quality, large compound pharma collection of over 250,000 compounds.

We screened compounds at 30 μM for their ability to block TNF- α -induced necroptosis in murine fibrosarcoma L929 cell line. For positive hits, we performed dose-response curves to quantitatively assess the inhibitory potency of the compounds in human and murine cell lines. From the full library screening, valid data was achieved for 251,879 compounds. For hit selection, exclusion criteria included qualitative and quantitative parameters, ZScore and percentage of cell death inhibition, respectively. A cut off threshold of > 70% inhibition of cell death by tested compounds and a ZScore inferior to -10, led to 3,353 active hits, corresponding to 1.3% hit rate for the full library. After hit selection, we performed dose-response curves to evaluate the inhibitory potency of selected compounds in murine L929 and human Jurkat T FADD^(-/-) cell lines. Further selection included exclusion criteria of $\text{piEC}_{50} < 5 \mu\text{M}$ ($\text{EC}_{50} < 6.7 \mu\text{M}$) in both cell lines, leading to 1,000 actives at 29,8% hit rate.

In sum, after this HTS workflow assay, fully designed at iMed.Ulisboa, we have reached a current number of about 1,000 hits from the initial full library. Further steps will lead us to narrowing and filtering these compounds until a reasonable group of hits is chosen. Lastly, in-house hit to lead optimization by the medicinal chemistry groups will deliver the molecules to then be evaluated using our experimental murine models of NASH.

Acknowledgements

Support for this work was provided by FCT through PTDC/BIM-MEC/0895/2014.

H. Brito acknowledges financial support from SFRH/BD/110672/2015.

References

[1] M.B. Afonso, P.M. Rodrigues, T. Carvalho, M. Caridade, P. Borralho, H. Cortez-Pinto *et al.*, *Clin. Sci. (Lond)*. 129(8) (2015) 721-739.

Purine nucleosides as butyrylcholinesterase inhibitors: Insights on structural features

Vasco Cachatra, Amélia P. Rauter

Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Lisboa, Portugal

Alzheimer's disease (AD) is the most common form of senile dementia. The etiology of this complex and fatal disease is still unknown and treatment options are based mainly on inhibitors of both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes. However, these therapeutics are not effective in preventing disease progression. While AChE activity decreases in specific brain regions as disease progresses, BChE activity is upregulated, making it an interesting target for drug discovery. Interestingly, it has been demonstrated that selective inhibition of BChE improved memory, cognitive functions and learning abilities in mice.¹

Our group has disclosed a new family of highly selective and potent BChE inhibitors based on a purine nucleoside scaffold, whose most active one has $k_i = 50$ nM for BChE and showed an extraordinary selectivity (selectivity factor of 340) over acetylcholinesterase inhibition². These promising results encouraged us to further investigate the role of glycosyl structure and configuration in promoting activity as BChE selective inhibitor. Synthetic approaches to either different protecting groups or glycosyl deoxygenation followed by synthesis of the respective purine nucleosides are now presented affording promising analogues of the lead nucleoside, bearing a perbenzyl protected α -D-manosyl N⁷ linked to a 2-acetamido-6-chloropurine.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and V. Cachatra acknowledges financial support from SFRH/BD/90359/2012. The European Union is gratefully acknowledged for the support of the project "Diagnostic and Drug Discovery Initiative for Alzheimer's Disease" (D3i4AD), FP7-PEOPLE-2013-IAPP, GA 612347.

References

- [1] U. Košak, B. Brus, D. Knez, R. Šink, S. Skelj, J. Trontelj, A. Pišlar, J. Šlenc, M. Gobec, M. Živin, L. Tratnjek, M. Perše, K. Sałat, A. Podkowa, B. Filipek, F. Nachon, X. Brazzolotto, A. Więckowska, B. Malawska, J. Stojan, I. M. Raščan, J. Kos, N. Coquelle, J.-P. Colletier, S. Gobec, *Sci. Rep.* 6 (2016) 39495-39511.
- [2] S. Schwarz, R. Csuk, A.P. Rauter, *Org. Biomol. Chem.* 12 (2016) 2446-2456.

Investigation of acetal protected sugars

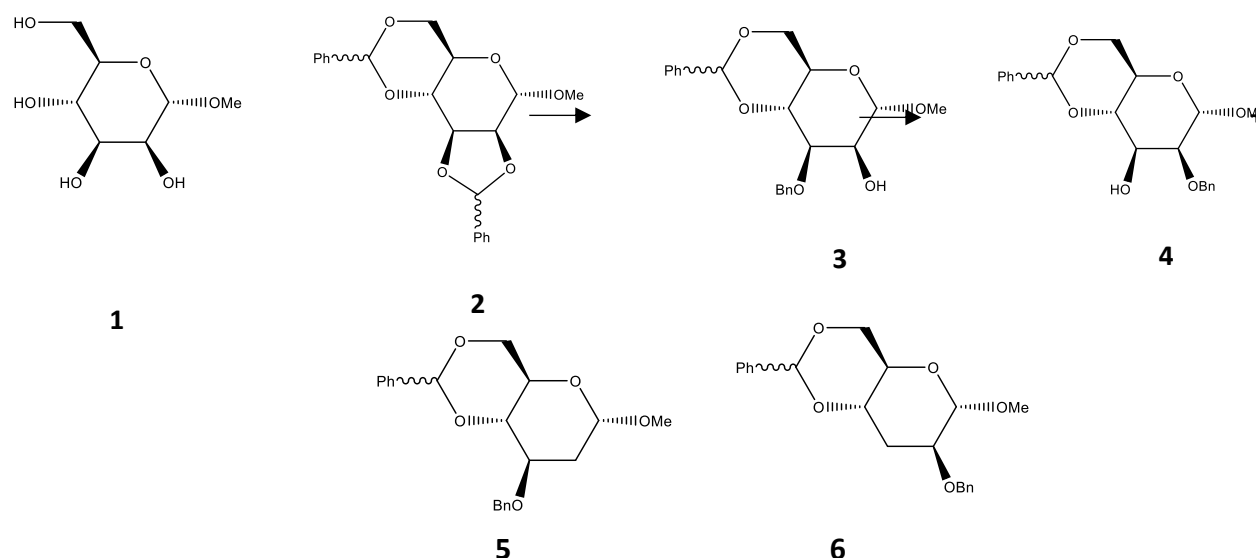
Patrícia Ferreira Calado, Vasco Cachatra, Amélia P. Rauter

Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Lisboa, Portugal

E-mail: patriciacalado95@hotmail.com

Butyrylcholinesterase (BChE) is an enzyme that catalyses the hydrolysis of the neurotransmitter acetylcholine. Evidences point to its important role in cholinergic neurotransmission.¹

Its inhibition is, therefore, relevant for the study of its involvement in neurodegenerative diseases, in particular in Alzheimer's disease. Purine nucleosides have been reported as potent and selective inhibitors of this enzyme.^{2,3} In this communication we disclose the synthesis of selectively benzyl protected sugars, required for their future transformation in deoxy purine nucleosides, embodying remaining hydroxy groups benzylated, as these protecting groups are key structural features for the required bioactivity². As described in the scheme below, the first step was to protect methyl α -D-mannopyranoside (**1**) free OH groups with two benzylidene acetal groups. The second step investigated aimed at a regioselective opening of the five-membered ring acetal in **2**, using Dibal-H as a reducing agent, to give compounds **3** and **4**. After successful isolation of both regioisomers, reaction with trimethylsilyltrifluoromethanesulfonate (TMSOTf) and tetrabutylammonium borohydride afforded the target deoxy compounds, namely the 4,6-O-benzylidene protected 2-deoxy-D-*arabino*-hexopyranoside (**5**) and the 3-deoxy-D-*arabino*-hexopyranoside in good yield.



Acknowledgements

Support for this work was provided by FCT funded project UID/MULTI/00612/2013 and by the European Union, gratefully acknowledged for the support of the project "Diagnostic and Drug Discovery Initiative for Alzheimer's Disease" (D3i4AD), FP7-PEOPLE-2013-IAPP, GA 612347.

References

- [1] S. Darvesh, D.A. Hopkins, C. Geula, *Nature Reviews Neuroscience* 4 (2003) 131-138.
- [2] F. Marcelo, F.V.M. Silva, M. Goulart, J. Justino, P. Sinay, Y. Blériot, A.P. Rauter, *Bioorg. Med. Chem.* 17(14) (2009) 5106-5116.
- [3] S. Schwarz, R. Csuk, A.P. Rauter, *Org. Biomol. Chem.* 12(15) (2014) 2446-2456.

**A New Synthetic Application of Nitrosugars:
Synthesis of 1,5-Dideoxy-5-C-hydroxymethyl-1,5-iminohexitols and
2,6-Dideoxy-6-C-hydroxymethyl-2,6-iminoheptitols**

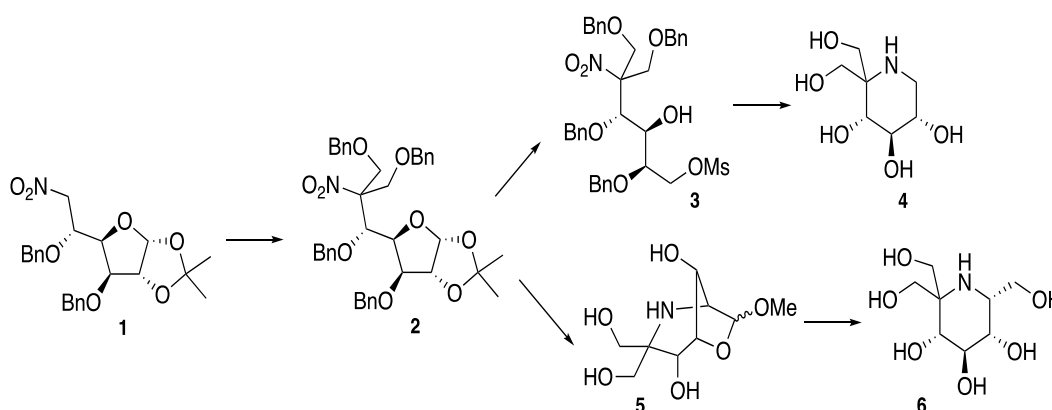
María Campos^{a,b}, José M. Otero^a, Juan C. Estévez^a, María-T. Blázquez-Sánchez,^b
Amélia P. Rauter^{b*} and Ramón J. Estévez^{a*}

^a *Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares and Departamento de Química Orgánica, Universidade de Santiago de Compostela, Spain*

^b *Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Portugal*

Glycosidase inhibitors have been extensively investigated over the last decades due to their potential as therapeutic agents. Imino sugars, which are analogues of furanoses or pyranoses where the endocyclic ring oxygen is replaced by nitrogen, have been reported as inhibitors of glycosidases. Derivatives of 1,5-dideoxy-1,5-iminohexitols and 2,6-dideoxy-2,6-iminoheptitols provide an opportunity for altering and hopefully increase the specificity of inhibition of individual glycosidases. Accordingly, it is of great interest to prepare families of branched derivatives of these targets, in order to test their activity against a range of glycosidases and hence to know how the introduction of branches can alter the biological activity.

As a continuation of our present interest on new synthetic approaches to branched imino sugars from nitro sugars¹, we describe herein enantiospecific syntheses of the known imino sugar **4** and the novel imino sugar **6**. It involves the early introduction of its two hydroxymethyl substituents at C-6 position of nitrosugar **1** by means of a double Henry reaction with formaldehyde (Scheme 1), using a strategy previously employed by us in the synthesis of five and seven-membered ring imino sugars¹. The target compounds are accessed by a divergent transformation of the key nitrosugar **2** into imino sugar **4**, via mesylate **3**, and into imino sugar **6**, via the complex bicyclic imino sugar **5**.



Acknowledgements

This work has received financial support from the European Union (European Regional Development Fund – ERDF), the Xunta de Galicia (Centro Singular de Investigación de Galicia accreditation 2016-2019 and Project GRC2014/040). FCT is also gratefully acknowledged for the support of project UID/MULTI/00612/2013.

References

[1] J.M. Otero, R.G. Soengas, J.C. Estévez, R.J. Estévez, D.J. Watking, E.L. Evinson, R.J. Nash, G.W.J. Fleet, *Org. Lett.* 9 (2007) 623.

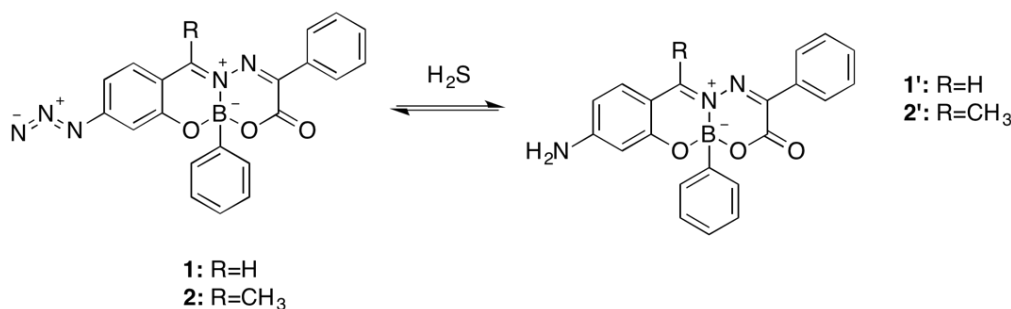
Boronic acid salicylidenehydrazone dyes (BASHY) in hydrogen sulphide detection

Joana Carvalho, Fábio Santos, Cátia Carvalho, Pedro Góis

iMed.ULisboa, Faculdade de Farmácia da Universidade de Lisboa, Lisboa, Portugal

Hydrogen sulphide, known as the third gasotransmitter, is a recognized signalling molecule in the cardiovascular system and is a potential biomarker of ischemia and injury.¹ The scientific progress in the area of fluorescent probes and bioimaging have led to the construction of more demanding probes, particularly the design of probes able to provide information about organelle-specific mechanisms. In respect to H₂S, it is necessary to clarify the regulation of lipid homeostasis signalling, in this context, boronic acid salicylidenehydrazone (BASHY) dyes may be adequate, considering their affinity and accumulation on lipid droplets.²

Our lab has been focus on the development of the fluorescent dyes BASHY, which are iminoboronates based heterocycles, constructed in a modular fashion. These dyes have shown marked brightness and photostability. In biological tests, BASHY were cell permeable and were accumulated in specific organelles, namely lipid droplets. Considering the intramolecular charge transfer (ICT) nature of BASHY dyes, the spectroscopic properties may suffer alteration through changes in π -conjugation or in intermolecular electron density distribution. Thus, we present the development of two BASHY probes containing an azide group strategically added on salicylhydrazone moiety, which may be reduced to amine group in the presence of H₂S (Scheme 1). This switch is followed by an alteration in electronic character and consequently, in spectroscopic properties, allowing the signalization of hydrogen sulphide.³



Scheme 1. BASHY probe reduction in the presence of hydrogen sulphide.

Acknowledgements

Support for this work was provided by FCT through PTDC/QEQMED/5512/2014; PTDC/QEQ-QOR/1434/2014; UID/DTP/04138/2013; SAICTPAC/0019/2015. J. Carvalho acknowledges financial support from PTDC/QEQMED/5512/2014.

References

- [1] a) M. Whiteman, S. Le Trionnaire, M. Chopra, B. Fox, Whatmore, *J. Clin Sci.* 121 (2011) 459-488; b) R.N. Carter, N.M. Morton, *J. Pathol.* 238 (2016) 321-332; c) A.K. Mustafa, M.M. Gadalla, N. Sen, S. Kim, W. Mu, S.K. Gazi *et al.*, *Sci. Signal.* 2 (2009) 1-8.
- [2] Z. Wang, C. Gui, E. Zhao, J. Wang, X. Li, A. Qin *et al.*, *Appl. Mater. Interfaces* 8 (2016) 10193-10200.
- [3] a) F.M.F. Santos, J.N. Rosa, N.R. Candeias, C.P. Carvalho, A.I. Matos, A.E. Ventura *et al.*, *Chem. Eur. J.*, 22 (2016) 1631-1637; b) A.D. Laurent, B. Le, G. Denis, *Theor. Chem. Acc.* 135 (2016) 1-8.

3-Oxo- β -Sultams as Activity-based Probes to target Human Neutrophil Elastase as a Potential Biomarker of Chronic Obstructive Pulmonary Disease

L. A. R. Carvalho^a, L. M. Gonçalves^a, F. Vaz^b, S. D. Lucas^a, D. Penque^b, R. Moreira^a

^a iMed.ULisboa, Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal

^b Instituto Nacional de Saúde Doutor Ricardo Jorge, Avenida Padre Cruz, 1649-016 Lisboa, Portugal

Chronic obstructive pulmonary disease (COPD) is characterized by progressive and self-sustained lung inflammation resulting in non-reversible limitation of lung airflow. New biomarkers to diagnose and evaluate COPD are urgently needed. We propose that the inflammatory process in COPD modulates proteolytic enzymes in the lung environment, like human neutrophil elastase (HNE), which are critical for disease development and are a potential source of new biomarkers. Our main goal is the validation of HNE as a new biomarker of COPD. Based on our previous experience with the development of small molecules for HNE inhibition¹ we synthesized a library of HNE inhibitors and activity-based probes (ABPs)² based on the 3-Oxo- β -Sultam warhead³ using Cu(I)-catalyzed Huisgen azide-alkyne 1,3-dipolar cycloaddition⁴. Our library proved to be very potent, with HNE inhibition values in the nanomolar region. ABPs selectively target only the active form of HNE and are currently being validated in gel-based assays. Once validated, ABPs will be applied in a library of nasal brushing and bronchoalveolar fluid human-derived samples and target identification will be achieved by mass spectrometry and proteomics techniques (Figure 1). The outcome of this project will ultimately lead to important advances for diagnostic tool development and biomarker discovery in COPD.

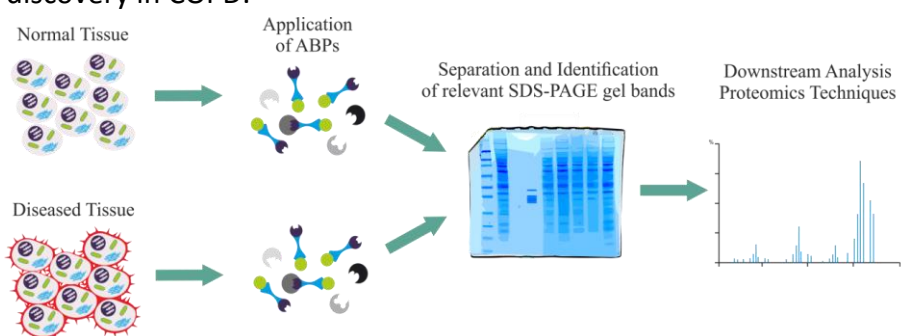


Figure 1. ABPs are applied in human-derived samples, followed by in-gel analysis and target identification using mass spectrometry.

Acknowledgements

Financial support by Fundação para a Ciência e Tecnologia (SFRH/BD/100400/2014).

References

- [1] a) J. Mulchande, R. Oliveira, M. Carrasco, L. Gouveia, R.C. Guedes, J. Iley, R. Moreira, *J. Med. Chem.* 53(1) (2010) 241-53; b) E.F.P. Ruivo, L.M. Gonçalves, L.A.R. Carvalho, R.C. Guedes, S. Hofbauer, J.A. Brito, M. Archer, R. Moreira, S.D. Lucas, *ChemMedChem* 11(18) (2016) 2037-42.
- [2] L.A.R. Carvalho, E.F.P. Ruivo, S.D. Lucas, R. Moreira, *Med. Chem. Commun.* 6 (2015) 536-546.
- [3] W. Tsang, N. Ahmed, K. Hemming, M.I. Page, *Org. Biomol. Chem.* 5 (2007) 3993-4000.
- [4] M. Meldal, C.W. Tomøe, *Chem. Rev.* 108 (2008) 2952-3015.

Targeted liposome nanoparticles for fibrin blood clot degradation

Patrícia M. Carvalho¹, Diogo Sequeira^{1,2}, Nuno C. Santos¹, Marco M. Domingues¹

¹ Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal

² Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Lisboa, Portugal

Fibrinogen shows a trinodular structure with distal D regions on both ends, and a central E region comprises the N-terminal sequences of all polypeptide chains. Fibrin polymerization starts by thrombin cleavage of fibrinopeptides A and B from the E region, exposing knobs A and B. These knobs interact with their respective binding pockets on the D region of another fibrin molecule, leading to formation and growth of protofibrils, which culminates in fibrin fibres (Figure 1). There is increasing evidence for a consistent association between denser fibrin clot structure, and more resistant to degradation (fibrinolysis), with CVD and (athero)thrombotic disorders¹, which account for nearly one-third of deaths worldwide. Liposome nanoparticles have drawn a lot of interest as pharmaceutical drug carriers due to their stability and content release in a controlled manner. We aim to develop an encapsulated fibrinolytic therapeutic strategy with lower bleeding risk and integration in the clot structure, and understand its impact on blood clot formation and lysis. We demonstrated that the drug delivery system does not seem to affect haemostasis properties by recording clot polymerization and lysis kinetics in its absence and presence. Also, the nanoparticle is stable over time without any measurable aggregation or change in its surface charge for 28 days. By conducting turbidimetry studies we are now gaining greater insight on how the presence of the vesicles performs in terms of fibrin fibres radius, protofibril packing, and protein content² (Figure 2), and already concluded that their presence is only reflected by a small increase in all of the parameters with lipid concentrations reaching 1.0 mM, from where on they seem to stabilize, not suffering any major alterations with the double of that concentration.

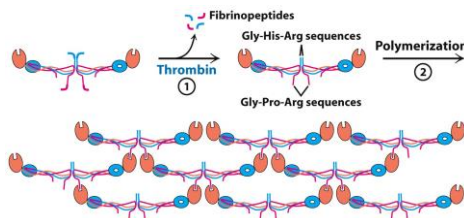


Figure 1. Thrombin-mediated release of fibrinopeptides from fibrinogen forms monomeric fibrin-containing exposed knobs (1). The self-assembly of monomeric fibrin is promoted via knob-hole interactions and the formation of half-staggered fibrin protofibrils (2). Continuous fibrin growth and protofibril lateral aggregation culminates in fibrin fiber formation.

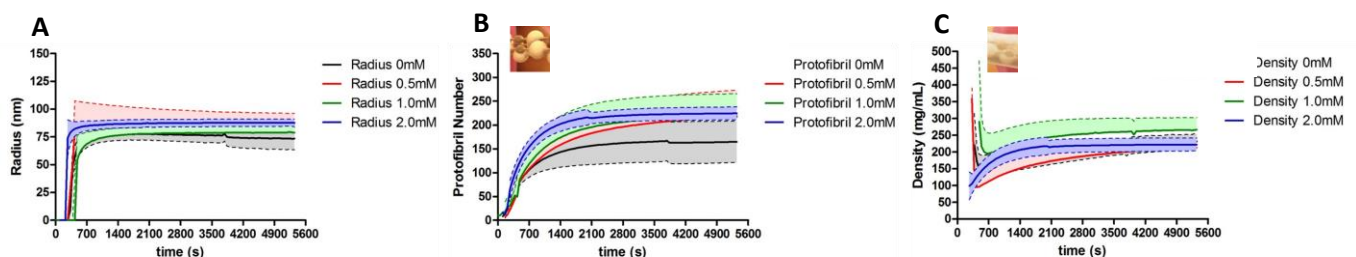


Figure 2. Turbidimetry (light scattering) analysis of fibrin formation concerning fibers radius (A), number of protofibrils (B), and their protein density (C) during polymerization. Raising the concentration of fibrinogen increases the radius of the fiber and the number of protofibrils, causing a higher protein concentration in fibrin fibers; this point seems to be a plateau, as doubling the concentration does not follow the same tendency and presents very similar values.

Acknowledgements

M.M. Domingues and P.M. Carvalho acknowledge financial support from FCT Individual Fellowships SFRH/BPD/122779/2016 and SFRH/BD/108077/2015, respectively.

References

- [1] R.A.S. Ariëns, J. Thromb. Haemost. 11 (2013) 294-305.
- [2] N.A. Kurniawan *et al.*, J. Thromb. Haemost. 12(10) (2014) 1687-1696.

Using peroxides-based compounds as chemical delivery systems for infectious diseases

Daniela Coutinho, Rita Capela, Rui Moreira, Francisca Lopes

*iMed.Ulisboa, Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto,
1649-003 Lisboa, Portugal*

Infectious diseases caused by viruses, parasites and bacteria are currently the second cause of mortality worldwide. *Leishmania sp.*, the protozoa responsible for leishmaniasis, and *Plasmodium sp.*, responsible for malaria, are among the most lethal infectious agents. The control of these diseases still relies on chemotherapy but the drugs currently prescribed have limited use due to lack of efficacy, severe adverse reactions, increasing parasite resistance and elevated cost.^{1,2} For these reasons, new drugs and new therapeutic approaches are required.

Endoperoxides are known to be reductively activated by iron(II)-heme to form carbon-centered radicals, reactive oxygen species and carbonyl species which can generate oxidative stress in the parasite.^{2,3} These compounds could be applicable to any infectious agents that require high levels of iron at critical steps of their life cycle, such as *Leishmania* and *Plasmodium*.⁴

Following this concept, we have designed and synthesized hybrid compounds containing 1,2,4,5-tetraoxanes scaffold to selectively deliver an electrophile capable of reacting with essential enzymes. The structural assignment of these compounds was acquired by usual techniques including 1D and 2D NMR, it was also studied the kinetics of these compounds using HPLC methods, including their activation with iron(II)-bromide.

References

- [1] N.K. Copeland, N.E. Aronson, *Curr. Opin. Infect. Dis.* 28 (2015) 426-437.
- [2] R. Oliveira, A.S. Newton, R. Guedes, D. Miranda, R.K. Amewu, A. Srivastava, J. Gut, P.J. Rosenthal, P.M. O'Neill, S.A. Ward, F. Lopes, R. Moreira, *Chem. Med. Chem.* 8 (2013) 1528-1536.
- [3] R. Oliveira, D. Miranda, J. Magalhães, R. Capela, M.J. Perry, P.M. O'Neill, R. Moreira, F. Lopes, *Bioorg. Med. Chem.* 8 (2015) 1528-1536.
- [4] A.R. Flannery, R.L. Renberg, N.W. Andrews, *Curr. Opin. Microbiol.* 16 (2013) 716-721.

C2-functionalization of indoles as a strategy for the synthesis of novel antimalarial compounds

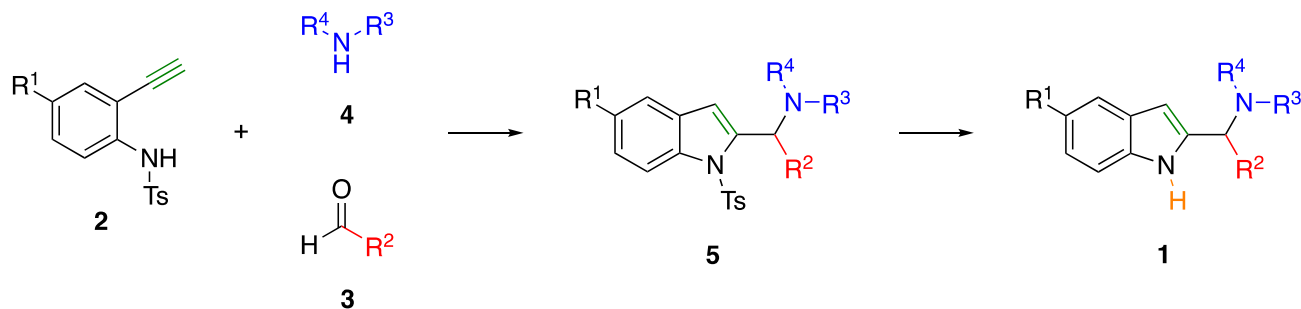
Gustavo da Silva^{a,b}, Maria M. M. Santos^a, Vera L. M. Silva^b, Artur M. S. Silva^b, Rui Moreira^a

^a *iMed.Ulisboa, Faculdade de Farmácia da Universidade de Lisboa, Lisbon, Portugal*

^b *QOPNA, Departamento de Química da Universidade de Aveiro, Aveiro, Portugal*

Copper-catalyzed A³ coupling (followed by intramolecular cyclization) is a versatile tool for the synthesis of C2-functionalized indoles.^{1,2} Rare examples of these type of C2-indoles revealed to be active against malaria parasites but some were already included in the Pathogen Box.³ A novel C2-functionalized indole revealed to be active against blood stage malaria parasites in the low micromolar range, which instigated the design of other synthetic analogues.

Based on these results, from our research group, a small library of C2-functionalized indoles **1** was prepared via A³ coupling of 2-ethynylanilines **2**, aldehydes **3** and secondary amines **4**, followed by *N*-detosylation of the indole synthetic intermediate **5** (Scheme 1). The influence of different secondary amines, aldehydes and 2-ethynylanilines in this three-component reaction, as well as the influence of the substituents R¹-R⁴ on the antimalarial activity will be discussed in this communication.



Scheme 3. Copper-catalyzed A³ coupling (and cyclization) of 2-ethynylanilines **2**, aldehydes **3** and secondary amines **4**, followed by *N*-detosylation of the indole synthetic intermediate **5**.

Acknowledgements

This work was supported by Fundação para a Ciência e Tecnologia (FCT) through iMed.Ulisboa (UID/DTP/04138/2013). Thanks are also due to University of Aveiro and FCT/MEC for the financial support to the QOPNA research project (FCT UID/QUI/00062/2013) financed by national funds and when appropriate co-financed by FEDER under the PT2020 Partnership Agreement, and to the Portuguese NMR Network. We also thank FCT for additional financial support: IF/00732/2013 (M.M.M. Santos), SFRH/BPD/108807/2015 (V.L.M. Silva) and SFRH/BD/103412/2014 (G. da Silva).

References

- [1] Y. Ohta, H. Chiba, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* 74 (2009) 7052-7058.
- [2] Y. Ohta, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* 11 (2009) 1979-1982.
- [3] W C. van Voorhis *et al.*, *PLoS Pathog.* 12 (2016) e1005763.

N-acetylgalactosamine mimetics: synthesis of potential candidates to block virus infection

João Manuel de Barros^{a*}, Filipa Marcelo^b, Amélia P. Rauter^b

^a *Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Ed C8, Piso 5, Campo Grande, 1749-016 Lisboa, Portugal*

^b *Unidade UCIBIO, Departamento de Química, Faculdade de Ciências e Tecnologias, Universidade Nova de Lisboa, Quinta da Torre, 2829-516 Caparica, Portugal*

*E-mail: jmvbarros@fc.ul.pt

C-type lectins play important roles in both innate and adaptive immune responses. The human macrophage galactose C-type lectin (MGL) is a key physiological receptor expressed on the surface immature dendritic cells (DCs) and macrophages. MGL binds with high affinity to the terminal *N*-acetylgalactosamine (GalNAc) residues, like the Tn antigen (α -GalNAc-Ser/Thr) of mucin-like glycoproteins in a Ca²⁺-dependent manner. MGL recognizes the mucin-like envelope glycoprotein of filovirus like Ebola, Marburg or Influenza and promotes the virus entry and infectivity.^{1,2} Design of MGL inhibitors could help to block the virus entry and represents a new strategy for developing more effective antiviral drugs. Also, a wide range of organic selenides are now known as useful antioxidants, antibiotics and antiviral agents.^{3,4}

Within this project we have synthesized mimetics of GalNAc, namely phenyl selenogalactosides bearing imide functionality at position 2 aiming at better binders than GalNAc itself towards MGL receptor, therefore competing to the interaction between the MGL and the GP of Ebola or Marburg filovirus. The synthesized molecules will also be tested for interactions with A β ₁₋₄₂ toxic small oligomers, and their fibrilization generating neuronal death, associated to the multifactorial Alzheimer's disease, since their structure bears functional groups able to establish π - π interactions and hydrogen bond formation, usually mandatory for binding.⁵

Acknowledgements

Support for this work is acknowledged to FCT through the project UID/MULTI/00612/2013 and to the European Union through the project "Diagnostic and Drug Discovery Initiative for Alzheimer's Disease" (D3i4AD), FP7-PEOPLE-2013-IAPP, GA 612347.

References

- [1] A. Takada, K. Fujioka, M. Tsuiji, A. Morikawa, N. Higashi, H. Ebihara, D. Kobasa, H. Feldmann, T. Irimura, Y. Kawaoka, *J. Virology* 78 (2004) 2943-2947.
- [2] F. Marcelo, F. Garcia-Martin, T. Matsushita, J. Sardinha, H. Coelho, A. Oude-Vrielink, C. Koller, S. André, E.J. Cabrita, H.J. Gabius, S.I. Nishimura, J. Jiménez-Barbero, F.J. Cañada, *Chem. Eur. J.* 20 (2014) 16147-16155.
- [3] K. Mamoru, I. Hideharu, H. Masahiro, *Res. Commun. Mol. Pathol. Pharmacol.* 101 (1998) 179-186.
- [4] J. Kirsi, *J. Antimicrob. Agents Chemother.* 24 (1983) 353-361.
- [5] A.M. Matos, M.P. Macedo, A.P. Rauter, *Med. Res.* (2017) [Rev DOI:10.1002/med.21440].

Characterization and purification of a protease from *Ficus benjamina* with nematicidal action by CM-cellulose chromatography

Isaias Moreira de Figueiredo¹, Lêdia Feitosa Wanderley¹, Tássio Rômulo Silva Araújo Luz¹, Carolina Rocha e Silva¹, André Teixeira da Silva Ferreira², Jonas Perales², José Tadeu Abreu Oliveira³, Livio Martins Costa-Júnior¹, Alexandra Martins dos Santos Soares¹

¹ Federal University of Maranhão, State of Maranhão, Brazil

² FIOCRUZ, State of Rio de Janeiro, Brazil

³ Federal University of Ceará, State of Ceará, Brazil

Haemonchus contortus is the major helminth pathogen of small ruminants. *H. contortus* control usually relies on the use of synthetic anthelmintics. Therefore, the development of new alternative control strategies is necessary, such as the use of natural products. Several nematicidal proteins have been isolated from plants and can be useful tools against *H. contortus*.¹ To evaluate the anthelmintic potential of *Ficus benjamina* protease on *H. contortus* larvae, protein samples were collected in 50 mM sodium phosphate buffer, pH 7.0, centrifuged (15,000 x g, 5 °C, 15 min), dialysed (*cut-off* 12kDa) against water, centrifuged again under the above conditions, and a resulting soluble protein extract (PE) recovery. PE was fractionated with ammonium sulfate at 60-90% saturation, dialyzed against water, and the protein fraction F60-90 obtained. F60-90 was further fractionated by CM-cellulose chromatography. The content and proteolytic activity of the protein fractions obtained were measured by hydrolysis of azocasein.² The proteins were also analysed by SDS-PAGE. The molecular mass and identity of the isolated protease were determined after mass spectrometry. Moreover, the action of this protease on *H. contortus* larval development was assessed.³ The chromatographic fraction eluted with 50 mM NaCl showed a single protein band on SDS-PAGE and displayed a proteolytic activity of 43666.6 AU/mL/mgProtein on azocasein. Mass spectrometry analysis revealed that the isolated protein is a cysteine protease with 23.972 kDa molecular mass. The protease activity was stable at a pH range varying from 6 to 10, with optimal activity at 60 °C. Furthermore, the protease showed anthelmintic activity with LC50 of 10.84 µM. It was concluded that *F. benjamina* has a cysteine protease with anthelmintic property on *H. contortus* larvae and thus potential for biotechnological applications.

Acknowledgements

Support for this work provided by National Council for Research and Development (CNPq), Foundation for Scientific Research and Development of Maranhão (FAPEMA) and Federal University of Maranhão (UFMA), Brazil. I.M. de Figueiredo acknowledges financial support from scholarship by Federal University of Maranhão.

References

- [1] C.M. Antao, F.X. Malcata, Plant Physiol. Biochem. 43 (2005) 637-650.
- [2] J. Xavier-Filho, J. Agric. Food. Chem. 37 (1989) 1139-1143.
- [3] J. Hubert, D. Kerboeuf, Vet. Rec. 130 (1992) 442-446.

Study of cell penetrating peptides as drug delivery systems for chemotherapeutic drugs and their anticancer properties

Filipa D. de Oliveira¹, João Freire^{1,2}, M. Paula Robalo^{3,4}, M. Fátima M. Piedade³, David Andreu⁵, Ana Salomé Veiga¹, M. Helena Garcia⁶, Miguel A. R. B. Castanho¹, Diana Gaspar¹, Tânia S. Morais^{1,6}

¹*Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Portugal*

²*Department of Virology, Institut Pasteur, Paris, France*

³*Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Portugal*

⁴*Área Departamental de Engenharia Química, ISEL–Instituto Superior de Engenharia de Lisboa, Instituto Politécnico de Lisboa, Portugal*

⁵*Department of Experimental and Health Sciences, Pompeu Fabra University, Barcelona Biomedical Research Park, Spain*

⁶*Centro de Química Estrutural, Faculdade de Ciências, Universidade de Lisboa, Portugal*

Cancer is a disease characterized by the uncontrolled growth and proliferation of abnormal cells and it is one of the main causes of death worldwide. Breast cancer is the most frequent cause of cancer-related death in women.

The most common procedures used nowadays to treat cancer include surgery, radiotherapy and chemotherapy. However, both radiotherapy and chemotherapy are responsible for secondary effects due to the damage of healthy cells and tissues. Moreover, cancer cells may develop resistance to the compounds used in chemotherapy. Thus, the scientific research regarding cancer treatment aims to develop new compounds to overcome the drawbacks of the conventional therapies.

In this work, we studied the anticancer activity and mode of action of a ruthenium organometallic complex (TM281), as well as the conjugates resulting from the link between this complex and several peptides. Since this link aimed the improvement of the complex internalization by cancer cells, the selected peptides – Tat, pepR, pepM, vCPP 2319 and CroTb – exhibit activity as cell penetrating peptides (CPPs). CPPs are membrane bioactive peptides with 5 to 30 amino acid residues and a positive net charge due to the high levels of arginine and lysine residues in their structure. These peptides have also an amphipathic character and membrane-crossing ability. Due to this ability, CPPs are being applied as drug delivery systems (DDS) and thus may be used for the improvement of chemotherapeutic agents.

From the results obtained in this work it was possible to conclude that the conjugates resulting from the link between the organometallic complex and the peptides exhibit high anticancer activity, overcoming the complex activity. For two of the most active conjugates, TM295 and TM298, the respective peptides, pepR and vCPP 2319, were responsible for the anticancer activity. Thus, it was possible to conclude that these peptides may not only act as part of the conjugates' structure, but they can also constitute a new investigation line in the field of anticancer peptides (ACPs) development.

Acknowledgements

The authors acknowledge Fundação para a Ciência e a Tecnologia (FCT I.P., Portugal) for financial support (UID/QUI/00100/2013 and IF/01179/2013 projects). Marie Skłodowska-Curie Research and Innovation Staff Exchange (RISE) is also acknowledged for funding: call H2020-MSCA-RISE-2014, Grant agreement 644167, 2015-2019. D. Gaspar and T.S. Morais thank FCT I.P. for fellowships SFRH/BPD/109010/2015 and SFRH/BPD/93513/2013. F.D. de Oliveira acknowledges financial support from PD/BD/135046/2017.

New sugar-based molecules for infectious and neurodegenerative diseases

Catarina Dias, Alice Martins, Rodrigo F. M. de Almeida, Amélia P. Rauter
*Centro de Química e Bioquímica, Departamento de Química e Bioquímica, Faculdade de Ciências,
Universidade de Lisboa, 1749-016 Lisboa, Portugal*

E-mail: cadias@fc.ul.pt

The increasing average life expectancy in developed countries led to an escalating concern regarding geriatric infectious diseases. Infections in elderly populations, particularly nosocomial infections, are known to be not only more frequent but also more severe, being this susceptibility often related to neurodegenerative diseases such as dementia and Alzheimer's.¹

Alkyl 2-deoxy/2,6-dideoxy-*arabino*-hexopyranosides with a potent antimicrobial activity in some *Gram*-positive bacteria have been previously described by our research group² and their mechanism of action was recently unravelled (unpublished results). Additionally, promising results arising from NMR interaction studies of some of these 2,6-dideoxyglycosides with cystatin B amyloid fibrils, show their potential for neurodegenerative diseases as well.

These results motivated us to explore the chemistry and bioactivity of 2-deoxy sugars as either neuroprotective or antimicrobial candidates. Thus, new alkyl 2-deoxyglycosides and their thio analogues were synthesized, as well as alkyl 3-deoxy, 4-deoxy and 6-deoxy glycosides, aiming at a better insight of the importance of the deoxygenation pattern. The action of the lead compound on the thermotropic behaviour of phosphatidylethanolamine liposomes was investigated, leading to the proposal of the mechanism of action for this family of compounds. In parallel, 2-deoxyglycosides embodying natural neuroprotective polyphenols were also prepared, envisioning the improvement of the activity and bioavailability of such molecules.

This work clearly demonstrates the uniqueness and versatility of carbohydrates as exceptional scaffolds for medicinal chemistry applications.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013, and by QREN – COMPETE program for the support of FACIB project (QREN – SI I&DT Co-Promotion project nr. 21547). C. Dias acknowledges financial support from FCT and CIPAN (SFRH/BDE/51998/2012). The European Union is gratefully acknowledged for the support of the project D3i4AD (FP7-PEOPLE-2013-IAPP, GA 612347).

References

- [1] G. Gavazzi, K.H. Krause, *Lancet Infect. Dis.* 2 (2002) 659-666.
- [2] A. Martins, M.S. Santos, C. Dias, P. Serra, V. Cachatra, J. Pais, J. Caio, V.H. Teixeira, M. Machuqueiro, M.S. Silva, A. Pelerito, J. Justino, M. Goulart, F.V. Silva, A.P. Rauter, *Eur. J. Org. Chem.* 8 (2013) 1448-1459.

Viral capsid proteins as a source for new membrane-targeting antibacterial peptides

S. A. Dias¹, J. M. Freire², C. P. Peinado³, M. M. Domingues¹, D. Gaspar¹, N. Vale⁴, P. Gomes⁵,
D. Andreu³, S. T. Henriques⁶, M. A. R. B. Castanho¹, A. S. Veiga¹

¹*Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal*

²*Department of Virology, Institut Pasteur, Paris, France*

³*Department of Experimental and Health Sciences, Pompeu Fabra University, Barcelona Biomedical Research Park, E-08003 Barcelona, Spain*

⁴*UCIBIO-REQUIMTE, Faculdade de Farmácia, Universidade do Porto, Porto, Portugal*

⁵*LAQV-REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Porto, Portugal*

⁶*Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland, Australia*

The increasing prevalence of multidrug-resistant bacteria urges the development of new antibacterial agents. With a broad spectrum activity and mechanisms of action that are different from the ones used by conventional antibiotics, antimicrobial peptides (AMPs) have been considered potential antibacterial drug leads. Using bioinformatic tools we have previously shown that viral structural proteins are a rich source for new bioactive peptide sequences, namely antimicrobial and cell-penetrating peptides (CPPs). In this work, the efficacy and mechanism of action of the most promising peptides, among those previously identified, were tested against both Gram-positive and Gram-negative bacterial strains. Given the proposed interplay between antimicrobial and cell-penetrating peptides activity, the antibacterial activity of selected viral protein-derived cell-penetrating peptides was evaluated. Two cell-penetrating peptides, vCPP 0769 and vCPP 2319, revealed strong antibacterial activity against all bacteria tested, being thus multifunctional. Also, one viral protein-derived peptide, vAMP 059, was identified as a potent antibacterial agent. The antibacterial mechanism of action of the two most active viral protein-derived peptides, vAMP 059 and vCPP 2319, was studied in detail. Both peptides revealed a fast killing kinetics against Gram-positive *S. aureus* and Gram-negative *P. aeruginosa*, with bacterial cell death occurring within minutes. Using flow cytometry and atomic force microscopy techniques, we showed that both peptides cause bacterial membrane permeabilization and damage of the bacterial envelope of *P. aeruginosa* cells. Overall, these results proved that structural viral proteins are an abundant and unexplored source for membrane-active peptides sequences with strong antibacterial properties.

Acknowledgements

This work was supported by FCT through PTDC/REQMED/4412/2014 and UID/QUI/50006/2013, by Marie Skłodowska-Curie Research and Innovation Staff Exchange (RISE): call H2020-MSCA-RISE-2014, Grant agreement 644167, 2015–2019. S.A. Dias acknowledges financial support from PD/BD/114425/2016.

Identifying LRRK2 inhibitors using homology model approach

S. Domingos^{a,b,c}, M. Teresa Duarte^b, L. Saraiva^c, R. Moreira^a, R. C. Guedes^a

^a *iMed.Ulisboa – Research Institute of Medicines, Faculdade de Farmácia da Universidade de Lisboa, Portugal*

^b *CQE – Centro de Química Estrutural, Instituto Superior Técnico da Universidade de Lisboa, Portugal*

^c *UCIBIO/REQUIMTE, Laboratório de Microbiologia, Faculdade de Farmácia da Universidade do Porto, Portugal*

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder, affecting approximately 1.5% of the population above 60 years of age and 4% of the 80-year-old population. Although PD remains rather uncommon, with the general aging of the population it is expected that its prevalence will quickly increase.^{1,2}

Leucine-rich repeat kinase 2 (LRRK2), also known as dardarin, is a multi-domain serine-threonine kinase belonging to the ROCO protein family, which seems to be involved in a complex array of intracellular processes.³ Although its biological role remains largely unknown, it is now well established that mutations in this protein are associated with autosomal dominant forms of PD.³ Therefore, inhibition of LRRK2 kinase activity is considered one of the most promising therapeutic strategies for the treatment of PD.³

With the aim of discovering new and innovative small molecules that can inhibit LRRK2 and be further used in the treatment of PD, a computational protocol combining virtual screening and structure-based drug design is being developed. Since no LRRK2 X-ray crystal structure is currently available, the first goal of this work was to identify a LRRK2 structure, using homology modelling, which could be used in the rational design of LRRK2 inhibitors. To accomplish this purpose, a series of LRRK2 kinase domain models were generated and optimized. Janus kinase 2 (JAK2)-based LRRK2 homology model was selected and further validated through docking studies on a diverse set of LRRK2 inhibitors. The main results of these studies will be presented and discussed.

Acknowledgements

Support for this work was provided by FCT through the iMed.Ulisboa UID/DTP/04138/2013, UCIBIO/REQUIMTE UID/QUI/50006/2013 and S. Domingos PhD grant PD/BD/114281/2016 from FCT [PhD Programme in Medicines and Pharmaceutical Innovation (i3DU)].

References

- [1] A. Elbaz, L. Carcaillon, S. Kab, F. Moisan, *Revue Neurologique* 172 (2016) 14-26.
- [2] L.V. Kalia, A.E. Lang, *Lancet* 386 (2015) 896-912.
- [3] R. Wallings, C. Manzoni, R. Bandopadhyay, *FEBS J.* (2015) 2806-2826.

Enantiopure bicyclic lactams as NMDA receptor antagonists

Margarida Espadinha^a, Jorge Dourado^a, Rocio Lajarin-Cuesta^{b,c},
Clara Herrera-Arozamena^d, Lidia M. D. Gonçalves^a, María Isabel Rodríguez-Franco^d,
Cristobal de los Rios^{b,c}, Maria M. M. Santos^a

^a *Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisboa, Portugal*

^b *Instituto Teófilo Hernando, Facultad de Medicina, Universidad Autonoma de Madrid, Madrid, Spain*

^c *Instituto de Investigacion Sanitaria, Hospital Universitario de la Princesa, Madrid, Spain*

^d *Instituto de Química Médica (IQM-CSIC), Madrid, Spain*

N-Methyl-D-aspartate (NMDA) receptors belong to the family of ionotropic glutamate receptors (iGluRs) and are localized in the cell membrane of neurons.¹ NMDA receptors have a vital role in the normal development of the nerve system, being important in sustaining healthy memory, learning, and cognitive processes. Although, the overactivation of these receptors leads to neuronal loss associated with major neurological disorders such as Parkinson's disease, Alzheimer's disease, schizophrenia, and epilepsy.¹ Therefore, the development of effective NMDA receptor antagonists is a promising therapeutic approach to treat some neurological disorders.¹

Here we present our latest results on the hit optimization of bicyclic lactams as NMDA receptor antagonists. Enantiopure oxazolopyrrolidone lactams were designed, synthesized, and biologically evaluated as NMDA receptor antagonists. The potential of the synthesized compounds as NMDA receptor antagonists was measured by their capacity to inhibit NMDA-induced increase of intracellular Ca²⁺ levels in *in vitro* cultures of embryonic rat cortical neurons, using the Ca²⁺-sensitive fluorescent dye Fluo-4. Most of the new compounds displayed NMDA receptor antagonism, and the most promising compound (**1a**) showed an IC₅₀ value of 27 μM, on the same order of magnitude as that of memantine (47 μM), an NMDA receptor antagonist in clinical use for the treatment of Alzheimer's disease. Further biological evaluation indicated that this compound is brain permeable (determined by an *in vitro* assay) and non-hepatotoxic.²

Acknowledgements

We thank the Fundação para a Ciência e Tecnologia for financial support through iMed.Ulisboa (UID/DTP/04138/2013), research project PTDC/QUI-QUI/111664/2009 and to FCT fellowship SFRH/BD/117931/2016 (M. Espadinha). We also want to thank for financial support through Instituto de Salud Carlos III, Spanish Ministry of Health (PI13/00789), and Spanish Ministry of Economy and Competitiveness (MINECO, grants SAF2012-31035 and SAF2015-64948-C2-1-R).

References

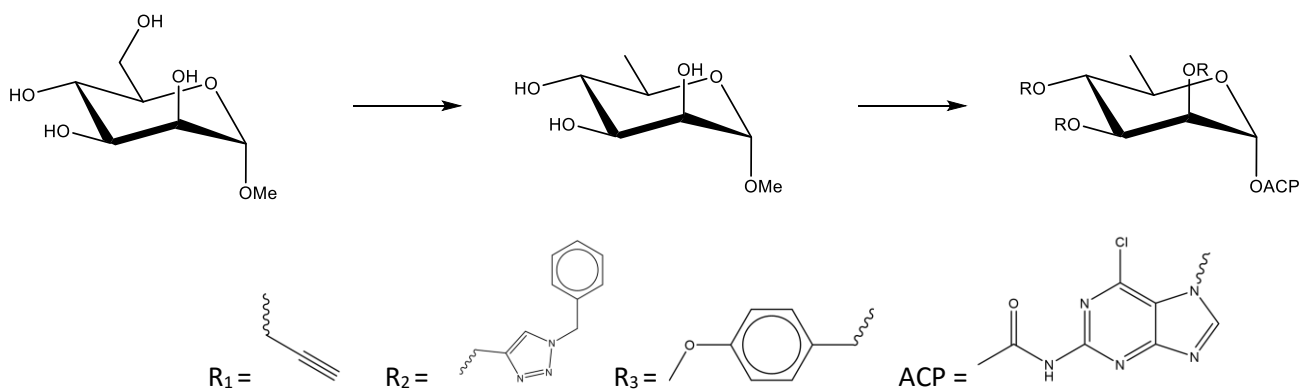
- [1] a) P. Stawski, H. Janovjak, D. Trauner, *Bioorg. Med. Chem.* 18 (2010) 7759-7772; b) R. Morris, *Neuropharmacology* 74 (2013) 32-40; c) N.A.L. Pereira, F.X. Sureda, M. Turch, M. Amat, J. Bosch, M.M.M. Santos, *Monatsh. Chem.* 144 (2013) 473-477.
- [2] M. Espadinha, J. Dourado, R. Lajarin-Cuesta, C. Herrera-Arozamena, L. Gonçalves, I. Rodríguez-Franco, C. de los Ríos, M.M.M. Santos, *ChemMedChem*. 12 (2017) 537-545.

Synthesis of purine nucleosides precursors with deoxygenated sugars: exploratory chemistry of potential butyrylcholinesterase selective inhibitors

Diogo D. Ferreira, Vasco Cachatra and Amélia P. Rauter

Grupo da Química dos Glúcidos, Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Portugal

The purpose of this work is to synthesise purine nucleosides precursors with deoxygenated sugars as potential butyrylcholinesterase (BChE) selective inhibitors to better understand the way butyrylcholine (BCh) affects Alzheimer's Disease (AD) in the final disease stages. As of today, work has been done with different purine bases and various sugar moieties of purine nucleosides, and it was found that perbenzyl D-mannosyl moiety α -N⁷-linked to 2-acetamido-6-chloropurine (ACP) led to the best selective inhibition of BChE ($IC_{50} = 50nM$).^{1,2} As an attempt to improve and further investigate factors that promote BChE inhibition, the deoxygenation of D-mannose to D-rhamnose and subsequent protection with protecting groups such as propargyl (R_1), 1-benzyl-4-methyl-1H-1,2,3-triazole (R_2) and *p*-methoxybenzyl (R_3) groups was carried on and will be presented and discussed. Compound structure evidence was provided by NMR spectra and will also be discussed.



Acknowledgements

Support for this work was provided by FCT through project UID/MULTI/00612/2013 and by the European Union's Seventh Framework Programme (FP7-PEOPLE-2013-IAPP, GA 612347).

References

- [1] F. Marcelo, F.V.M. Silva, M. Goulart, J. Justino, P. Sinaÿ, Y. Blériot, A.P. Rauter, *Bioorg. Med. Chem.* 17 (2009) 5106-5116.
- [2] S. Schwarz, R. Csuk, A.P. Rauter, *Org. Biomol. Chem.* 12 (2014) 2446-2456.

Reversing multidrug resistance (MDR) in cancer cells by targeting P-glycoprotein

Ricardo J. Ferreira^a, Daniel J. V. A. dos Santos^{a,b}, Maria José U. Ferreira^a

^a iMed.Ulisboa, Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto,
1649-003 Lisboa, Portugal

^b LAQV@REQUIMTE, Faculdade de Ciências da Universidade do Porto, Rua do Campo Alegre,
4169-007 Porto, Portugal

Multidrug resistance (MDR) in cancer is currently one of the major impairments in the success of chemotherapy regimens. Accordingly, one of the most promising approaches in overcoming MDR is the development of efflux modulators for P-glycoprotein (P-gp). Furthermore, a greater knowledge on the P-gp efflux mechanism is important to clarify the key steps by which drug efflux occurs and how it can be prevented. The main objective of this work was to identify and optimize novel MDR reversers, derived from *Euphorbia* species, and to gain novel insights on the drug efflux mechanism by P-gp.

The phytochemical study of *Euphorbia pedroi* yielded several new macrocyclic diterpenes of the lathyrane and jatrophane-type together with other new and known terpenoids and flavonoids. Moreover, small libraries of *ent*-abietane and flavanone derivatives were built through molecular derivatization of compounds isolated from this species. The structures of compounds were deduced from physical and spectroscopic data (IR, MS and NMR experiments).

The MDR reversal activity of compounds was evaluated by combining transport and chemosensitivity assays using the *MDR1*-transfected mouse T-lymphoma and Colo320 cell models. While several natural compounds showed good MDR reversal activities, *ent*-abietane and flavanone derivatives also revealed increased potencies towards the MDR cell lines when compared with the parent compounds. The effects of flavanone derivatives on other ABC transporters was also assessed, with several compounds being selective for breast cancer resistance protein (BCRP) and multidrug resistance protein 1 (MRP1) efflux pumps, respectively.

The efflux mechanism was also studied by means of molecular dynamics and docking studies. Based on a previously refined P-gp structure, three distinct drug-binding sites could be identified and characterized, in a good agreement with published experimental data. Drug transit from bulk water into the DBP was characterized as an overall free-energy downhill process, with no activation energy required for crossing the 'entrance' gate found between transmembrane domains. Furthermore, as substrates and modulators were showed to have different free energies of adsorption in both lipid/water and protein/water interfaces, important differences in drug-protein interactions, protein dynamics and membrane biophysical characteristics were able to be characterized.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013, PEst-OE/QUI/UI0612/2013, PTDC/QEQ-MED/0905/2012 and UID/DTP/04138/2013. R.J. Ferreira acknowledges financial support from the PhD grant SFRH/BD/84285/2012.

Torin-based compounds: Exploring their potential towards the treatment of protozoan Neglected Tropical Diseases

Lara Fidalgo^{a,*}, Jorge Grilo^{a,*}, Rosario Diaz^b, Miguel Navarro^b, Dolores G. Pacanowska^b, Rui Moreira^a, Ana S. Ressurreição^a

^a *iMed.Ulisboa, Faculty of Pharmacy, Universidade de Lisboa, Av. Professor Gama Pinto, 1649-003 Lisbon, Portugal; E-mail: lgfidalgo@ff.ulisboa.pt* *LF and JG contributed equally to the work

^b *Instituto de Parasitologia y Biomedicina "Lopez-Neyra", Consejo Superior de Investigaciones Científicas (CSIC), Granada 18100, Spain*

Of the 850 new therapeutic products registered in the last decade, only 5 (0.6%) were indicated for neglected tropical diseases (NTDs), none of them being a new chemical entity or vaccine. One important approach to overcome this gap is generically referred to as drug repurposing, namely by exploitation of existing drugs in different therapeutic areas.¹

Kinases represent a large proportion of the druggable genome and, as such, have been the focus of drug discovery programs. Comparative analysis on the genomes of the protozoan parasites responsible for some NTDs revealed hundreds of protein kinases (PKs) in *Trypanosoma brucei* (176), *Trypanosoma cruzi* (190) and *Leishmania major* (199), most of which are orthologous across these species.² Therefore, the kinase gene family represents a rich source of potential biological targets for pursuing anti-parasitic agents. Repurposing current knowledge about molecular targets that pathogens hold in common with humans is one of the most powerful strategies to bridge the gap between biology and drug discovery for NTDs, using scaffolds that are known as potent inhibitors of the human homologues of essential kinases in the parasites.

Our group has recently disclosed Torin2, an ATP-competitive mTOR kinase inhibitor,³ as a potent antimalarial with *in vivo* activity against both liver and blood stages and a distinct mode of action compared with currently used antimalarials.⁴ These findings inspired us to further explore Torin2 in other protozoan parasites and our results showed that the compound is consistently efficient against *T. brucei* and *T. cruzi* (IC₅₀ in the nM range). Based on the gathered knowledge, we have synthesized a highly diversified library of Torin-based analogues in order to establish the key structural features that determine biological activity and those that can contribute to parasite selectivity.

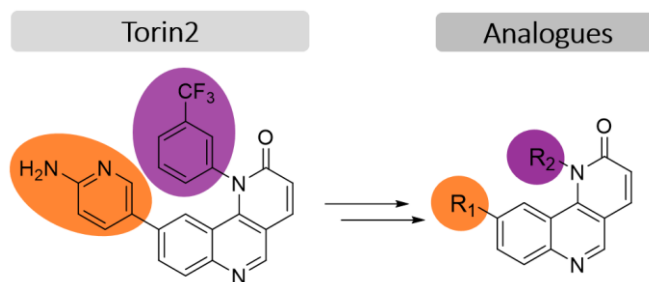


Figure 1. Probing the chemical space around Torin2 scaffold.

Acknowledgements

We thank the Fundação para a Ciência e Tecnologia for financial support through the project PTDC/QEQ-MED/7097/2014 and the PhD fellowship grant PD/BD/128260/2016 awarded to J. Grilo.

References

- [1] B. Pedrique, N. StrubWourgaft *et al.*, *Lancet Glob. Health* 1 (2013) E371.
- [2] M. Parsons, E.A. Worthey *et al.*, *BMC Genomics* 6 (2005) 19.
- [3] Q. Liu, J. Wang, S.A. Kang *et al.*, *J. Med. Chem.* 54 (2011) 1473.
- [4] K.K. Hanson, A.S. Ressurreição, K. Buchholz, M. Prudêncio *et al.*, *Proc. Natl. Acad. Sci. USA* 110 (2013) E2838.

Novel azido nucleosides and their phosphoramidates as potential anticancer agents

Rita Gonçalves-Pereira^a, Radek Jorda^b, Eva Řezníčková^b, Vladimír Kryštof^b
and Nuno M. Xavier^a

^a *Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa,
Ed. C8, 5º Piso, Campo Grande, 1749-016 Lisboa, Portugal; E-mail: nmxavier@fc.ul.pt*

^b *Laboratory of Growth Regulators, Palacký University & Institute of Experimental Botany,
AS CR, Šlechtitelů 27, 78371 Olomouc, Czech Republic*

Synthetic nucleosides, nucleotides and analogs constitute privileged classes of molecules in medicinal chemistry, particularly in anticancer and antiviral research, which is well demonstrated by the various compounds of these types in clinical use.¹ These molecules have the ability to mimic natural nucleotides and to be recognized by nucleotide-dependent enzymes, interfering and inhibiting essential biological pathways, whose deregulation or over-activation drive the progress of some diseases such as cancer or viral infections.

Among the nucleotide analogs that have shown potent biological effects associated with good cell permeability are the nucleoside phosphoramidates,² which are neutral and rather lipophilic molecules in which an amino group replaces a phosphate alkoxy or hydroxyl group. The reported bioactive nucleoside phosphoramidates, such as the clinically used antiviral drug sofosbuvir³ and the anticancer agent cytarabine phosphoramidate⁴, contain the phosphoramidate moiety linked to the nucleoside at C-5' by an oxygen atom.

We present herein the synthesis and anticancer potential of new xylofuranosyl and glucopyranosyl nucleoside phosphoramidates, comprising the phosphoramidate system connected by the nitrogen atom to the furanose or to the pyranose moiety at C-5' or at C-6', respectively⁵. Their access was based on the N-glycosylation of a nucleobase derivative with 5'/6'-azido-1,2-di-O-acetyl glycosyl donors and further Staudinger-phosphite reaction.

The nucleoside phosphoramidates as well as the 5'/6'-azido nucleoside precursors were evaluated for their antiproliferative activities on cancer cells. Some azido nucleosides displayed activities at single-digit micromolar concentration range. Flow cytometry was further performed in order to determine the effect of the most active nucleosides on the cell cycle.

Acknowledgements

Support for this work was provided by FCT through projects UID/MULTI/00612/2013 and IF/01488/2013/CP1159/CT0006.

References

- [1] L.P. Jordheim, D. Durantel, F. Zoulim, C. Dumontet, *Nat. Rev. Drug Discovery* 12 (2013) 447-464.
- [2] U. Pradere, E.C. Garnier-Amblard, S.J. Coats, F. Amblard, R.F. Schinazi, *Chem. Rev.* 114 (2014) 9154-9218.
- [3] G.M. Keating, *Drugs* 74 (2014) 1127-1146.
- [4] S.C. Tobias, R.F. Borch, *Mol. Pharm.* 112 (2004) 112-116.
- [5] N.M. Xavier, R. Gonçalves-Pereira, R. Jorda, E. Řezníčková, V. Kryštof, M.C. Oliveira, *Pure Appl. Chem.* (2017).

Development of Novel Affinity-Based Probes Targeting African Trypanosomiasis

Jorge Grilo^{a,*}, Lara Fidalgo^{a,*}, André Dias^a, Rosario Diaz^b, Miguel Navarro^b,
Ana S. Ressurreição^a

^a *iMed.Ulisboa, Faculty of Pharmacy, Universidade de Lisboa. Av. Professor Gama Pinto,
1649-003 Lisbon, Portugal*

^b *Instituto de Parasitología y Biomedicina "Lopez-Neyra", Consejo Superior de Investigaciones Científicas
(CSIC), Granada 18100, Spain*

* Both author contributed equally to this work

Neglected tropical diseases are a group of infectious diseases prevalent in tropical regions that burden the lives of billions, mainly those living in developing countries. *Trypanosome brucei* caused African Trypanosomiasis, also known as Sleeping Sickness, is one of the major protozoan parasite infections plaguing the African continent.¹

Following the previous findings that Torin2, a known mTOR kinase inhibitor², selectively inhibit malaria development *in vivo*³, by a mechanism of action that does not involve interaction with human targets, and with the knowledge that protozoan parasites in the *Plasmodium* and *Trypanosoma* genus share several orthologous kinase proteins⁴, our group has developed a library of Torin2 analogues that show promising activity (nM range) towards *T. brucei* parasites.

To unveil the target of this class of compounds, we will report the development of a set of photo-affinity based probes, through the incorporation on the Torin scaffold of a photo-activated crosslinker moiety and a click handle for subsequent bioconjugation with fluorophore reporters (Figure1). These selective modifications enable a viable route for proteome profiling and identification of the parasite druggable targets.

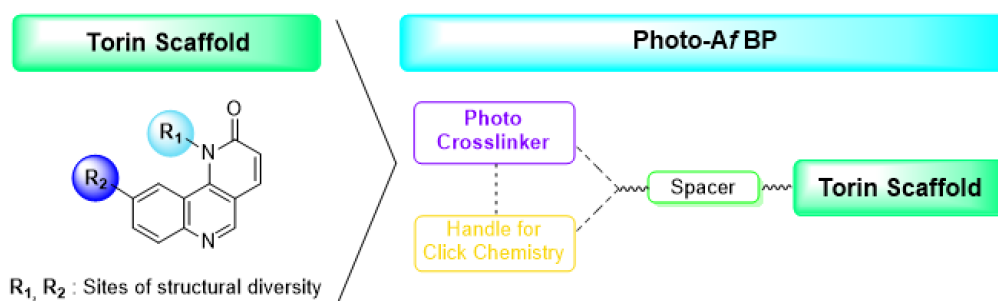


Figure 1. Development of Photoaffinity-based Probes (Photo-AfBP) from the Torin2 scaffold.

Acknowledgements

Support for this work was provided by FCT through PTDC/QEQ-MED/7097/2014. J. Grilo acknowledges financial support from FCT through PD/BD/128260/2016. A.S. Ressurreição is a FCT Investigator (Starting Grant).

References

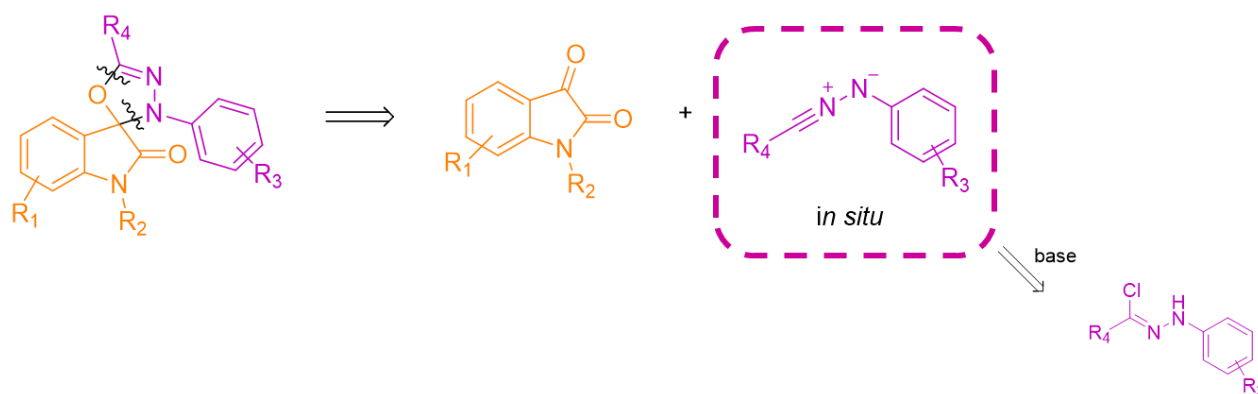
- [1] WHO, Neglected tropical diseases. http://www.who.int/neglected_diseases/diseases/en (May 7, 2017).
- [2] a) Q. Liu, J. Wang, S.A. Kang, S. A. *et al.*, *J. Med. Chem.* 54 (2011) 1473.
- [3] K.K. Hanson, A.S. Ressurreição, K. Buchholz *et al.*, *Proc. Natl. Acad. Sci. USA* 110 (2013) E2838.
- [4] M. Parsons, E.A. Worthey *et al.*, *BMC Genomics* 6 (2005) 19.

Spirooxadiazoline oxindoles: potential anticancer agents

Elizabeth Lopes, Damla Uyar, Lídia M. Gonçalves, Maria M. M. Santos
Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa,
Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal

Cancer is one of the modern world's most common and deadly non-infectious disease. According to WHO Cancer Report of 2015, it is one of leading causes of morbidity and mortality worldwide with 8.8 million deaths in 2015 and it's expected to rise about 70% over the next 20 years.¹ The non-selectivity and acute toxicity of many antitumor agents has prompted the search for new antitumor agents with improved tumor selectivity, efficiency and safety.

In this area of research, we have been working in the development of spirooxindole scaffolds that possess promising *in vitro* anti-tumor activities in colon cancer cell lines.² In this communication, we report the synthesis of a novel library of spirooxadiazoline oxindoles, by 1,3-dipolar cycloaddition of isatin derivatives with different nitrile imines formed *in situ* from hydrazonyl chlorides derivatives (Scheme), as well as the results obtained from the screening of this library in breast cancer cell lines.



Scheme. Retrosynthesis of spirooxadiazolines oxindole library

Acknowledgements

This work was supported by FCT (Fundação para a Ciência e a Tecnologia) through iMed.ULisboa (UID/DTP/04138/2013). M.M.M. Santos would like to acknowledge Fundação para a Ciência e a Tecnologia (FCT, Portugal), "Programa Operacional Potencial Humano" and the European Social Fund for the IF Program (IF/00732/2013).

References

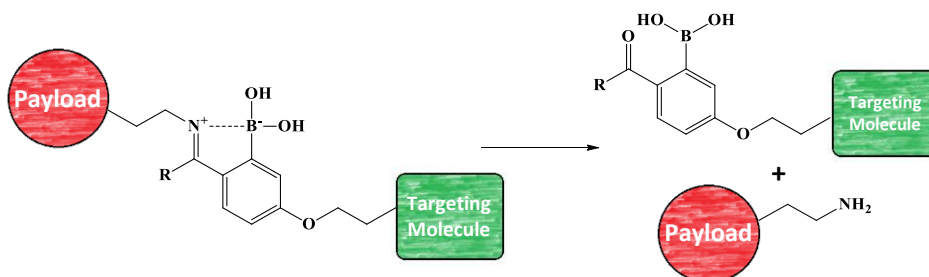
- [1] World Health Organization. <http://www.who.int/mediacentre/factsheets/fs297/en/> (accessed on 02-05-2017).
- [2] a) C.J. Ribeiro, J.D. Amaral, C.M. Rodrigues, R. Moreira, M.M.M. Santos, *MedChemComm* 7(3) (2016) 420.
b) Â. Monteiro, L. Gonçalves, M.M.M. Santos, *Eur. J. Med. Chem.* 79 (2014) 266.

Evaluation of iminoboronates as linker for payload delivery in biological systems

R. M. Lopes, A. E. Ventura, P. M. M. Gois

Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, Universidade de Lisboa,
Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal

Chemotherapy uses small potent molecules with high activity towards specific tumour targets. However, with such high activity comes high off target toxicity and severe side effects. Fortunately, chemotherapy can be now targeted thanks to powerful linkers that connect a ligand molecule with affinity to interesting biological receptors and a cytotoxic drug. These linkers must have very specific properties, such as high stability in plasma, no toxicity, no interference with ligand affinity nor drug potency, and at the same time, be able to self-lyse once inside the target cell. Bipolar environments as seen between tumoural extracellular and intracellular medias are usually exploited by these linkers in order to release the therapeutic warhead. This work explores a new model for the same task, specific cancer drug delivery.¹ Iminoboronates were studied due to its remarkable selective stability towards a wide pH range and endogenous molecules.² Bioconjugates were design to prove this iminoboronate linker's effectiveness. The ability to be uptaken by a cancer cell through endocytosis process and delivery of specific payload are two features expected for this construct.



Scheme 1. Iminoboronate as payload delivery system model.

Acknowledgements

Support for this work was provided by FCT through SFRH/BD/121664/2016, PTDC/QEQMED/5512/2014, PTDC/QEQ-QOR/1434/2014, UID/DTP/04138/2013, SAICTPAC/0019/2015.

References

- [1] P.M.S.D. Cal, R.F.M. Frade, V. Chudasama, C. Cordeiro, S. Caddick, P.M.P. Gois, *Chem. Commun.* 50 (2014) 5261-5263.
- [2] P.M.S.D. Cal, J.B. Vicente, E. Pires, A.V. Coelho, L.F. Veiros, C. Cordeiro, P.M.P. Gois, *J. Am. Chem. Soc.* 134(24) (2012) 10299-10305.

New diterpenes from *Euphorbia* species

L. Lourenço, N. Duarte, M. J. U. Ferreira

iMed.ULisboa – Research Institute for Medicines, Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal

Even though there has been a significant progress in cancer chemotherapy in the last years, resistance of cancer cells to chemically unrelated drugs, often with different mechanisms of action, known as multidrug resistance (MDR), has hampered the successful therapy of cancer diseases. The overexpression of the transmembrane proteins from the ATP-binding cassette (ABC) transporters, being P-glycoprotein (P-gp) the most studied, is one of the most relevant mechanisms of MDR.¹ *Euphorbia* species have been the source of compounds with interesting biological activities. In particular, the discovery of jatrophone- and lathyrane-type diterpenes as a new class of potent modulators of P-gp has promoted an increasing interest in the research of this genus.²

Aiming at finding new macrocyclic or polycyclic diterpenes as effective P-gp modulators, the phytochemical study of some fractions of the methanol extracts of *Euphorbia boetica* and *Euphorbia pubescens* was carried out. Four novel diterpenes and several known terpenic compounds were isolated. Two of the new isolated compounds have the premirsinane skeleton, an uncommon polycyclic scaffold derived from the rearrangement of the lathyrane skeleton by intramolecular cyclization at positions C-6/C-12. The other novel diterpenes are polyacylated tiglane esters, one of them presenting a rare stereochemistry. Moreover, helioscopinolide E, an α,β -unsaturated polycyclic diterpenic lactone that was found to be active as a P-gp modulator³, was submitted to several chemical transformations, aiming at generating compounds with improved multidrug resistance modifying activity. The chemical structures of all the compounds, including stereochemical features, were deduced from their physical and spectroscopic data, which included: infrared spectroscopy, mass spectrometry (MS), and extensive one- and two-dimensional nuclear magnetic resonance studies (COSY, HMQC, HMBC and NOESY).

Acknowledgements

Support for this work was provided by FCT through projects: PTDC/QEQ-MED/0905/2012 and Pest-OE/SAU/UI4013/2014.

References

- [1] J. Dinic, A. Podolski-Renic, T. Stankovic, J. Bankovic, M. Pesic, *Curr. Pharm. Des.* 21 (2015) 5589-5604.
- [2] M.J.U. Ferreira, N. Duarte, M. Reis, A.M. Madureira, J. Molnár, *Phytochem. Rev.* 13 (2014) 915-935.
- [3] M.J.U. Ferreira, N. Gyémánt, A.M. Madureira, J. Molnár, *Anticancer Res.* 25 (2005) 3259-3262.

In vitro cytotoxicity evaluation of new drug candidates for neurodegenerative diseases

Alice Martins¹, Ana Marta Matos¹, Catarina Dias¹, Vasco Cachatra¹,
Marialessandra Contino², Roberta Giampietro², Nicola Colabufo², Amélia P. Rauter¹

¹ Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Ed C8,
Campo Grande, 1749-016 Lisboa, Portugal

² Biofordrug, Via Edoardo Orabona, 4, 70125 Bari, Italy

The degeneration of the central nervous system is characterized by a progressive loss of the structure and functions of neuronal system, increasing with age, in mid-to-late adult life.¹ Pathologically, a frequent characteristic of neurodegenerative diseases is the accumulation and aggregation of abnormal or misfolded proteins, as amyloid- β (A β) in Alzheimer's, α -synuclein in Parkinson's and huntingtin protein in Huntington's diseases, among others.² However, there are many other mechanisms involved in neurodegenerative disorders. So, efforts regarding the research of new and effective multitarget drugs with less side-effects and low cytotoxicity can contribute to alter the course of such diseases and to improve the patients' quality of life.

In this communication, we report the *in vitro* cytotoxicity of a small library of synthesized glycosylated phenols and purine nucleosides with potential for the treatment of neurodegenerative diseases. Assays were performed on Caco-2 and HepG2 cell lines, and cell viability evaluated by the MTT method³. After 24 and 48 h incubation time, glycosylated phenolic compounds denoted no toxicity on both cell lines, even at high concentrations (100 μ M). On the contrary, purine nucleoside scaffolds revealed significant cytotoxicity at concentrations higher than 10 μ M. However, their strong anticholinesterase activity up to 10 nM evidences a broad therapeutic window for this group of compounds. These results can contribute to develop new leads with optimized non-toxic and bioactive structures for further application on the treatment of neurodegenerative conditions.

Acknowledgements

The European Union is gratefully acknowledged for the support of the project "Diagnostic and Drug Discovery Initiative for Alzheimer's Disease" (D3i4AD), FP7-PEOPLE-2013-IAPP, GA 612347. Support for this work was also provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013. FCT is also acknowledged for the PhD grants SFRH/BDE/51998/2012 (to C. Dias), SFRH/BD/93170/2013 (to A.M. Matos) and SFRH/BD/90359/2012 (to V. Cachatra).

References

- [1] W.-W. Chen, X. Zhang, W.-J. Huang. *Mol. Med. Rep.* 13 (2016) 3391-3396.
- [2] V.K. Ramanan, A.J. Saykin. *Am. J. Neurodegener. Dis.* 2 (2013) 145-175.
- [3] N.A. Colabufo, F. Berardi, M. Cantore, M.G. Perrone, M. Contino *et al.*, *Biorg. Med. Chem.* 16 (2008) 362-373.

Synthesis and evaluation of antitumor activity of novel thiobenzanilides

Maria João Martins^a, Filomena Martins^a, Rita Pacheco^{a,b}, Susana Santos^a

^a Centro de Química e Bioquímica, Faculdade de Ciências da Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal; E-mail: fc44349@alunos.fc.ul.pt

^b Área Departamental de Engenharia Química, Instituto Superior de Engenharia de Lisboa, Av. Conselheiro Emídio Navarro, 1959-007 Lisboa, Portugal

Cancer is a generic term for a large group of diseases where there is an uncontrolled growth of cells¹ and, according to the World Health Organization², caused 8.8 million of deaths in 2015. The number of cancer cases has been increasing worldwide due to the growth and/or aging of the population, as well as the prevalence of risk factors, including smoking and sedentary lifestyles, among others. Melanoma is not the most common type of skin cancer but it is the deadliest one³, with a global incidence of almost 132000 cases each year². Breast cancer is the most incident in women (almost 25% of the cases) both in developed and developing countries.² Due to the complexity and specificity of each cancer, it is necessary to develop new drugs and new and more effective therapies, in order to combat this problem.

In this context, we decided to synthesize a series of new thiobenzanilides and evaluate their activity against melanoma and breast cancer cell lines. Thiobenzanilides are compounds which are well known for their broad biological spectrum, showing antifungal, antimycotic, antibacterial, spasmolytic and also antitumoral activity⁴. In the present work, five new thiobenzanilide derivatives (Figure 1) were synthesized in a two steps pathway, and were characterized by 1D/2D NMR and IR. The structure of the compounds was chosen so that we could study the influence of R₁ substituents on their anticancer activity. This activity was assessed against breast cancer human cells (MCF 7) and human melanoma cells (A375) using the MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) colorimetric test, being determined for each compound the concentration which killed 50% of the cells, *i.e.*, the EC₅₀ value.

So far, the majority of the compounds tested positive against both cell lines, in the micromolar range, and these are very promising results for this type of compounds.

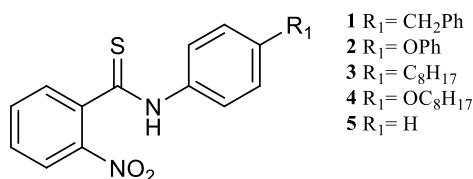


Figure 7. Structure of the new synthesized thiobenzanilides.

Acknowledgements

Support for this work was provided by FCT through PEst-OE/QUI/UI0612/2013 and project PTDC/QUI/67933/2006.

References

- [1] H.A. Bhuva, S.G. Kini, J. Mol. Graph. Model. 29 (2010) 32-37.
- [2] <http://www.who.int/cancer/en/> (accessed on May 8, 2017).
- [3] <http://www.skincancer.org> (accessed on May 8, 2017).
- [4] M. Kucinska, H. Piotrowska-Kempisty, N. Lisiak, M. Kaczmarek, H. Dams-Kozłowska, W.H. Granig, M. Höferl, W. Jäger, M. Zehl, M. Murias, T. Erker, Toxicol. Vitro. 37 (2016) 148-161.

Exploiting the Potential of C-Glucosyl Flavonoid Analogues against Diabetes and Alzheimer's Disease

Ana M. Matos, Alice Martins and Amélia P. Rauter

Carbohydrate Chemistry Group, Centro de Química e Bioquímica, Faculdade de Ciências,
Universidade de Lisboa, Portugal

E-mail: amamatos@fc.ul.pt

According to the International Diabetes Federation, type 2 diabetes accounts for at least 90% of all cases of diabetes, affecting over 415 million people around the world. Family history of diabetes, unhealthy lifestyles and increasing age are known major risk factors for this metabolic disorder. On the other hand, the risk of dementia (particularly Alzheimer's disease) is up to 73% higher in people with type 2 diabetes and, therefore, the increasing incidence of Alzheimer's disease is perhaps not only a consequence of population ageing alone, but also a result of the diabetes epidemic itself.¹

The discovery of an extremely potent antidiabetic C-glucosyl isoflavone isolated from *Genista tenera*² prompted us to further explore the ability of this and other related compounds to exert antidiabetic and neuroprotective effects as well. Hence, in this communication we will present our efforts to combine key features of the flavone scaffold with the reported benefits of the sugar moiety. Aiming at the disclosure of structural requirements of flavonoid derivatives with optimal physicochemical properties against therapeutic targets such as $A\beta_{1-42}$, we have focused on the synthetic introduction of structural variations on the flavonoid core, which culminated in the development of a small library of nature-inspired flavone analogues with therapeutic potential against type 2 diabetes and Alzheimer's disease.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013, as well as the PhD grant SFRH/BD/93170/2013, awarded to A.M. Matos.

The authors acknowledge financial support from the European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreement n°612347.

References

- [1] A.M. Matos, M.P. Macedo, A.P. Rauter, *Med. Res. Rev.* (2017) [DOI:10.1002/med.21440].
- [2] A.R. Jesus, C. Dias, A.M. Matos, R.F. de Almeida, A.S. Viana, F. Marcelo, R.T. Ribeiro, M.P. Macedo, C. Airoidi, F. Nicotra, A. Martins, E.J. Cabrita, J. Jimenez-Barbero, A.P. Rauter. *J. Med. Chem.* 57(22) (2014) 9463-9472.

Anti-tumoral Fe(III) aminophenolate complexes

Cristina P. Matos^{a,b}, Zelal Adiguzel^c, M. Helena Garcia^b, João Costa Pessoa^a,
Ceyda Acilan^c, Ana Isabel Tomaz^b, Isabel Correia^a

^a Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais 1, 1049-001 Lisboa, Portugal

^b Centro de Química Estrutural, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

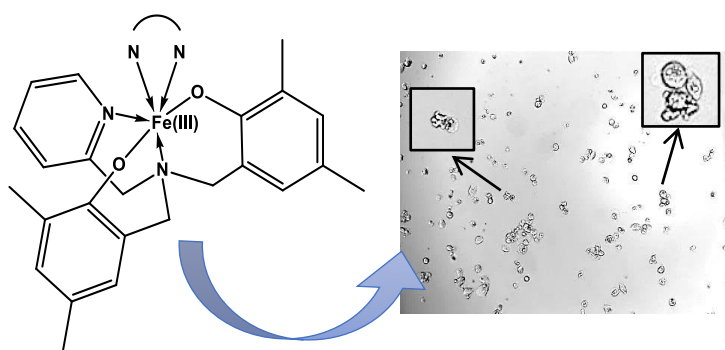
^c TUBITAK, Marmara Research Center, Genetic Engineering and Biotechnology Institute, Gebze, Kocaeli, Turkey

Cancer remains one of the most challenging diseases and cancer-related deaths are estimated to rise as life expectancy increases. The success of cisplatin proved that metallodrugs have a role to play in the fight against cancer. The development of drugs based on biologically essential transition metals aims to surpass one of the major metallodrugs limitations: their toxicity. Iron, being redox-active and involved in the regulation of cell-growth and differentiation, is an appealing candidate to achieve highly effective, as well as less toxic chemotherapeutic agents.

Iron(III)-complexes containing phenolate ligands with tripodal amines have been intensively studied as mimics of enzyme active sites and metal-binding sites of iron proteins, but few reports deal with their application as therapeutic agents. Tripodal aminophenolate compounds are quite versatile ligands, as substituents at the phenolate rings, as well as the position and nature of the donor atoms, are easily tuneable features.¹ The introduction of a NN aromatic heterocyclic co-ligand in these complexes could enforce their biological activity, as metal complexes containing, for example,

phenanthrolines, are reported to be active against various pathologic conditions.²

We synthesized a family of complexes bearing a tripodal aminophenolate ligand and NN bidentate co-ligands (Figure 1). The complexes exhibit cytotoxic activity against several human cancer cell lines. Cells treated with the complexes display typical morphological features of



apoptosis (Fig.1). DNA induced damage may be related to the complexes ability to generate ROS.

Acknowledgements

Authors thank Dr. Fernanda Marques (C²TN-IST) for A2780 cell studies, the Portuguese NMR Network (IST Nodes) and financial support from FCT, TUBITAK Internal Funding, the Investigador FCT programme 2012 and 2013 (project IF/01179/2013, POPH and the European Social Fund), project UID/QUI/00100/2013 and PhD grant SFRH/BD/101214/2014.

References

- [1] T. Marshall-Roth, S.N. Brown, Dalton Trans. 44 (2015) 677-685.
- [2] S. Jagadeesan, V. Balasubramanian, P. Baumann, M. Neuburger, D. Haussinger, C.G. Palivan, Inorg. Chem. 52 (2013) 12535-12544.

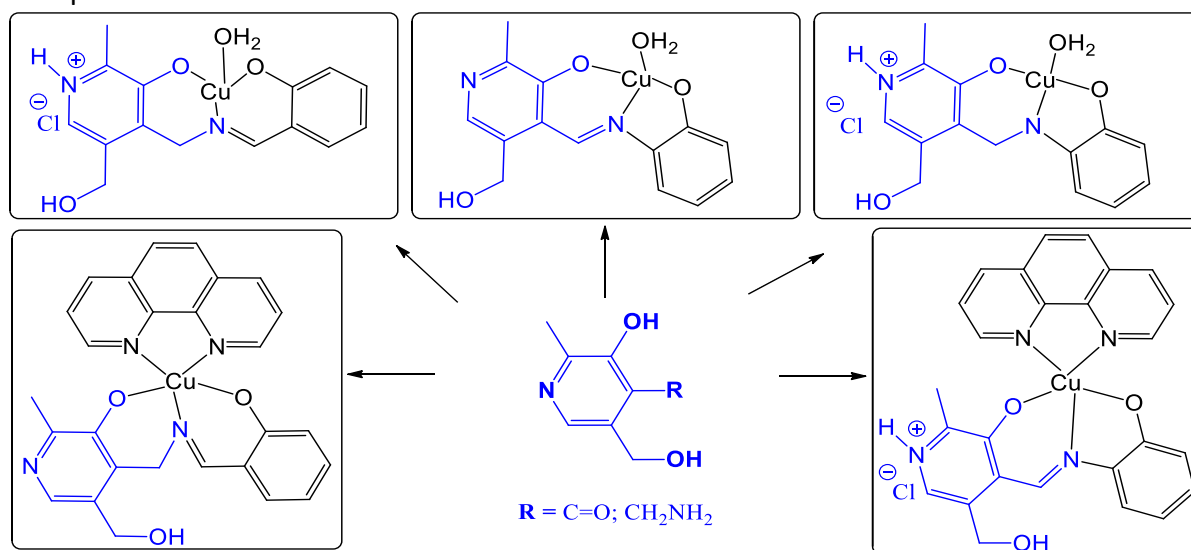
Therapeutic copper complexes of vitamin B₆ related compounds

Patricque Nunes^a, Fernanda Marques^b, João Pessoa^a, Isabel Correia^a

^a Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Portugal

^b Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa, Portugal

It is known that copper deficiency or toxicity is involved in diverse diseases. Therefore, copper-complexes have been studied for their therapeutic and diagnostic potential, showing potential in cancer treatment due to their cytotoxicity and tendency to stimulate oxidative stress.¹ Vitamin-B₆ serves as coenzyme in numerous biochemical reactions involved in cell metabolic processes. B₆-vitamers have gathered increasing attention since enzymatic reactions have been mimicked by non-enzymatic reactions in which pyridoxal in the presence of a suitable metal ion acts as catalyst.² The reaction mechanism has been associated with the Schiff base (SB) complexes formation.³ A SB complex involving VO(IV) and pyridoxal – vitamin B₆ form – has shown high selectivity and cytotoxicity for two carcinoma cells lines which involve apoptosis through ROS formation.⁴ Moreover, vitamin B₆, besides being an antioxidant, has shown that high concentrations of pyridoxal in cancer cells induce significant reductions in cell-proliferation.⁵ Therefore, investigation of pyridoxal Cu-complexes has high potential to successfully develop effective chemotherapeutics. In the current work, five SB copper(II) complexes containing B₆-vitamers were synthesized and characterized by several techniques. Preliminary results on antioxidant activity and cytotoxicity for two cancer lines (MCF7 and A2780) are reported. Most complexes showed moderate or high cytotoxicity against MCF7, with the compounds containing the phenantroline co-ligands showing the best performance in both cell lines.



Acknowledgements

Support for this work was provided by FCT through SFRH/BD/108743/2015a and UID/QUI/00100/2013. The Portuguese NMR and Mass Spectrometry IST–UL Centers are acknowledged for the access to the equipment.

References

- [1] C. Duncan, A.R. White, *Metallomics*. 4 (2012) 127-138.
- [2] D.E. Metzler, J.B. Longenecker, E.E. Snell, *J. Am. Chem. Soc.* 75 (1953) 2786-2787.
- [3] A.E. Martell, *Acc. Chem. Res.* 22 (1989) 115.
- [4] M. Strianese, A. Basile, S. Morello, M. Turco, C. Pellecchia, *J. Cell Physiol.* 228 (2013) 2202-2209.
- [5] T.D. Shultz, D. Lee, D.R. Stickney, D.S. Gridley, *Nutrition Research* 9(2) (1989) 133-151.

Synthesis and Hepatotoxicity of Psychoactive Cathinones

Catarina Oliveira¹, Soraia Bronze¹, Susana Santos¹, Rita Pacheco^{1,2}, Helena Gaspar¹

¹ Centro de Química e Bioquímica, Faculdade de Ciências da Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal; E-mail: fc42391@alunos.fc.ul.pt

² Área Departamental de Engenharia Química, Instituto Superior de Engenharia de Lisboa, Av. Conselheiro Emídio Navarro, 1959-007 Lisboa

Several synthetic analogues of cathinone (the main psychoactive compound present in the leaves of Khat) have emerged in the market of recreational drugs as legal substitutes of illicit substances such as amphetamine, MDMA (ecstasy) and cocaine. This type of compounds, known as synthetic cathinones, are the second largest group of new psychoactive substances (NPS) reported to EMCDDA^{1,2}; just in the past ten years 103 new synthetic cathinones were found. These NPS are a public health issue, not only due to the secondary effects, such as fatal intoxication, observed in some cases, but also because of their easy availability to the general public.^{1,3} Considering that these compounds are synthesized illegally in laboratories, the knowledge of a simple synthetic route that resembles the one used in those labs became important to predict the structure of new compounds that may appear on the market. Moreover, it is urgent to understand how these drugs lead to liver toxicity since it is known that this organ is the main target of amphetamine-like compounds.

This work describes a two-step pathway to synthesize 20 psychoactive cathinones (Figure 1) and their characterization by NMR and GC-MS, along with the evaluation of their toxicity towards the liver cancer cell line HepG-2, considered a good model to screen the potential hepatotoxicity of new compounds. So far, the results suggest a relation between the hepatocellular toxicity of cathinones and their chemical structure, showing a toxicity enhancement with the increase of the alkyl chain length of the ketone moiety, as well as with the substitution of an aromatic-H by a methyl group.

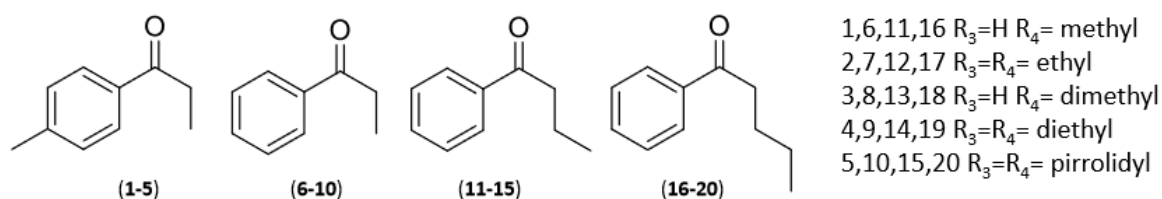


Figure 8. Psychoactive cathinones.

Acknowledgements

The authors acknowledge FCT for financial support through the project UID/MULTI/00612/2013. This work was done within the protocol between Faculdade de Ciências da Universidade de Lisboa and Laboratório de Polícia Científica da Polícia Judiciária.

References

- [1] EMCDDA, European Drug Report 2016: Trends and Developments, EU Publications Office, Luxembourg, 2016.
- [2] UNODC, The Challenge of New Psychoactive Substances, United Nations Publication, Austria, 2013.
- [3] M. Coppola, R. Mondola, Toxicology Letters 211 (2012) 144-149.

Mechanisms of hyperammonemia and therapeutic targets

Antonina Pereira, Marco F. Moedas and Margarida F. B. Silva*

Research Institute for Medicines – iMed.Ulisboa, Metabolism and Genetics Group, Faculty of Pharmacy,
Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal

*E-mail: mbsilva@ff.ulisboa.pt

Hyperammonemia (HA) is a metabolic disturbance resulting from an imbalance between ammoniogenesis and ammonia disposal via the urea cycle (UC), a liver-specific biochemical pathway. This condition may be a potential adverse effect of numerous drugs during therapy and may evolve to a potentially fatal encephalopathy. The possible inhibition by drug metabolites of the mitochondrial steps of ureagenesis may result in the accumulation of ammonia. Our research interest has been focused on one of the mechanisms underlying HA that involves the impairment of *N*-acetylglutamate (NAG) synthesis.¹ NAG is an allosteric activator of carbamylphosphate synthetase 1, the enzyme that triggers UC activity. It is produced in the mitochondrial compartment of hepatocytes from acetyl-CoA and glutamate through a reaction catalyzed by the enzyme NAG synthetase (NAGS). Therefore, both NAG and NAGS play a pivotal role in regulating ammonia detoxification in humans. This work aimed to elucidate the NAG status *in vivo* and its correlation with the mitochondrial therapeutic target, NAGS. A novel analytical method was devised using stable isotope dilution gas chromatography coupled to mass spectrometry to detect and quantify NAG in biological samples. Anion exchange solid phase extraction and organic solvent extraction methods were tested. Validation parameters of the analytical method were studied following international guidelines.² NAG levels were determined in human plasma samples obtained from patients under chronic treatment with valproate, an important antiepileptic drug potentially associated with HA¹, versus reference non-treated controls. The set-up and validation of this analytical method will contribute to gain insights on mechanisms underlying drug-induced HA and human inherited metabolic diseases of urea cycle, distinct clinical conditions of potential dramatic consequences. Toward safer and better HA treatment, this analytical tool is a major asset to pursue functional studies on the modulation of NAGS activity through new chemical entities with therapeutic interest.

Acknowledgements

Support for this work was provided by FCT through iMed.Ulisboa (Pest-OE/2016).

References

- [1] C.C. Aires *et al.*, *Journal of Hepatology* 55(2) (2011) 426-434.
- [2] Guidance for Industry, Food and Drug Administration, 2014.

Evaluation of the potential antifungal activity of two thia-tetraaza macrocycles and their Cu(II) and Ni(II) metal complexes

Jorge Pereira^b, Fábio Delgado^b, Judite Costa^{a,b}, Matilde Castro^{a,b},

Maria Manuel Lopes^{a,b}, Maria de Fátima Cabral^{a,b}

^a *iMed.ULisboa, Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto,*

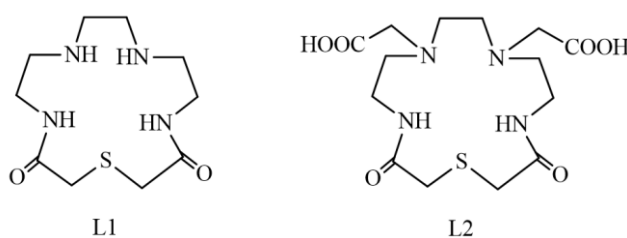
1649-003 Lisboa, Portugal

^b *Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*

In recent years, invasive fungal infections are becoming increasingly more common and difficult to treat, leading to high mortality worldwide and causing global concern. The growing population of hospitalized and immunocompromised patients that are subject to invasive procedures, coupled with the misuse of broad-spectrum antibiotics, have led to an increase in the number of infections, with *Candida sp.* being one of its main aetiological agents.¹

The lack of variety in commercially available antifungal agents coupled with the development of multi-drug resistant yeast strains have made research into new compounds paramount. Macrocyclic compounds and their transition metal complexes are potentially promising subjects in this area, given their ubiquity in biological systems, favourable drug-like properties and high stability.²

In this work, two thia-tetraaza macrocycles: dioxo-[15]aneN₄S (**L1**) and ac₂-dioxo-[15]aneN₄S (**L2**) were synthesised and structurally characterized by 1D and 2D NMR and FT-IR spectroscopies and by mass spectrometry. Additionally, potentiometric and antifungal studies of these ligands and their Cu(II) and Ni(II) complexes were performed. For the compounds that exhibited the best antifungal activity, in order to investigate their mechanism of action (MoA), we also assessed their action against the cell wall (Sorbitol Protection Assay) and membrane (Ergosterol Affinity Assay).³ The results suggest that **Cu-L1**, **Ni-L1**, **L2** and **Ni-L2** have potential to be developed as promising new antifungal agents, with their MoA potentially targeting both the fungal cell wall and membrane.



Acknowledgements

We thank the Fundação para a Ciência e Tecnologia for financial support (UID/DTP/04138/2013) and for the project REDE/1518/REM/2005 for ESI-MS/MS experiments at LCLEM/FFULisboa.

References

- [1] M.J.S. Mendes Giannini, T. Bernardi, L. Scoronzi, A.M. Fusco-Almeida, J.C.O. Sardi, *J. Med. Microbiol.* 62 (2013) 10-24.
- [2] N. Torres, S. Gonçalves, A. Fernandes, J.F. Machado, M.J.V. de Brito, N.G. Oliveira, M. Castro, J. Costa, M.F. Cabral, *Molecules* 19 (2014) 550-567.
- [3] M.C.A. Leite, A.P.D.B. Bezerra, J.P. de Sousa, F.Q.S. Guerra, E.D.O. Lima, *Evidence-Based Complement. Altern. Med.* 2014 (2014) 1-9.

Synthesis of novel furanosyl nucleoside analogs as potential inhibitors of cholinesterases

Margarida P. Pereira^a, Sofia G. Serra^a, Rita Gonçalves-Pereira^a,
René Csuk^b and Nuno M. Xavier^a

^a Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa,
Ed. C8, 5º Piso, Campo Grande, 1749-016 Lisboa, Portugal; E-mail: nmxavier@fc.ul.pt

^b Bereich Organische Chemie, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Str. 2,
D-06120 Halle (Saale), Germany

Synthetic nucleosides, nucleotides and their analogs are relevant target molecules in medicinal chemistry, due to their biological properties, which include anticancer, antiviral or antimicrobial efficacies.^{1,2} Some few recent studies showed the ability of nucleos(t)ide analogs to inhibit cholinesterases (ChEs)^{3,4}, which hydrolyse the neurotransmitter acetylcholine and remain major therapeutic targets for Alzheimer's disease.

In the context of our research towards the development of novel nucleoside and nucleotide analogs of therapeutic potential, we have previously reported the synthesis of pyranosyl 6'-isonucleosides and glucuronamide derivatives having inhibitory effects on ChEs^{5,6}. In particular, a triazole-containing isonucleoside and a theobromine counterpart showed potent and selective inhibition of acetylcholinesterase. These results prompted us to explore the synthesis of related analogs, keeping a triazole or a theobromine motif while changing the nature/size of the sugar ring, *i.e.* furanosyl systems, aiming at further screening their biological profile.

In this communication, we present the synthesis of furanosyl theobromine 5'-isonucleosides and glucofuranuronamide-based triazole nucleosides. The synthetic strategies employed D-glucose diacetone and D-glucuronolactone as precursors and relied on regioselective Mitsunobu coupling, N-glycosylation, anomeric azidation and 'click chemistry' methods.

The synthetic work and preliminary results on the assessment of the compounds' inhibitory abilities towards ChEs will be revealed.

Acknowledgements

Support for this work was provided by FCT through projects UID/MULTI/00612/2013 and IF/01488/2013/CP1159/CT0006.

References

- [1] N.M. Xavier, in: J. Reedijk (Ed.), Elsevier Reference Module in Chemistry, Molecular Sciences and Chemical Engineering, Elsevier, Waltham, MA, 2017, pp. 1-15 [DOI: 10.1016/B978-0-12-409547-2.12655-1].
- [2] M. Serpi, V. Ferrari, F. Pertusati, *J. Med. Chem.* 59 (2016) 10343-10382.
- [3] C. Meier, C. Ducho, U. Gorbig, R. Esnouf, J. Balzarini, *J. Med. Chem.* 47 (2004) 2839-2852.
- [4] S. Schwarz, R. Csuk, A.P. Rauter, *Org. Biomol. Chem.* 12 (2014) 2446-2456.
- [5] N.M. Xavier, S.D. Lucas, R. Jorda, S. Schwarz, A. Loesche, R. Csuk, M.C. Oliveira, *Synlett* 26 (2015) 2663-2672.
- [6] D. Batista, S. Schwarz, A. Loesche, R. Csuk, P.J. Costa, M.C. Oliveira, N.M. Xavier, *Pure Appl. Chem.* 88 (2016) 363-379.

The role of counterions in constant-pH MD simulations of PAMAM dendrimers

Pedro B. P. S. Reis¹, Diogo Vila-Viçosa¹, Sara R. R. Campos², António Baptista²
and Miguel Machuqueiro¹

¹ *Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal*

² *Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa, Av. da República, EAN, Ap. 127, 2781-901 Oeiras, Portugal*

We have recently shown that the most common approach to deal with charged membrane systems, namely the full system neutralization, leads to excessively ordered lipid bilayers in a 30% DMPA/DMPC system.¹ However, when a significantly smaller number of ions, estimated from Poisson-Boltzmann calculations at a defined ionic strength value, is used, we were able to reproduce the correct isothermal pH dependent lipid phase transition.

An important conclusion of these findings is that, in charged membrane systems, full neutralization only takes place at several nanometers away from the lipid interface. Therefore, we are now raising the question of whether this issue of estimating and using the correct number of counter-ions in MD simulations is also determinant to correctly model charged globular systems. In these systems, like proteins, dendrimers, etc., it is possible to become significantly charged, depending on pH, and the amount of counter-ions added could influence its conformation space and protonation profile.

In this work, we used our Constant-pH MD method² to study the conformational space and titration profile of polyamidoamine (PAMAM) dendrimers (2nd generation) with two different ionic strength treatments: an implicit approach (with no explicit counter-ions) using the generalized reaction field; and PME with explicit ions to approximate system neutrality.

The main question now is whether the most common approach used by the scientific community (PME/neutralization) is able to correctly describe highly charged globular systems. We already know the answer and will share it with you in our poster.

Acknowledgements

We acknowledge financial support from FCT through projects PTDC/QEQCOM/5904/2014 and UID/MULTI/00612/2013.

References

- [1] D. Vila-Viçosa, V.H. Teixeira, A.M. Baptista, M. Machuqueiro, *J. Chem. Theory Comput.* 11 (2015) 2367.
- [2] M. Machuqueiro, A.M. Baptista, *J. Phys. Chem. B* 110 (2006) 2927.

Synthesis of tetraoxane-pyrimidine chemical probes to study the biology of liver stage malaria parasites

Joana Ribeiro, Rita Capela, Rui Moreira

^a iMed.ULisboa, Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal

Malaria is a disease caused by Plasmodium parasites. Development of antimalarial drugs has been traditionally focused on the blood stage (BS) of the malaria parasite that causes clinical symptoms. The liver stage (LS) of Plasmodium infection is an obligatory step in the maturation and replication of mosquito-delivered parasites toward generating the erythrocyte-infective forms that cause malaria symptoms¹. To target the hepatic stage is therefore highly desirable in the context of malaria eradication, not only because its asymptomatic nature makes it ideally suited for prophylactic intervention², but also because only few chemical tools are available to investigate the LS biology and the liver can serve as a reservoir for *P. vivax* hypnozoites³.

Currently, only a few number of drug targets are fully validated for the hepatic stage of malaria, so we now report the synthesis of tetraoxane-pyrimidine chemical probes designed to be used in biorthogonal reactions with fluorescent tags for target imaging. These probes can be seen inside living infected hepatocytes and, allow a better understanding of the mechanism of action as well as identify the target for this class of liver stage inhibitors. The structural assignment of these compounds was made by usual NMR characterization techniques as ¹H and ¹³C NMR (1D, 2D).

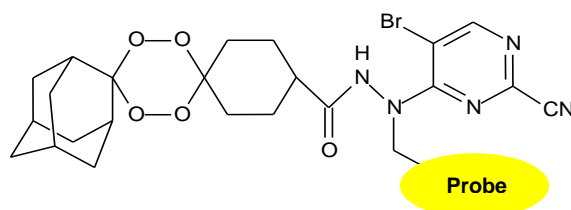


Figure 1. General structure of Tetraoxanes-Pyrimidine Nitriles Probes.

References

- [1] M. Prudencio, A. Rodriguez, M.M. Mota, Nat. Rev. Microbiol. 4 (2006) 849-856.
- [2] D. Mazier, L. Renia, G. Snounou, Nat. Rev. Drug Discov. 8 (2009) 854-864.
- [3] T.N.C. Wells, J.N. Burrows, J.K. Baird, Trends Parasitol. 26 (2010) 145-151.

New Cu(II) complexes with pyrazolyl Schiff base: synthesis and biological evaluation

Nádia Ribeiro^a, Nataliya Butenko^{a,b}, Isabel Cavaco^{a,b}, Teresa Pinheiro^c, Irina Alho^d,
Fernanda Marques^e, Fernando Avecilla^f, João Costa Pessoa^a and Isabel Correia^a

^a Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Portugal

E-mail: nadia.ribeiro@tecnico.ulisboa.pt

^b Departamento de Química, Bioquímica e Farmácia, Universidade do Algarve, Faro, Portugal

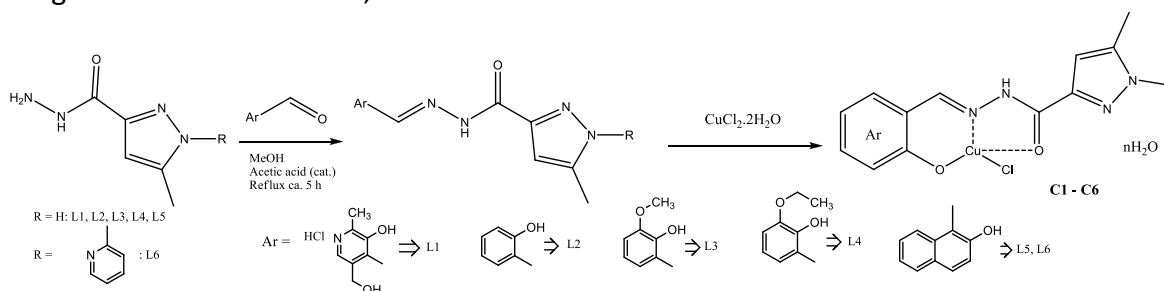
^c Instituto de Bioengenharia e Biociências, Instituto Superior Técnico, Universidade de Lisboa, Portugal

^d Instituto de Medicina Molecular, Universidade de Lisboa, Portugal

^e Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa, Portugal

^f Departamento de Química Fundamental, Universidade da Coruña, Spain

Pyrazole derivatives have gained increasing attention and there are several reports on the anticancer, antibacterial and antiviral activities of pyrazole metal complexes.¹ Moreover, there is a growing interest in developing new anticancer drugs based on endogenous metal ions, such as copper, considered to have less side-effects, improved spectrum of efficacy and lower toxicity.² Therefore, we hypothesized that copper complexes of pyrazole Schiff bases could be good candidates as anticancer drugs. The syntheses, structural characterization, interaction with biological macromolecules and cytotoxicity of new copper(II) complexes of pyrazole based “ONO” tridentate Schiff base ligands (see Scheme 1) were carried out. All compounds were characterized by analytical techniques; the complexes were found to have square based geometries with $d_{x^2-y^2}$ ground-state. The tridentate ligands coordinate copper forming two chelate rings and the coordination sphere is completed with a chloride atom. Quenching fluorescence experiments showed that all complexes (except **C3**) are able to interact with DNA and HSA. Complexes **C5** and **C6**, with larger aromatic systems, showed much higher cytotoxicity (in the low μM range) than **C1-C4**, as well as IC_{50} values much lower than *cisplatin* in the tested cell lines (MCF7 and PC3). For **C6** the results suggest that the mechanisms of cell death do not seem to be mediated by apoptosis, through caspases 3/7 activation, but by involving membrane potential and imbalance in physiological elements such as P, K and Ca.



Scheme 1: Syntheses of the ligands and Cu(II) complexes.

Acknowledgements

This work was supported by Fundação para a Ciência e Tecnologia (FCT) (projects UID/QUI/00100/2013, UID/MULTI/04349/2013, UID/BIO/04565/2013, RECI/QEQ-QIN/0189/2012, RECI/QEQ-MED/0330/2012), Programa Operacional Regional de Lisboa (LISBOA-01-0145-FEDER-007317) and programme Investigador FCT. The NMR and Mass Spectrometry IST–UL Centers are acknowledged for the access to the equipment.

References

- [1] F.K. Keter, J. Darkwa, *Biomaterials* 25 (2012) 9.
- [2] a) C. Santini *et al.*, *Chemical Reviews* 114 (2014) 815; b) C.-H. Zhou *et al.*, “Recent Developments in Organometallic Supramolecular Complexes as Anticancer Drugs” in: M. Prudhomme (Ed.), *Advances in Anticancer Agents in Medicinal Chemistry*, vol. 2, Bentham e-Books, 2013.

3-Hydroxyquinolinones as reversible molecular handles for boronic acid bioconjugation

Roberto Russo^{a,b}, Roberta Paterna^a and Pedro M.P. Gois^a

^a *iMed.ULisboa, Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*

^b *Instituto de Medicina Molecular (iMM), Faculdade de Medicina da Universidade de Lisboa, Av. Prof. Egas Moniz, 1649-028 Lisboa, Portugal*

E-mail: robertorusso@fm.ul.pt

Protein bioconjugation has been one of the hot topics in medicinal chemistry during the recent years, expanding the tools available for biological investigation and bringing innovative therapies to the clinic. In this field, there is an increasing demand for bioconjugations reactions that are not only bioorthogonal, but also reversible under selected conditions, in order to achieve the maximum control possible over the system.¹

Boronic acids are excellent candidates for this kind of applications as they are stable under physiological conditions and show in general good biocompatibility, they are also known for reversibly binding to diols in aqueous environment, a feature that we exploited to develop a new bioconjugation technique.^{2,3}

Our work revolves around 3-Hydroxy Quinolinones (3HQs), a class of compounds that exist in a tautomeric equilibrium between the amide form and a diphenolic one, with the first one favored over the latter in aqueous environment.⁴ The diphenolic form is, however, capable of binding boronic acids, leading to the formation of a highly aromatic structure that results in an overall stabilization of the system.

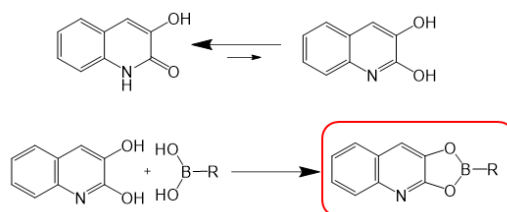


Figure 1. Tautomeric equilibrium of 3HQs and binding to boronic acids.

Based on this discovery, we developed a series of 3HQs derivatives, these compounds showed remarkable binding capabilities with boronic acids in buffer solution and were further developed to be inserted in peptidic fragments via classic bioconjugation techniques.

The peptides modified with our molecules gained the ability to bind boronic acids in aqueous environment with moderate to good efficiency, thus demonstrating the possibility to use them as functionalization tool for boronic acid ligation.

Acknowledgements

This work was supported by Marie Skłodowska-Curie actions (MSCA-ITN-2015-ETN-675007) in the framework of the ITN – ProteinConjugates, and the funding from PTDC/QEQMED/5512/2014, PTDC/QEQ-QOR/1434/2014, UID/DTP/04138/2013 and SAICTPAC/0019/2015.

References

- [1] E.M. Sletten, C.R. Bertozzi, *Angew. Chem. Int. Ed.* (2009) 6974.
- [2] B. Akgun, D.G. Hall, *Angew. Chem. Int. Ed.* 55 (2016) 1-6.
- [3] D.Y.W. Ng, M. Arzt, Y. Wu, S.L. Kuan, M. Lamla, T. Weil, *Angew. Chem. Int. Ed.* 53 (2014) 324-328.
- [4] S.B. Strashnova, O.V. Kovalchukova, B.E. Zaitsev, A.I. Stash, *Russ. J. Coord. Chem.* 34 (2008) 775-779.

Towards the synthesis of polyphenols containing deoxy sugars:
a strategy against diabetes and Alzheimer's disease

Sabrina Aït Saïd, María Teresa Blázquez Sánchez, Amélia Pilar Rauter
Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa,
Campo Grande, 1749-016 Lisboa, Portugal
E-mail: sasaid@fc.ul.pt

Polyphenols have been shown to be effective against the development of diabetes and neurodegenerative diseases such as Alzheimer's disease (AD).¹ In AD, beta-amyloid fibrils accumulate as extracellular plaques in the gray matter of the brain, while in diabetes islet amyloid polypeptide (IAPP) is accumulated in the pancreas. Previous work in our group showed the action of a glycosyl flavonoid, 8- β -D-glucopyranosylgenistein (8G), as an inhibitor of the formation of these islet amyloid peptide (IAPP) and β -amyloid fibrils.² In this work, we are interested in synthesizing compound **1**, an 8G analog containing 6-deoxyglucose as saccharidic residue that could improve the permeability properties. In this work, we present our efforts to synthesize compound **1** so far. This target molecule will be tested in the context of diabetes and Alzheimer's disease.

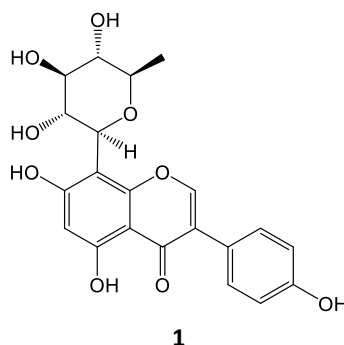


Figure 1. Structure of 8-(6-deoxy- β -D-glucopyranosylgenistein) **1**.

Acknowledgements

Support for this work was provided by FCT funded project UID/MULTI/00612/2013 and by the European Union, gratefully acknowledged for the support of the project "Diagnostic and Drug Discovery Initiative for Alzheimer's Disease" (D3i4AD), FP7-PEOPLE-2013-IAPP, GA 612347.

References

- [1] K.M. Pate, M. Rogers, J.W. Reed, N. van der Munnik, S.Z. Vance, M.A. Moss, *Neurosci. Ther.* 23 (2017) 135-144.
- [2] A.R. Jesus, C. Dias, A.M. Matos, R. de Almeida, A.S. Viana, F. Marcelo, R.T. Ribeiro, M.P. Macedo, C. Airoidi, F. Nicotra, A. Martins, E.J. Cabrita, J. Jiménez-Barbero, A.P. Rauter, *J. Med. Chem.* 57 (2014) 9463-9472.

Purine Nucleosides able to chelate copper: synthesis and metal binding studies

Ignazio Schino^{a,b}, Mariangela Cantore^{a,b}, Nicola Antonio Colabufo^{b,c},

Amélia Pilar Rauter^a

^a Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa,

Ed C8, piso 5, 1749-016 Lisboa, Portugal

^b Biofordrug-Scienze del Farmaco, Università degli Studi di Bari, via Orabona 4, 70124 Bari, Italy

^c Dipartimento di Farmacia-Scienze del Farmaco, Università degli Studi di Bari "A. Moro",

Via Orabona, 4, 70125 Bari, Italy

Transition metals play a crucial role in vital processes. In particular, Cu^{2+} is the third bivalent ion after Fe^{2+} and Zn^{2+} in terms of abundance in the human body. Cu^{2+} plays an important role in various physiological processes as a catalytic cofactor for a variety of metal-enzymes such as superoxide dismutase, cytochrome oxidase, lyxoxidase and tyrosinase. However, an excess of Cu^{2+} may be toxic in biological systems and when it exceeds cellular requirements it may affect other metal ions involved in physiological processes. In recent years, the involvement of Cu^{2+} in the onset of many neurodegenerative disorders has been documented. Systemic copper dyshomeostasis alter neurotransmission and may lead to neurodegenerative diseases such as Alzheimer's Disease.¹ Recent studies have shown that the serum free copper-bound fraction (free copper) increases in a percentage of patients with Alzheimer's disease and slight cognitive deterioration.² For these reasons there is a great interest into the development of new probes able to chelate Cu^{2+} with high affinity. We present herein the synthesis and characterization of new purine nucleosides (general formula shown in Figure 1) starting from the findings that, in preliminary studies, purine benzamides were able to chelate copper with high affinity and selectivity towards other bivalent cations. Furthermore, the presence of the sugar moiety in the chemical structure increases the hydrophilicity of the chelating ligands improving the lipophylic/hydrophylic balance required for the physiological barriers crossing. Preliminary evaluation of nucleoside metal binding ability was carried out. Results will be presented and discussed.

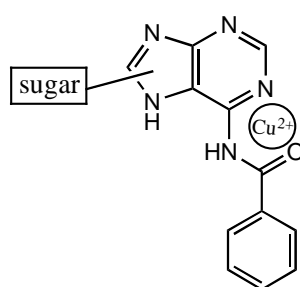


Figure 1. General formula of purine nucleosides able to chelate copper.

Acknowledgements

Support for this work was provided by the European Union through the project "Diagnostic and Drug Discovery initiative for Alzheimer's Disease" (D3i4AD), FP-PPEOPLE-2013-IAPP, GA 612347.

References

- [1] P. Chen, M. Rahman Mia, M. Aschner, F1000Res. 5 (2016) F1000 Faculty Rev-366.
- [2] D.J. Bonda, H. Lee, J.A. Blair, X. Zhu, G. Perry, M.A. Smith, Metallomics 3 (2011) 267-270.

Bioactivity of natural compounds

Maria Luísa Serralheiro^{a,b,c}, Pedro Luís Falé^{a,b,c}, Rita Pacheco^{a,c},
Maria Helena Florêncio^{a,b}

^a Centro de Química e Bioquímica, ^b Departamento de Química e Bioquímica, ^c BioISI – Biosystems & Integrative Sciences Institute; Campo Grande, C8, 1749-016 Lisboa, Portugal

We have been developing studies on the bioactivity of infusions and isolated compounds from several origins (Figure 1). Different molecules have been found with biological activity such as inhibition of the intestinal absorption of cholesterol¹, antioxidant activity², inhibition of enzymes as acetylcholinesterase³ and HMG CoA-reductase¹, and also compounds with anticancer activity⁴. The compounds have been identified by LC-MS / MS and the biochemical action studied using several cell lines. FTIR spectroscopy methodologies and electrophoresis are also in use to determine structural changes in proteins when in contact with bioactive molecules. Natural compounds permeation studies through simulated intestinal barrier have also been carried out.¹ Activity studies are underway in therapeutic targets of the mechanism of inhibition of cholesterol absorption by the isolated compounds and also interaction between drugs and bioactive molecules.



Figure 1. Examples of natural sources of bioactive compounds used in our group.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013 and PEst-OE/QUI/UI0612/2013.

References

- [1] A.A. Arantes, P.L. Falé, L.C.B. Costa, R. Pacheco, L. Ascensão, M.L. Serralheiro, *Brazilian Journal of Pharmacognosy* 26 (2016) 738-743.
- [2] J. Henriques, M.J. Ribeiro, P.L. Falé, R. Pacheco, L. Ascensão, M.H. Florêncio, M.L.M. Serralheiro, *Eur. Food Res. Technol.* 243 (2017) 1-11 [DOI:10.1007/s00217-017-2845-y].
- [3] A. Ressaissi, N. Attia, P.L. Falé, R. Pacheco, V.H. Teixeira, M. Machuqueiro, C. Borges, M.L.M. Serralheiro, *IJGHC* 5 (2016) 337-348.
- [4] M.J. Martins, F. Martins, R. Pacheco, S. Santos, "Synthesis and evaluation of antitumor activity of novel thiobenzanilides" (Poster, CQB Day 2017).

Development of novel spirooxindoles to efficiently inhibit neural tumorigenesis

D. Silva, J. D. Amaral, S. Solá, Maria M. M. Santos

*Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, Universidade de Lisboa,
Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*

The spirooxindole system is the core structure of many medicinal agents, and several 5-membered spirooxindoles were described to activate p53 by inhibiting the p53-MDM2 interaction.¹ Recently, p53 has been shown to inhibit stem cell tumorigenic potential by promoting cellular differentiation processes, including neurogenesis. Therefore, the identification of molecules that also modulate p53 in neural stem cells (NSCs) might have a huge impact in NSC-based therapies. In this area of research, we have developed a novel chemical family of spirooxindoles (spiropyrazoline oxindoles) to ultimately modulate the stemness and differentiation potentials of a mouse neural stem cell line. The spiropyrazoline oxindoles (**1**) were synthesized by 1,3-dipolar cycloaddition reaction between nitrile imines (**2**) and 3-methylene indolinones (**3**) (Figure 1). The substituted 3-methylene indolinones were synthesized by aldolic condensation of substituted indolin-2-ones (**4**) with different aldehydes (**5**) in the presence of piperidine.

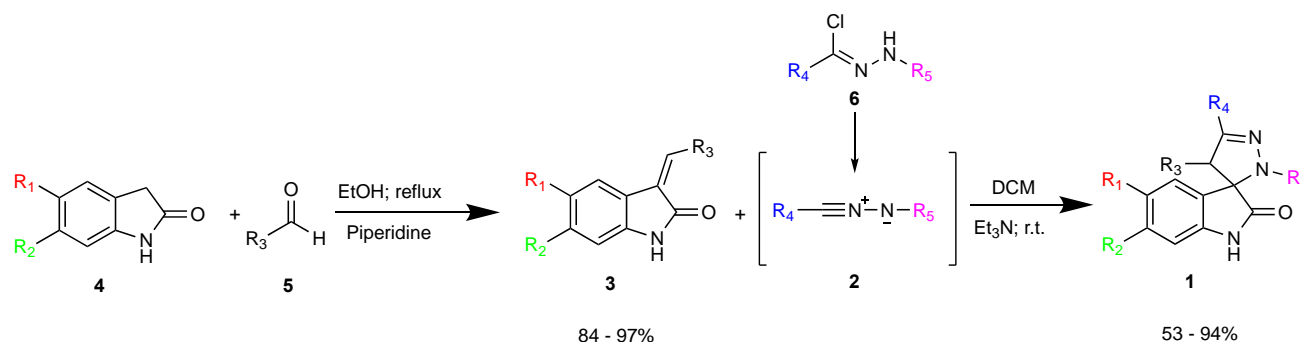


Figure 1. Synthesis of spiropyrazoline oxindoles.

From the first screening, we have identified one spiropyrazoline oxindole that significantly reduced the stemness while improved differentiation of neural stem cells, as assessed by a reduction in Sox2 expression and increase of neural marker β III-tubulin. In conclusion, we discovered a novel small p53 activator molecule with therapeutic potential to repress brain cancer and increase neural regeneration.

Acknowledgements

We thank Fundação para a Ciência e a Tecnologia (FCT): UID/DTP/04138/2013, SFRH/BPD/100961/2014 (J.D. Amaral), IF/00732/2013 (M.M.M. Santos). This work was also partially funded by iMed.Ulisboa (Young Investigator's Project for Collaborative Cross-disciplinary Studies 2015).

References

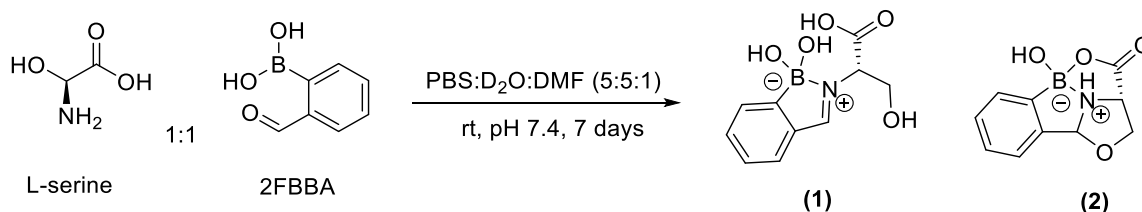
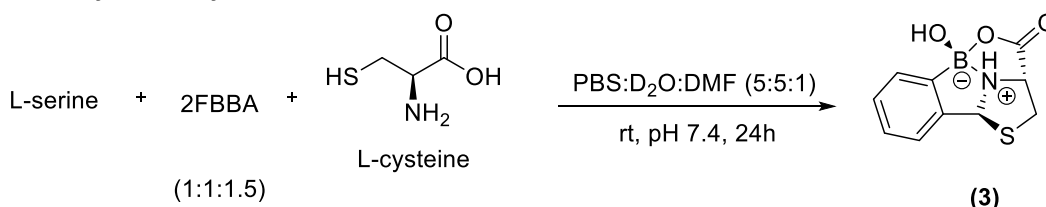
- [1] M.M.M. Santos, *Tetrahedron* 70 (2014) 9735-9757.

Thiazolidine cyclization to orthogonal modification of *N*-Terminal cysteine

Maria J. S. A. Silva, Hélio Faustino, Pedro M. P. Gois

*iMed.UL, Faculdade de Farmácia da Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal**E-mail: maria.silva7@campus.ul.pt*

By far the most explored property has been the nucleophilic reactivity of amino acid residues with respect to proteins bioconjugation. In fact, lysine and cysteine have been the election targets especially due their own reactivity since they bear the most reactive nucleophiles in their residue chain.¹ Despite this, there are also other nucleophilic substrates available to react, such as serine hydroxyl.² We have shown the high reactivity of formyl benzo boronic acid (2FBBA) with *N*-terminal cysteines to form a boronated thiazolidine featuring a B–N bond under mild aqueous conditions (pH 7.4, 23°C).³ We reasoned that other type of *N*-terminal amino acids such as serine or threonine could participate in similar reactions. In fact, preliminary data shows that when 2FBBA reacts with serine, it generates a mixture of iminoboronate (**1**) and oxazolidine (**2**), although in low conversion (Scheme 1). Notwithstanding the addition of cysteine shifts the equilibrium to the cyclization of thiazolidine in the competition assay (**3**) (Scheme 1). Herein we will provide some results on the development of this methodology for orthogonal modification of *N*-terminal cysteine in peptides and proteins.

Specificity Assay with 2-Formyl benzo boronic acid**Competition Assay with L-cysteine**

Scheme 1. Specificity and Competition Assay adding L-cysteine to the reaction mixture of 2FBBA with L-serine. The reactions' conversion was evaluated by ¹H-NMR spectra based on the comparison of the signal of aldehyde (≈9.8 ppm), imine (≈8.4-8.7 ppm), thiazolidine proton (≈6.2 ppm) and oxazolidine proton (≈6.1 ppm).

Acknowledgements

Support for this work was provided by FCT through PTDC/QEQMED/5512/2014, PTDC/QEQ-QOR/1434/2014, UID/DTP/04138/2013, SAICTPAC/0019/2015.

References

- [1] (a) G.J.L. Bernardes, J.M. Chalker, B.G. Davis, *Ideas in Chemistry and Molecular Sciences* (2010); (b) P.M. Cal, J.O.B. Vicente, E. Pires, A.V. Coelho, L.F. Veiros, C. Cordeiro, P.M.P. Gois, *J. Am. Chem. Soc.* 134 (2012) 10299; (c) P.M. Cal, R.F. Frade, C. Cordeiro, P.M.P. Gois, *Chem. Eur. J.* 21 (2015) 8182; (d) P.M. Cal, G.J.L. Bernardes, P.M.P. Gois, *Angew. Chem. Intl. Ed.* 53 (2014) 10585.
- [2] O. Koniev, A. Wagner, *A. Chem. Soc. Rev.* 44 (2015) 5495.
- [3] H. Faustino, M.J.S.A. Silva, L.F. Veiros, G.J.L. Bernardes, P.M.P. Gois, *Chem. Sci.* 7 (2016) 5052.

Assessment of GROMOS force fields without the twin-range cutoff scheme

Tomás Silva, Pedro Reis, Bruno Victor, Diogo Vila-Viçosa and Miguel Machuqueiro

Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa,

1749-016 Lisboa, Portugal

Email: tfsilva@ciencias.ulisboa.pt

With the advancement in technology over the years, computers have become significantly faster and more powerful. An increase in computing power allows improvements in molecular dynamics (MD) simulations' times from nanoseconds, to microseconds or even to milliseconds. Coupled to better computing power, simulation quality can be tied to the accuracy of the used methods and force field reliability. Nevertheless, many force fields have been parametrized using short simulations, outdated methods and modest cutoffs, which require continuous updates and validation.

The GROMOS force field parameter sets (43A1, 53A6 and 54A7) have been developed and validated using charge groups, a twin-range scheme (0.8 and 1.4 nm), and a reaction field method for the treatment of Coulombic interactions.¹ However, newer MD codes, like GROMACS, have discontinued the twin-range support, due to incompatibilities with the leap-frog version of the reversible Trotter decomposition scheme. In an attempt to rescue the reaction field method and GROMOS force fields in newer versions of GROMACS, we evaluate the use of plain cutoffs in both MD and constant-pH MD simulations. The plain cutoffs of 1.2 and 1.4 nm will be tested in protein (Lysozyme),² membrane (DMPC and 25% DMPA/PC),³⁻⁴ and dendrimer (PAMAM) simulations,⁵ and their conformational spaces will be compared with the ones obtained with the twin-range cutoff scheme (0.8/1.4 nm).

Acknowledgements

We acknowledge financial support from FCT through projects PTDC/REQCOM/5904/2014 and UID/MULTI/00612/2013.

References

- [1] W. Huang, Z. Lin, W.F. van Gunsteren, *J. Chem. Theory Comput.* 7(5) (2011) 1237-1243.
- [2] M. Machuqueiro, A.M. Baptista, *Proteins* 72(1) (2008) 289-298.
- [3] D. Poger, A.E. Mark, *J. Chem. Theory Comput.* 6 (2010) 325-336.
- [4] H.A.F. Santos, D. Vila-Viçosa, V.H. Teixeira, A.M. Baptista, M. Machuqueiro, *J. Chem. Theory Comput.* 11(12) (2015) 5973-5979.
- [5] D. Cakara, J. Kleimann, M. Borkovec, *Macromolecules* 36 (2003) 4201-4207.

Bicyclic aziridines synthesis by flow assisted photochemical transformation of pyridinium salts

F. Siopa, J. P. M. António, J. R. Vale and C. A. M. Afonso

Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, University of Lisbon,
Av. Prof. Gama Pinto, 1649-003, Lisboa, Portugal

E-mail: filipasiopa@ff.ulisboa.pt

Photochemistry is a very exciting area of organic chemistry as it allows the access to novel transformations which would otherwise be inaccessible through classical methods. However, photochemical reactions present a series of drawbacks, mainly due to the complexity of the processes and the difficult scale-up. Scalability is hampered due to the attenuation effect of photon transport which prevents the use of a simple dimension-enlarging strategy for scale-up. If larger reactors are used, over-irradiation of the reaction may become an essential issue as the reaction times are substantially increased, resulting in the formation of unwanted byproducts. An increasingly popular solution to solve the aforementioned problem is the development of continuous-flow reactors.¹ Our group has been working on the ring opening of aziridines in water under mild conditions² and the formation of these aziridines from pyridine salts are a classical example of a photochemical reaction, thus being envisioned as a perfect transformation to be optimized under flow conditions.

We hereby present the development of two new photochemical reactors and their performances in comparison with the batch processes.

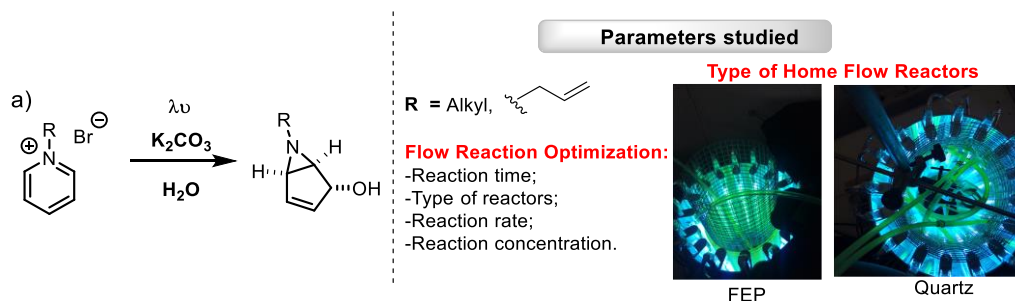


Figure 1. Photochemical transformation of pyridinium salt to bicyclic-aziridines.

Acknowledgements

We thank the Fundação para a Ciência e Tecnologia (SFRH/BPD/88666/2012, SFRH/BD/128239/2016 and SFRH/BD/120119/2016) and the European Research Area Network ERANet LAC (ref. ELAC2014/BEE-0341) for financial support.

References

- [1] a) L.D. Elliott, J.P. Knowles, P.J. Koovits, K.G. Maskill, M.J. Ralph, G. Lejeune, L.J. Edwards, R.I. Robinson, I.R. Clemens, B. Cox, D.D. Pascoe, G. Koch, M. Eberle, M.B. Berry, K.I. Booker-Milburn, *Chem. Eur. J.* 20 (2014) 15226; b) D. Cambie, C. Bottecchia, N.J.W. Straathof, V. Hessel, T. Noel, *Chem. Rev.* 116 (2016) 10276; c) Y.H. Su, N.J.W. Straathof, V. Hessel, T. Noel, *Chem. Eur. J.* 20 (2014) 10562.
- [2] J.R. Vale, F. Siopa, P.S. Branco, C.A.M. Afonso, *Eur. J. Org. Chem.* (2016) 2048.

Understanding the effects of anticancer peptides on cancer cells and their selectivity towards exosomal membranes

Julia Skalska¹, Érica O. Mello², Manuel Rodríguez López³, Roberto Jiménez-Monzón³,
Grant McNaughton-Smith³, Valdirene M. Gomes², Diana Gaspar¹,
Miguel A. R. B. Castanho¹

¹*Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal*

²*Laboratório de Fisiologia e Bioquímica de Microrganismos do Centro de Biociências e Biotecnologia da
Universidade Estadual do Norte Fluminense Darcy Ribeiro, Rio de Janeiro, Brazil*

³*CEAMED - Centro Atlántico del Medicamento, S.A., San Cristobal de La Laguna, S/C Tenerife, Spain*

Metastases are the major cause of death in patients with solid tumors and their formation occur through a series of events. Recent progresses on tumor extracellular matrix (ECM) research revealed that cell-cell and cell-microenvironment communication is essential for the dissemination of cancer cells. This process is partially mediated by extracellular vesicles (EVs), including exosomes. Different studies show that breast cancer-derived exosomes affect the metastatic cascade. Exosomes are small vesicular bodies secreted by cells after the fusion of a cytosolic endosome with a cellular membrane.

In this work we aim to target cell-to-cell communication mediated by exosomes in metastatic breast cancer and consequently impair the migration and proliferation of cancer cells. Our approach is based on the use of antimicrobial peptides (AMPs) to target cancer cells and respective exosomes. The selective interaction between cancer cells and AMPs is mediated by specific membrane properties that distinguish tumor from healthy cells. Many membrane characteristics such as overexpression of negatively charged components like phosphatidylserine (PS) are inherited by cell exosomes that carry signatures from their mother cells. We use a variety of biophysical and imaging techniques for following cellular and exosome changes after peptide interaction.

*PvD*₁ is a plant defensin isolated from the seeds of *Phaseolus vulgaris* L. with confirmed antimicrobial activity. In our studies *PvD*₁ presented a high cytotoxic activity on breast cancer MCF-7 cells (IC₅₀ = 0.24 μM ± 0.04 μM). Studies of cell membrane charge were also performed and exosomes derived from breast cancer cells were isolated and characterized. This work will allow us to understand the anticancer action of *PvD*₁ and envision a new strategy for the development of selective and effective anticancer therapeutics.

Acknowledgements

The authors thank Fundação para a Ciência e a Tecnologia (FCT I.P., Portugal) for funding: PTDC/BBB-BQB/1693/2014. Marie Skłodowska-Curie Research and Innovation Staff Exchange (RISE) is also acknowledged for funding: call H2020-MSCA-RISE-2014, Grant agreement 644167, 2015-2019. J. Skalska and D. Gaspar acknowledge FCT I.P. for fellowships: PD/BD/114177/2016 and SFRH/BPD/109010/2015.

Design of new urea and thiourea based receptors for anion recognition

Paulo Vieira¹, Sílvia Carvalho¹, Cristina Moiteiro¹, Igor Marques², Vítor Félix²

¹ Centro de Química e Bioquímica, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

E-mail: scfcarvalho@fc.ul.pt; paulo_cruzvieira@hotmail.com; cmmoiteiro@fc.ul.pt

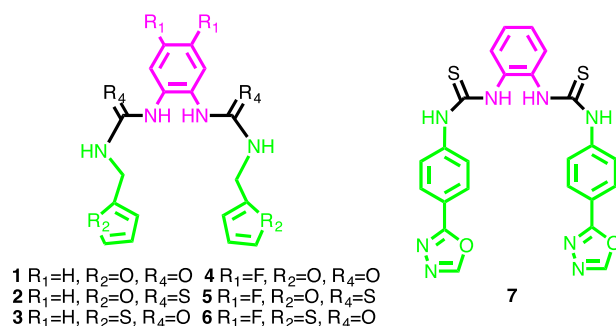
² Department of Chemistry, CICECO – Aveiro Institute of Materials, Department of Medical Sciences, iBiMED – Institute of Biomedicine, University of Aveiro, 3810-193 Aveiro, Portugal

E-mail: igor.marques@ua.pt; vitor.felix@ua.pt

It is well known that the transport of solutes across the plasma membrane is a crucial process in the living beings. In spite of the transport through the membranes of some small uncharged molecules be made by simple diffusion, anions, amino acids and other charged species must also pass through the membranes. This transport is made by the assistance of proteins and a defect in those proteins may lead to many diseases known as “channelopathies”. For instance, a chloride transport deficiency is expressed in cystic fibrosis (CF), which is the most common life-threatening genetic disease in humans. In the specific case of CF, the World Health Organization estimates that, in EU, one in 2000-3000 new borns suffers from this disease. CF is yet an incurable disease and consequently it is important to procure substitution therapies.¹

Inserted in an ongoing FCT project, herein we report the synthesis of novel ureas and thioureas-based receptors containing heteroaromatic units for selectively recognition of anions (Scheme 1).

The ability of those receptors to recognize chloride and others anions was studied by ¹H NMR titrations in DMSO solution. The strongest binding constants were observed for chloride due to multiple hydrogen bonds between the anion and the ureas/thioureas groups of the receptors.^{2,3}



Scheme 1. Representation of the synthetic receptors.

Acknowledgements

This work was financially supported by National Funds through FCT under projects FCT PTDC/QEQ-SUP/4283/2014 and UID/MULTI/00612/2013.

References

- [1] a) A. Vankeerberghen, H. Cuppens, J.-J. Cassiman, *Journal of Cystic Fibrosis* 1 (2002) 13; b) F.M. Ashcroft, *Ion Channels and Disease*, Academic Press, San Diego, 1st ed., 1999, vol. 1.
- [2] V.B. Bregovic, N. Basaric, K. Mlinaric-Majers, *Coord. Chem. Rev.* 295 (2015) 80.
- [3] P.A. Gale, N. Busschaert, C.J.E. Haynes, L.E. Karagiannidis, I.L. Kirby, *Chem. Soc. Rev.* 43 (2014) 205.

A pH replica exchange scheme coupled to the stochastic titration constant pH MD method

Diogo Vila-Viçosa¹, Chris Oostenbrink² and Miguel Machuqueiro¹

¹ *Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal*

² *Institute of Molecular Modeling and Simulation, University of Natural Resources and Life Sciences, Vienna, Austria*

pH is a crucial physicochemical property that affects most biomolecules. Changes in protonation equilibrium of susceptible sites will modify the electrostatic environment and, consequently, have an effect on the molecular structure, stability, and catalysis. However, the protonation behavior of pH sensitive biomolecules is difficult to study using experimental techniques and can strongly benefit from using computational approaches.

In this context, we have successfully studied several systems using the stochastic constant-pH molecular dynamics (CpHMD) method. In these studies, we were able to obtain titration curves for proteins, membranes, and peptides at the membrane water interface. In the latter case, it was observed that, when the titrable groups are deeply inserted in the membrane, the conformational / protonation sampling becomes very limited.

In this project, we extended the stochastic CpHMD method to introduce enhanced protonation sampling. We implemented a pH replica exchange scheme and applied it to ethylenediamine, a simple molecule with two strongly coupled macroscopic pK_a values. In the future, we will use this method to study challenging pH dependent phenomena in complex biological systems.

Acknowledgements

Support for this work was provided by FCT through UID/MULTI/00612/2013, PEst-OE/QUI/UI0612/2013 and PTDC/QEQ-COM/5904/2014.

Exploring the synthesis and the antiproliferative action of new D-glucuronamide-derived *N*-glycosyl compounds

Nuno M. Xavier^a, Alexandre Porcheron^a, Radek Jorda^b, Eva Řezníčková^b,
Vladimír Kryštof^b

^aCentro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa,
Ed. C8, 5º Piso, Campo Grande, 1749-016 Lisboa, Portugal; E-mail: nmxavier@fc.ul.pt

^bLaboratory of Growth Regulators, Palacký University & Institute of Experimental Botany,
AS CR, Šlechtitelů 27, 78371 Olomouc, Czech Republic

N-Glycosyl compounds have attracted significant interest as synthetic targets due to their biological profile.¹ Among them, synthetic nucleosides, nucleotides and their analogs occupy a prominent place in anticancer and antiviral drug research owing to their ability to mimic their physiological counterparts and interfere with nucleotide-mediated pathways, as nucleic acid antimetabolites or as inhibitors of nucleotide-dependent enzymes.²

N-Glycosyl derivatives containing uronic acid or uronamide moieties are relatively less reported. The few described examples include natural nucleosides displaying antimicrobial activities, such as gougerotin,³ and synthetic nucleosides showing antiviral effects.⁴

In the context of our continuing interest in the access to new bioactive *N*-glycosyl compounds of glucuronic acid derivatives, which has previously led to new inhibitors of enzymes of therapeutic relevance, such as cholinesterases and carbonic anhydrase II,⁵ and as part of our ongoing research on the development of novel nucleoside and nucleotide analogs/mimetics of biological potential, we report herein on the synthesis of *N*-glycosylsulfonamides, *N*-glycosylphosphoramidates and nucleosides containing *N*-substituted D-glucuronamide units. The sulfonamide and the phosphoramidate moieties were planned as potential bioisosteres for a phosphate group. Units of different polar character, which may enable different types of interactions with a biological target, were introduced at C-6. Among the motifs installed was the benzyltriazole system, leading to nucleotide-like structures.

The new molecules were evaluated for their antiproliferative effects on cancer cells and some of the nucleosides showed activity at micromolar concentration. Studies aiming at unveiling the mode of action of the most active compound were performed.

In this communication, the synthetic methodologies and the bioactivity results will be disclosed.

Acknowledgements

FCT is acknowledged for funding through UID/MULTI/00612/2013 and IF/01488/2013/CP1159/CT0006.

References

- [1] P. Norris, *Curr. Top. Med. Chem.* 8 (2008) 101-113.
- [2] N.M. Xavier, in: J. Reedijk (Ed.), *Elsevier Reference Module in Chemistry, Molecular Sciences and Chemical Engineering*, Elsevier, Waltham, MA, 2017, pp. 1-15 [DOI: 10.1016/B978-0-12-409547-2.12655-1].
- [3] M.T. Migawa *et al.*, *Org. Lett.* 7 (2005) 3429-3432.
- [4] V.A. Timoshchuk *et al.*, *Pharm. Chem. J.* 22 (1988) 41-49.
- [5] N.M. Xavier *et al.*, *Synlett* 26 (2015) 2663-2672.

