New polymer-ruthenium cyclopentadienyl-porphyrin conjugates for photodynamic therapy of cancer

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References:

INTRODUCTION
During the last years, our group has developed new ruthenium(II) complexes with potential application in cancer chemotherapy. In this presentation we will disclose our recent advances in a novel family of compounds with the core \[
[Ru^{II}(\eta^5-C_5H_5)(CO)(bipy)]
\] where bipy is a bipyridine containing two polymeric chains chain end functionalized with a porphyrin for application in photodynamic therapy of cancer. Photodynamic therapy is an alternative therapy for the treatment of cancer, based on the interaction between a photosensiticizing (PS), light and oxygen, which when reacted form reactive oxygen species (ROS), such as singlet oxygen, leading to cell death.

SYNTHESIS AND CHARACTERIZATION

![Figure 1. Reaction scheme for the synthesis at the new polymer-ruthenium cyclopentadienyl-porphyrin conjugate.](image)

PHOTOPHYSICAL STUDIES

![Figure 2. Graphic showing the \(^{1}\text{O}_2\) formation over time.](image)

![Figure 3. Spectrum of absorbance and fluorescence of macromolecular ligand and complex](image)

CONCLUSIONS
It was possible to synthesize and purify a high molecular weight complex containing a core with antimetastatic properties\(^2\), a Biopolymer and a photosensitizer with adequate photochemical properties.

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IDENTIFICATION OF TOXIC COMPOUNDS USED TO KILL DOMESTIC ANIMALS IN FORENSIC CONTEXT

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INTRODUCTION

Killing animals by poisoning, is unfortunately a frequent criminal behavior. However, most of these criminal offenses are not conveniently penalized due to the unavailability of standard methodologies for the identification of chemical compounds suspected to have caused the intoxication.

OBJECTIVES

Using high resolution mass spectrometry (HRMS)-based methodologies, this work has as objective the identification of the poisoning substance in material collected from poisoned baits found in public places.

RESULTS

CASE STUDY 1. RESIDUES FOUND IN A DOG BOWL

The identification of parathion and its metabolite amino-parathion in a forensic sample was based on identical Tandem mass spectrum obtained for the sample and parathion standard.

CASE STUDY 2. A MEAT BAIT FOUND IN A BACKYARD

The identification of the insecticide imidacloprid in this sample was possible based on the accuracy obtained for the protonated molecule and fragment ions obtained in the HRMS full scan and MS/MS spectra, respectively.

CONCLUSION

Poisoning episodes of domestic animals present a major investigational problem for toxicologists and forensic laboratories. Accidental toxic disasters are difficult to prevent and control, but of greater concern are cases of illegal and deliberated use of poisons.
Synthesis and characterization of rGO/M 2wt%-N co-doped (M=Co, Fe, Mn, Ni, Cu and Rh) as abiotic electrocatalyst for oxygen reduction reaction

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BACKGROUND AND INTRODUCTION

The development of new and non-precious metal electrocatalysts based on transition metals for the oxygen reduction reaction (ORR) is the key to improve the energy conversion technology.

Strategy:

Increase the catalytic sites by an atom dispersion over a conductive and large surface area.

Main goals:

- Synthesis of a 2 wt% single-atom transition metal catalyst supported in nitrogen-reduced graphene oxide;
- Electrochemical evaluation of ORR by linear sweep voltammetry (LSV) with a rotating disc electrode in PBS pH 7.4 and 0.1 KOH solutions.

METHODS

- Extra exfoliation of graphene
- Incorporation of defects
- Co-doping with N and metal

Physical Characterization by:

- XPS
- Raman
- AFM

Electrocatalysts & Oxygen Reduction Reaction – Discussion and Results

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>E_onset/V</th>
<th>E_1/2/V</th>
<th>J_lim/mA cm⁻²</th>
<th>Nr of e⁻</th>
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</thead>
<tbody>
<tr>
<td>rGO/Fe 2%</td>
<td>-0.025</td>
<td>-0.190</td>
<td>-0.734</td>
<td>3.1</td>
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<tr>
<td>rGO/Co 2%</td>
<td>-0.050</td>
<td>-0.335</td>
<td>-0.562</td>
<td>3.7</td>
</tr>
<tr>
<td>rGO/Mn 2%</td>
<td>-0.040</td>
<td>-0.215</td>
<td>-0.804</td>
<td>2.6</td>
</tr>
<tr>
<td>rGO/Cu 2%</td>
<td>-0.140</td>
<td>-0.310</td>
<td>-0.667</td>
<td>2.8</td>
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<tr>
<td>rGO/Ni 2%</td>
<td>-0.155</td>
<td>-0.385</td>
<td>-0.799</td>
<td>1.6</td>
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<tr>
<td>rGO/Rh 2%</td>
<td>-0.055</td>
<td>-0.260</td>
<td>-0.570</td>
<td>2.5</td>
</tr>
<tr>
<td>rGO/Pt NPs 2%</td>
<td>-0.065</td>
<td>-0.230</td>
<td>-0.799</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Raman spectra of rGO and its derivates and AFM measurements confirm the incorporation of defects in the graphene structure.

XPS general spectrum and high-resolution N 1s core level spectrum of rGO/Fe 2% show the co-doping with nitrogen and metal.

CURRENT & FUTURE WORK

- Incorporation of porphyrins in the rGO structure and its electrochemical and physical characterization.
- Synthesis of new electrocatalyst with 10% wt (or more) of transition metal and their characterization by AFM, Raman, XPS and ICP.
- Electrochemical oxidation of glucose in both neutral and alkaline media in the presence of rGO/M 10%.
The influence of glaze on the tribological properties of zirconia dental pieces obtained by subtractive and additive manufacturing

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Background

- Ceramic based prosthetic materials are highly used for the repairing/replacing a damaged/missing tooth, due to their suitable mechanical and aesthetic properties, chemical stability and biocompatibility [1-3].
- Subtractive manufacturing (SM) is commonly used to obtain core pieces by removing surplus material from ceramic blocks.
- Robocasting is an Additive manufacturing (AM) technique that involves the production of 3D structures by depositing materials in a layer-by-layer manner based on a 3D model, with minimum materials’ waste and production time relatively to the conventional manufacturing methods [4].
- Generally, ceramic restorations are coated with a ceramic glaze paste, which is applied over the surface in order to improve their aesthetic properties.

Objectives

- Evaluate the potential of an additive manufacturing (AM) technique (Robocasting) to produce reliable zirconia dental structures. AM samples properties are compared with those of SM samples.
- Study the influence of glazing on the tribological performance of the samples.

Materials and Methods

Materials

- SM samples were produced from Yttria (3% mol) - stabilized zirconia blocks 1ce Zirkon Translucent [Zirkonzahn].
- AM samples were produced from a paste containing 350 g of ZrO2 (yttria (3% mol)-stabilized zirconia powder Zpex [Tosoh]), 75.6 g of water, 8.75 g of corn syrup, 10.5 g of fructose, 0.84 g of Zusoplast C32, 0.105 g of Dolapix CE 64.

Methods

- Zirconia samples produced by both methods were sintered at 1500ºC, polished to obtain the same surface finishing and glazed.
- Density, porosity, Vickers hardness, toughness and roughness measurements were performed.
- Chewing simulation tests against dental human cusps were carried out in artificial saliva, before and after glazing.
- The counter-faces’ wear was quantified and the wear mechanisms investigated.

Results and Discussion

Zirconia Samples Characterization

<table>
<thead>
<tr>
<th></th>
<th>SM</th>
<th>AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density</td>
<td>6.06 ± 0.02</td>
<td>5.88 ± 0.10</td>
</tr>
<tr>
<td>Superficial porosity (%)</td>
<td>0.10 ± 0.03</td>
<td>3.92 ± 1.85</td>
</tr>
<tr>
<td>Hardness (HV)</td>
<td>1400 ± 16</td>
<td>1175 ± 29</td>
</tr>
<tr>
<td>Fracture toughness (MPa.m1/2 )</td>
<td>5.6 ± 0.6</td>
<td>4.5 ± 0.7</td>
</tr>
<tr>
<td>Linear roughness (nm)</td>
<td>243 ± 9</td>
<td>241 ± 16</td>
</tr>
</tbody>
</table>

Dental Cups Wear Rate

<table>
<thead>
<tr>
<th></th>
<th>SM glazed</th>
<th>AM glazed</th>
<th>AM unglazed</th>
<th>SM unglazed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cups wear rate (µm)</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

In both SM and AM glazed zirconia:
- Glaze suffered wear, leaving some zones of zirconia exposed
- Dental particles from the cusps wear adhered to zirconia/glaze
- Some parts of the glaze coating did not suffer wear

Conclusions

Additive manufacturing seems to be a promising technique to produce zirconia dental pieces.
The development of sustainable and green processes for the synthesis of pharmaceutical substances continues to be one of the main challenges for the pharmaceutical industry. In this communication we present the one-pot conversion of carbohydrates into a variety of important intermediates for the pharmaceutical industry with good overall yields. 1-3

**Synthesis of 5-HMF**

5-Hydroxymethylfurfural (5-HMF) is a sustainable and versatile precursor for the pharmaceutical industry and also for the petrochemical industry and biofuel chemistry. 5-HMF can be obtained selectively from fructose in 100% yield using HReO₄ as catalyst and DMSO as solvent.¹

![Synthesis of 5-HMF](image)

**Synthesis of HMF from different carbohydrates**

5-HMF was also obtained in 78% and in 66% yields from inulin and sucrose, respectively. In contrast, only 20% yield of 5-HMF was formed from glucose.

![Synthesis of HMF from different carbohydrates](image)

**Synthesis of Levulinic Acid (LA)**

LA is a useful precursor for the pharmaceutical industry, biofuel industry and food industry. The reaction of fructose in 1,4-dioxane catalyzed by HReO₄ at 140 °C during 1 h gave LA with 100% yield.²

![Synthesis of Levulinic Acid (LA)](image)

**Synthesis of LA from different carbohydrates**

LA can also be obtained in excellent yields from inulin (97%) and sucrose (85%) and in moderate yield (50%) from glucose.

![Synthesis of LA from different carbohydrates](image)

**One-pot synthesis of amines from carbohydrates**

Furfurylamines are important intermediates in the synthesis of pharmaceuticals such as antiseptic agents, antihypertensives and diuretics. We developed a novel one-pot process for the synthesis of furfurylamines from carbohydrates. This chemical transformation involves three consecutive reactions, including the conversion of xylose to furfural, followed by in situ reaction of furfural with aniline to form the imine and the selective reduction of imine by the silane, giving the furfurylamines with moderate to good overall yields (55-80%).²

![One-pot synthesis of amines from carbohydrates](image)

**One-pot synthesis of α-aminophosphonates from carbohydrates**

α-Aminophosphonates are amino acid analogues, which have found a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry. In our group, we developed the first methodology for the sustainable synthesis of heteroatom compounds, containing N and P atoms, from biomass resources catalyzed by HReO₄. This one-pot multi-reaction process allows the conversion of xylose and xylan into a large variety of α-aminophosphonates with moderate to good overall yields.³

![One-pot synthesis of α-aminophosphonates from carbohydrates](image)
Microporous materials for the storage and therapeutic release of H₂S

Ana C. Fernandes a,b,*, Beatriz Cambaio b, Mary Batista b, Fernando Antunes b, Moisés Pinto c, João Rocha a, Luís Mafra a, João Pires b

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Ana C. Fernandes and Mary Batista thank FCT by the Post-doc Grants SFRH/BPD/115953/2016 and SFRH/BPD/84542/2012.

References:

MAIN THERAPEUTICAL APPLICATIONS OF HYDROGEN SULFIDE

Long known as a toxic gas[1], hydrogen sulfide (H₂S) is also a biological signaling molecule that is produced by organisms ranging from bacteria to man.

In 2005, a paper in Science drew attention to its beneficial physiological effects[2]. Despite numerous studies reporting various biological effects of hydrogen sulfide in physiology and diseases in different organs/tissues, little is known about the signaling mechanisms underlying the H₂S effects.[3]

MICROPOROUS MATERIALS FOR THE STORAGE AND THERAPEUTICAL RELEASE OF H₂S

Zeolites Y and 4A adsorbed high amounts of H₂S. The modification of 4A with Chitosan and PCL polymers didn’t improve its adsorption. It seemed the polymers created a coating preventing the gas to enter the zeolite pores.

activated carbon obtained by chemical activation presented a higher capacity to adsorb H₂S, comparing to the carbon obtained by thermal activation. Its adsorption capacity was similar to zeolite 4A. The carbon modification with chitosan also lead to a decrease on the capacity on the H₂S adsorption.

Zeolites and carbon materials present an enhanced biocompatibility with HeLa cells, even after 72h of exposure. Commercial zeolites 4A and Y present high H₂S adsorption capacity. Carbon obtained by chemical activation present a similar adsorption capacity to 4A, it seemed that chemical activation originates carbons with higher adsorption capacity for H₂S than thermal activation.

The introduction PCL and chitosan, both on 4A and CG@Carbon, decreased the materials capacity to adsorb H₂S. Although carbons have the capacity to adsorb H₂S, they are not able to release it.

Zeolites not only are able to adsorb and then slowly release H₂S, but also present an enhanced biocompatibility with HeLa cells, which suits them to be used as vehicles for drug delivery.
The main goals of Laboratory of Catalysis cover: i) the production of value-added chemicals and fuels, such as hydrocarbons, methanol or syngas, using major gaseous pollutants (e.g. CO, CH₄, N₂O) as raw materials; ii) the development, preparation and characterization of nanostructured intermetallic compounds containing the f-block elements (lanthanides, Th and U), bimetallic oxides, metal borides, pnictides and chalcogenides with specific functionalities and applications in environment and energy.

For catalytic studies, different heterogeneous systems using transition metals and f-block elements as masic or supported (SiO₂ or Al₂O₃) catalysts were tested, either at atmospheric pressure or under high-pressure conditions. On the other hand, pnictides (e.g. CoSb₅) and chalcogenides (e.g. Cu₃SbS₂ and Cu₃Sb₃S₁₃) were prepared using unusual approaches, such as electrospinning and solvothermal method.

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Nanostructured bimetallic nickel-lanthanide or actinide oxides present a remarkable stability in the gaseous stream for at least 60 h, which was also confirmed by the low carbon deposition measured after reaction (< 1%).

This work has a strong societal impact since it contributes to the reduction/removal of major greenhouse gases, namely CO₂, contributing to alleviating global climate changes and contributing to the development of more clean and efficient industrial processes, targeting the production of value-added products (e.g. CH₄) that can be used as fuel or fuel precursors.

New objectives includes the development of new nanoporous/nanofoams f-block element based catalysts that can economical be competitive when compared to the present state of art used by the industry.

Very active and selective nanostructured bimetallic nickel-lanthanide or actinide oxides to production of CH₄. Yield to CH₄ (LCO₂/m²h) is significant higher when compared to the reference catalysts.

For catalytic studies, different heterogeneous systems using transition metals and f-block elements as masic or supported (SiO₂ or Al₂O₃) catalysts were tested, either at atmospheric pressure or under high pressure conditions.
Margarida P. Pereira1,2, João Franco Machado1,2,3, M. Fátima M. Piedade2,4, M. Helena Garcia1,2, 
Tânia S. Morais1,2,*

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Sythesis and characterization of a new family of ruthenium(II) complexes with phenanthroline derivate ligands for anticancer applications

Introduction

Cancer is the second leading cause of death worldwide (9.6 million deaths in 2018). Cisplatin is still one of the most commonly used drugs in cancer chemotherapy, however show broad and severe side effects. Our group has been developing new ruthenium(II) complexes with higher cytotoxicity than cisplatin against several cancer cell lines (e.g. ovarian, breast, colon and prostate). One of these compounds was evaluated in an orthotopic triple negative breast cancer mouse model, revealing significant capacity to suppress tumour growth and to inhibit the development of metastases, without presenting the common side-effects of cisplatin.

Herein, we report the synthesis and characterization of a new family of complexes of formula [Ru(n^3-C_3H_5)(PPh_3)(NN)][CF_3SO_3], in which NN corresponds to phenanthroline-derived ligands (Scheme 1).

Synthesis

Ru(II) complexes were synthesized according to Scheme 1, with yields of 43 to 85% upon purification by recrystallization.

X-Ray Diffraction

X-ray diffraction studies were performed and the results support the proposed structures for the complexes. As example, the [Ru(PPh_3)_3(phen)][CF_3SO_3] complex crystallized in monoclinic crystal system, space group P 21/n, with one cationic complex molecule and one CF_3SO_3^- as a counter ion in the asymmetric unit.

Stability Assays

The stability of the Ru(II) complexes in dimethyl sulfoxide over 24 hours was determined by UV-Visible spectrophotometry. All compounds revealed to be stable, and therefore suitable for further biological assays, namely test their anticancer activity in different human cell lines.

Structural Characterization

NMR analysis are in good agreement with the proposed structures for all the compounds.

In general, in 1H NMR spectrum, upon coordination of the ligand to the metal center a deshielding is observed in the cyclopentadienyl and phenanthroline signals. Also, a deshielding is observed in the signal of 31P NMR after coordination of phenanthroline-derived ligand.

UV-Visible Studies

[Ru(PPh_3)_3(CyPyzPhen)][CF_3SO_3] show an intense absorption band in the UV region with maximum circa 250-280 nm, characteristic of n→π* transitions of the aromatic fragments. A second broad less intense band between 370 and 445 nm is observed too, corresponding to a metal to ligand charge transfer band (MLCT).

Conclusions

• A new family of complexes of formula [Ru(n^3-C_3H_5)(PPh_3)(NN)][CF_3SO_3] (NN = phenanthroline-derived ligands) was synthesized with high purity.

• All complexes were structurally characterized by NMR, FT-IR, UV-Vis and elemental analysis.

• 2 structures were determined by single crystal X-ray diffraction studies.

• The stability of the complexes supports their suitability to proceed to further biological assays, namely testing their anticancer activity in different human cell lines.
Synthesis of Theobromine Isonucleosides as Potential Cholinesterase Inhibitors

Margarida P. Pereira,1,2 Eduardo C. de Sousa,1 Anne Loesche,3 René Csuk,3 and Nuno M. Xavier1,2

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2 Centro de Química Estrutural, Faculdade de Ciências, Universidade de Lisboa; margaridamag1992@gmail.com; nmxavier@fc.ul.pt
3 Bereich Organische Chemie, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Str. 2, D-06120 Halle (Saale), Germany

Introduction

Isonucleosides are regiosomers of nucleosides in which a nucleobase is linked to the sugar moiety at a non-anomeric position. These groups of molecules have attracted significant interest in the investigation of nucleoside analogs with therapeutic potential, namely in the context of anticancer and antiviral drug research.1,2

In a previous work,1 a isonucleoside comprising a theobromine unit linked to a methyl glucoside moiety (A) was shown to be a good inhibitor of acetylcholinesterase with a Ki value of 4.3 µM. The activity of this compound motivated the synthesis of novel analogs, which are presented in this poster.

Theobromine 3′-O-Benzyl Xylofuranos-5′-yl Isonucleoside and N-Isonucleosidyl Sulfonamide

Scheme 1. Reagents and conditions: (a) BnBr, NaH; (b) AcOH 60% aq.; (c) NaIO4; (d) NaBH4, EtOH/H2O; (e) PPh3, DEAD, 57%; (f) TFA/H2O; (g) Ac2O/py, 61%; (h) BF3-Et2O, 30%.

Theobromine 3′-O-Dodecyl Xylofuranos-5′-yl Isonucleoside

Scheme 2. Reagents and conditions: (a) C12H25Br, NaH, 93%; (b) AcOH 70% aq., 78%; (c) NaIO4, 79%; (d) NaBH4, EtOH/H2O, 81%; (e) PPh3, DEAD, 44%.

Theobromine 3′-O-Dodecyl Xylofuranos-5′-yl N-Isonucleosidyl Derivatives

Scheme 3. Reagents and conditions: (a) TFA 70% aq., 83%; (b) Ac2O, py, 69%; (c) CH3SO2NH2, BF3-Et2O, 81%; (d) TMSO, TMSOTf, 86%; (e) P(OMe)3, 56%.

Cholinesterase Inhibitory Activities

<table>
<thead>
<tr>
<th>Compounds</th>
<th>AChE</th>
<th>BChE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ki (µM) (%) Inhibition</td>
<td>&gt; 100 (19%)</td>
</tr>
<tr>
<td>% I = 28</td>
<td>3.1 ± 0.2</td>
<td>5.4 ± 0.3</td>
</tr>
<tr>
<td>% I = 53</td>
<td>[Ki &gt; 100]</td>
<td>[Ki &gt; 60]</td>
</tr>
</tbody>
</table>

% Inhibition at 50 µM.

Conclusions

❖ Novel theobromine isonucleosides based on pyranose and furanose templates and N-isonucleosidyl derivatives were synthesized by efficient methodologies.

❖ The ability of some compounds to display inhibition of cholinesterases with Ki values at single digit micromolar concentrations demonstrates their potential interest as anti-Alzheimer’s disease agents.
Chemical and Thermal Study of the *Catostylus tagi* for the development of a new biopolymer

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¹ Centro de Química Estrutural - CQE, ² Centro de Recurso Naturais e Ambiente - CERENA, ³ Centro de Ciências do Mar e do Ambiente - MARE

**INTRODUCTION:** *Catostylus tagi* (Cnidaria, Scyphozoa) is a jellyfish that can be readily found in the Tagus estuary as it has one of its most important and large populations. The body of this species of jellyfish has about 97% water making them quite fragile as they have less than 5% of solid organic matter [1]. The research conducted is a preliminary study into the possibility of using this species of jellyfish in the development of new biopolymers for marine applications.

**METHODS:** The specimens were collected between May and June 2018, in the region of São João da Talha. After washing with distilled water and lyophilization, the jellyfishes were characterized using SEM, FTIR-ATR, DSC and TGA.

**RESULTS AND DISCUSSION:** The SEM images revealed in the mesoglea zone a porous network composed of collagen fibers, allowing most of the water present in these animals to be considered free water. The FTIR-ATR of the lyophilized *C. tagi*, revealed the relevant peaks of collagen, the largest component of these animals. The DSC characterization of this species presents a peak transition at 200 °C that can be related to decomposition of the smallest collagen fibers. On the other hand, the degradation of the collagen takes place at 300 °C in the TGA analysis, but it was not possible to define the total degradation of the jellyfish since at the end of the experiment, 15% of the total mass sample still remained [2].

**CONCLUSIONS:** It was observed that the lost of water, of the lyophilized samples, led to a remarkable increase of the mechanical properties due to the strong interactions between the fibers and the mesoglea membranes. Such effect may be the result from the high closeness of those fibers, making the lyophilized jellyfish almost insoluble in most common organic solvents [3]. This behavior makes this species a potential additive to the development of a new biopolymer.
Innovative Materials for Nitric Oxide Adsorption and Therapeutic Releases

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Motivation

Nitric oxide (NO) is a gaseous molecule with well-known therapeutic properties, being a strong vasodilator, antibacterial, tumor repressor and promotes wound healing.

Existing NO donors are limited due to their high solubility, instability and release toxic degradation products.

Porous materials stand as a new system for NO release, storing NO by chemisorption. Previous results for zeolites and titanosilicates demonstrated high capacity to store NO however their release kinetics in biological media are not sufficiently slow for most potential applications (most of them release almost all stored NO in the first hour).

Objectives

- Obtain longer release rates by covering the porous solids with a biopolymer (polycaprolactone (PCL)) without compromising the following requirements:
  - Low toxicity
  - High NO adsorption capacity
  - High stability
  - Therapeutic application

Materials

PCL/zeolite microcomposites particles were prepared using the oil in water solvent evaporation method.

PCL/zeolite microcomposites were compressed in disks and melted at 100 °C to form the films.

<table>
<thead>
<tr>
<th>Composite materials designation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCL/4A [2:1] 600</td>
<td>PCL and Zeolite 4A films at 2:1 w/w with microparticles obtained under stirring at 600 rpm.</td>
</tr>
<tr>
<td>PCL/4A [8:5]</td>
<td>PCL and Zeolite 4A films at 8:5 w/w with microparticles obtained under stirring at 1200 rpm.</td>
</tr>
</tbody>
</table>

Materials Characterization

Infrared Spectroscopy

Termogravimetry

Contact angle

SEM/EDS

Zeolite 4A confers higher hydrophilicity to the PCL films.

Conclusions

- Moderate hydrophilicity of the composite films facilitates slower NO release rates.
- Composite PCL/Zeolite indicated slower and a controlled NO release comparing with the release profile of the adsorbent.
- Uniform distribution of the adsorbent through the film ensures the target release of pure NO.
- This new composite formulation pave the way for the design of new NO delivery systems with potential application as transdermal patches for wound healing treatments.

Results

NO adsorption/release

1. Gaseous phase

2. Liquid phase

- Composite PCL/4A films feature high storage capacity and a slower NO release rate.

References


Funding:
Centro de Química Estrutural is funded by Fundação para a Ciência e Tecnologia (FCT) – project UID/QUI/00100/2019.
The work was financed by FCT through projects IF/00993/2012/CP0172/C T013 and PTDC/MED- QUI/28721/2017. This work was developed in the scope of the Projects UID/MULTI/06012/2019 (CQB), UID/EQI/04028/2019 (CERENA).
New sustainable approaches to the synthesis of 1,2- and 1,4-naphthoquinones

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3 Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, 2780-15 Oeiras, Portugal.

Importance
Naphthoquinones are a very important class of organic compounds in pharmaceutical chemistry due to their extremely rich redox and acid-base properties. Quinone cores are known to be electron transporters and quinone redox cycling, that yields “reactive oxygen species” (ROS), is important for many biological oxidative processes that are essential to living organisms. The predominant scaffold in nature is the naphthalene 1,4-dione (Figure 1) whose different derivatives exhibit a wide range of biological activities and pharmacological properties including anti-inflammatory, antibacterial, antitumor and other chemotherapeutic agents. However, also the 1,2-dione isomers have a very important role in the development of new substances for medical purposes with a wide range of derivatives exhibiting significant therapeutic properties.1-3

Synthesis
The synthesis of naphthoquinone frameworks is quite-well documented, and some strategies involve the use of natural naphthoquinones as starting materials, which involves their extraction from plants using organic solvents. On the other hand, other traditional methods/protocols involve as first step the oxidation of the hydronaphthoquinone core with chemical oxidants such as H2O2, Fremy’s salt ([KSO]3NO), chromium trioxide or other chemical oxidants.2 Although there are reports of new environmentally friendly methodologies4, it is still a challenge to explore new sustainable synthetic routes for these compounds, that assume importance in the field of both synthetic and medicinal chemistry.

Methodologies
In pursuit of our research interest devoted to exploiting environmentally friendly protocols to obtain original compounds or to improve known reactions, we report herein two methodologies, a biocatalytic and a microwave irradiation process, to obtain phenylamino 1,2- and 1,4-naphthoquinone derivatives, respectively, with different substituents at the 4-position of the phenylamine ring.

Biocatalysis
CotA-laccase is a copper containing oxidoreductase isolated from Bacillus subtillis. The active site contains four copper ions responsible for the oxidation of substrates with concomitant reduction of oxygen to water.

Microwave irradiation
Microwave radiation is nowadays considered as a powerful option in the field of sustainable pharmaceutical synthesis specially due to shorter reaction times, lower energy consumption and higher product yield.

Conclusions
Two environmentally benign protocols, Biocatalysis and Microwave irradiation, have been implemented towards the synthesis of 1,2- and 1,4- naphthoquinone derivatives as target molecules with good to excellent yields. The presented methodologies are in accordance with the principles of Green Chemistry and can be faced as sustainable alternatives to the synthesis of these classes of compounds.

References:
Poly(ionic liquid)/ionic liquid membranes with fluorosulfonyl derivative anions: characterization and CO₂/H₂ separation

Andreia S.L. Gouveia, Liliana C. Tomé and Isabel M. Marrucho

Introduction

Despite the recognized potential of biohydrogen (bioH₂) for sustainable development, there are still challenges to be overcome regarding its production and purification, such as the elimination of CO₂, N₂, and other impurities (H₂O and H₂S), so that an enriched H₂ stream can be obtained for efficient energy generation [1].

Ionic liquids (ILs) have been used as a successful platform to design novel task-specific materials for CO₂ separation [2]. Moreover, different studies have been unveiling that the use of poly(ionic liquid)s (PILs) and their composites (PIL–IL) is a powerful strategy to design improved CO₂ separation membranes [2]. In this work, PIL–IL membranes of pyrrolidinium-based PILs containing [TFSAM]⁺, [FSI]⁻ and [TSAc]⁻ anions were prepared by the incorporation of ILs containing the same anions. The composite membranes as well as the pure PIL and IL components were characterized by different techniques (TGA, DSC, FT-IR and Raman) and their CO₂/H₂ separation performance was evaluated using the time-lag method at biohydrogen production conditions.

Experimental Section

Results and Discussion

From the TGA results, different trends were observed for degradation temperatures of the PIL–IL composites with the addition of free IL. In fact, the thermal stability of the prepared PIL–IL membranes not always follows a simple mixing rule.

Conclusions

- PILs and ILs containing anions based on fluorosulfonyl derivatives were synthesized and characterized.
- PIL–IL membranes were prepared and their CO₂ and H₂ permeation properties were studied.
- The prepared PIL–IL membranes revealed CO₂/H₂ separation performances above the upper bound.

Higher CO₂/H₂ selectivities were obtained for both PIL FSI–40 [C₄mim][FSI] (α = 9.0) and PIL TFSAM–40 [C₄mim][TFSAM] (α = 7.1) compared to those of reported composites containing the conventional [NTf₂]⁻ anion (PIL NTf₂–40 [C₄mim][NTf₂]) (α = 6.5) and PIL NTf₂–60 [Pyrr₃][NTf₂] (α = 6.3).
Poly(vinyl alcohol) hydrogels for cartilage replacement: Impact of processing conditions on the materials properties

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INTRODUCTION
Over the past few years, hydrogels have demonstrated their potential as promising materials to be used as replacement options for cartilage damaged tissues. In particular, hydrogels made of poly(vinyl alcohol) (PVA) have attracted much attention due to their similarities to native tissue. PVA hydrogels are biocompatible, present a high swelling capacity and have a rubbery and elastic nature. In addition, PVA is easy to process and manipulate and is stable at human body temperature.

OBJECTIVE
The aim of this study was to evaluate the effect of the preparation conditions on the swelling capacity, microstructure, mechanical properties and thermotropic behavior of PVA-based materials.

RESULTS AND DISCUSSION

CD samples present lower swelling ratios than FT samples.

Thermotropic behavior almost was not affected by the materials preparation conditions.

CD samples are more rigid and dissipate less energy.

CONCLUSION
The results demonstrate that the mechanical properties of PVA hydrogels are strongly determined by the preparation conditions. The CD method allowed to obtain hydrogels with greater mechanical resistance and with promising characteristics for cartilage substitution.
Optimization of metal loaded hierarchical zeolite structures MOR, BEA, and MFI for catalytic oxidation reactions

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Introduction
In this work hierarchical zeolite structures MFI, BEA and MOR (Figure 1) were prepared by desilication procedures, followed by acid treatment.

![Figure 1. Zeolite structures studied](image)

The catalytic behavior of metal loaded (Fe) hierarchical zeolites structures was explored in the oxidation of 1-phenylethanol into acetophenone (Figure 2). The metal was introduced by mechanochemical grinding using a ball mill and the catalytic reaction was performed using microwave radiation as a heating source.

![Figure 2. Oxidation of 1-phenylethanol into acetophenone under microwave heating.](image)

Experimental Procedure

- **Preparation of the hierarchical zeolites:**

  - Commercial zeolite (Na+, NMR)
  - Alkaline treatment: 30 min, vigorous mixing; 65 °C; 0.2/0.4/0.8 M NaOH, m/V=1:30:3
  - Ionic change: 2 h, vigorous mixing; 80 °C; 1 M NaOH, m/V=25
  - Calcination: 5 h, 550 °C; 1 atm; atmospheric conditions.

- **Immobilization of Iron in zeolite support:**

  - Zeolite in p·2H2O·FeCl3·6H2O
  - Precursor metal salt (FeCl2·4H2O or FeCl3·6H2O)
  - Zeolite with immobilized metal
  - Code name: Fe@zeolite structure [NaOH/(AT)

- **Characterization methods:**

  - X-Ray Diffraction – Analytical X’Pert PRO with X’Celerator detector with an angular scan (2θ) ranging between 5 and 40, with a step of 0.017° and a time/step of 20s.
  - Adsorption of N2 at -196 °C – Micromeritics ASAP 2010; m-sample = 50 mg; degasification at T=150 °C, for 2 h under vacuum better than 10-2 Pa.

Results

- **Characterization:**

  - All modified samples present the diffraction patterns characteristic of each structure although some crystallinity loss is detected, especially when high [NaOH] is used.
  - For BEA based samples the development of mesoporosity does not compromises the microporosity.
  - For MOR and ZSM-5 samples the development of mesoporosity occurs but for [NaOH]=0.4 M the loss of microporosity takes places whereas for [NaOH]=0.8 M larger micropores are formed during treatments.

- **Catalytic tests:**

  - The catalytic tests were performed in a microwave reactor under previously optimized conditions: 100 °C, 600 rpm and 50 min.

Product analysis - Gas Chromatograph Fisons Instruments. Nitromethane was used as internal standard.

- For Fe@BEA samples both alkaline and acid treatment led to an increase in yield and product selectivity.
- For Fe@MOR the catalytic behaviour does not seem to affect the catalytic behaviour.
- For Fe@ZSM-5 the catalytic activity is higher according to the [NaOH], besides lower selectivities and yields were found:
  - For 0.4 M there is an important increase of selectivity and product yield is verified.

Conclusions

- Hierarchical zeolite supports were successfully prepared exhibiting micro + mesoporosity with good crystallinity.
- The treatments affect the catalytic behaviour distinctively for each support.
- Fe@BEA catalysts present the most promising catalytic behaviour so far.
Synthesis of metallo-macrocycle and coordination polymers with pyridine-based amido-carboxylate ligand and their catalytic activities towards Henry and Knoevenagel reactions

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

Introduction

Coordination polymers (CPs) are compounds consisting of inorganic metal ions and organic linkers, which have attracted a significant interest recently. The rapid development in this field is due to their attractive structures and topologies, as well as to their uses in various areas, e.g., catalysis, nonlinear optics, gas storage and separation and magnetism. On the other hand, the synthesis of metallo-macroyclic (MMC) molecules using metal-directed self-assembly is a current area of research activity.

Synthesis and Structures of Metallo-macrocycle and Coordination polymers

<table>
<thead>
<tr>
<th>Catalysts</th>
<th>Yield for Henry Reaction</th>
<th>Selectivity for Henry reaction (syn:anti)</th>
<th>Yield for Knoevenagel Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>62:38</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>67:33</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>60:40</td>
<td>73</td>
</tr>
</tbody>
</table>

Reactions conditions: 3.0 mol% of catalyst, benzaldehyde (52 μL, 0.5 mmol), nitroethane (0.2 mL, 2.6 mmol) and water (1.0 mL) for 48h at 70°C. Knoevenagel conditions: 2.0 mol% of catalyst, solvent (THF) 1 mL, malononitrile (66 mg, 1.0 mmol) and benzaldehyde (52 μL, 0.5 mmol) for 1.5h at 50°C.

Catalysis, Size selectivity and Recycling

Effect of catalyst recycling on Henry and Knoevenagel reactions

References:
**Effect of alkyl substituent’s on the biological activity of benzimidazole-based Schiff base copper(II) complexes**

**Authors:** Anup Paul,¹ Sallemuthu Anbu,¹ Gunjan Sharma,² Maxim L. Kuznetsov,¹ Biplob Koch,² M. Fátima C. Guedes da Silva,¹ Armando J. L. Pombeiro¹

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

²Departments of Zoology, Faculty of Science, Banaras Hindu University, Varanasi - 221 005 (U.P.) India.

**Background**

The majority of platinum based drugs used for cancer treatment have numerous and severe side-effects and this lead to the exploration of non-platinum metal based drugs. Amongst all the metal complexes, Schiff base Copper(II) complexes are regarded as a promising anticancer drug alternative and the design of improved antitumour agents occupies a significant place in cancer chemotherapy.¹-³

In view of this, we have reported a new benzimidazole-based Schiff base copper(II) complexes (1-3) by varying the N-alkyl substituents' and their anti cancer properties (Fig. 1).

**Results**

**DNA interaction studies**

- The absorption titration profiles of 1-3 suggests intercalation between the complexes and DNA. As a representation only the titration profile of 1 is presented here [Fig. 2 (A)].
- The binding constant (K₆) of the complexes 1-3 with CT DNA, was found to be 3.45±0.23 x 10⁶ M⁻¹ (1), 3.33±0.18 x 10⁶ M⁻¹ (2), and 3.15±0.16 x 10⁶ M⁻¹ (3). The non-linear plot for 1 is shown in [Fig. 2 (B)].

**Molecular docking**

- The docking experiments revealed that the complexes interact with B-DNA (PDB ID: 18NA) to the G-C rich intercalation site of the minor groove with relative binding energy of -341.83 (1, Shown in Fig. 3), -302.5 (2) and -301.9 (3) kJ mol⁻¹.
- The binding affinity follows the order 1 > 2 > 3.

**Cytotoxicity studies MTT assay**

- The cytotoxicities of complexes 1-3 against three different human cancer cell lines, A-549 (lung carcinoma), MDA-MB-231 (breast cancer) and HeLa (cervical cancer) cells, were evaluated (Table 1).
- Complex 1 exhibits a significant inhibitory effect on proliferation of the A-549 cancer cells and is found to be more potent than the widely used drug cisplatin (IC₅₀ = 27.2 ± 1.71 µM) under similar experimental condition.

**Table 1**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Incubation time (24 h)</th>
<th>IC₅₀ (±) µM</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-549</td>
<td>MDA-MB-231</td>
<td>HeLa</td>
</tr>
<tr>
<td>1</td>
<td>16.7 ± 0.29</td>
<td>29.58 ± 1.17</td>
</tr>
<tr>
<td>2</td>
<td>24.0 ± 1.99</td>
<td>31.92 ± 0.73</td>
</tr>
<tr>
<td>3</td>
<td>29.1 ± 1.12</td>
<td>46.03 ± 1.12</td>
</tr>
</tbody>
</table>

**DNA fragmentation**

- In DNA fragmentation assay [Fig. 6] control DNA do not have any detectable ladder pattern, whereas the introduction of 1 (15 µM) caused a remarkable appearance of DNA fragmentation/ladder pattern. The effect becomes more prominent at higher concentrations 18 and 21 µM (lanes 4 and 5, respectively), comparable to etoposide, a known DNA damaging agent.
- As shown in Fig. 7, after 24 h treatment, the complex under study induces an elevated level of ROS generation in a dose dependent manner. These results demonstrate that complex 1 may induce apoptotic pathways mediated by ROS.

**Conclusions**

- Three new N-alkyl substituted benzimidazole-based Schiff base copper(II) complexes (1-3) were synthesised and their anti-cancer properties were evaluated.
- They effectively bind to DNA through intercalative mode, in the order of 1 > 2 > 3 and the binding of the complexes to DNA minor groove through intercalative mode has been rationalized by molecular docking studies.
- The complexes exhibit in vitro cytotoxic activity against lung (A-549), breast (MDA-MB-231) and cervical (HeLa) cancer cell lines, with potency of 1 (with the shortest alkyl substituent, i.e., methyl) being even higher than that of the widely used drug cisplatin (IC₅₀ = 27.2 ± 1.71 µM) against lung cancer (A-549) cell line. The greater antiproliferative activity of the complex 1 was further proved by morphologic, cell cycle, DNA fragmentation and ROS studies.

**References**


Acknowledgment

A. Paul acknowledges financial support from FCT for post-doctoral fellowship (SFRH/BPD/88450/2012).
Synthesis and structures of Al(III), Fe(III) and Cu(II) formazanates

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Formazans have been attracted much attention due to their optical properties, E/Z isomerization, analytical and biomedical applications, etc. [1,2]. Attachment of substituents to formazan moiety allows to improve their properties and control/direct reactivity. In fact, cooperation of optical and redox properties makes them attractive ligands for coordination chemistry. However, the number of publications devoted to structurally characterized formazan complexes is very limited. Herein we have synthesized a new formazan ligand namely sodium 2-(2-((E)-cyano((E)-(2-sulfonatophenyl)diazenyl)methylene)hydrazineyl)benzenesulfonate (Na2HL) and its Al(III), Fe(III) and Cu(II) (Scheme). The synthesized Al(III), Fe(III) and Cu(II) formazanates were characterized by IR, elemental analysis, ESI-MS, and single crystal X-ray diffraction.

Scheme: Synthesis and structures of a formazan ligand and its Al(III), Fe(III) and Cu(II) complexes.

Keywords: Formazan; Al(III), Fe(III) and Cu(II) complexes, X-ray analysis.


Funding: This work was supported by projects UID/QUI/00100/2013 and UID/QUI/00100/2019 Fundação para a Ciência e a Tecnologia (FCT).

References:
The carbonate system is one of the most important and complex systems in the oceans. Increasing concentrations of CO$_2$ in the atmosphere is followed by its dissolution in seawater with consequent acidification.

**Results**

- pH measurement in seawater requires TRIS-TRIS HCl solutions in ASW for calibration of measurement equipment ⇒ Associated uncertainty below target value (<0.02)
- TA is measured with $U'$ =1.5%. Method allows the determination of [HCO$_3^-$] and [CO$_3^{2-}$] with $U'$ < 4%
- Uncertainty propagation for the other variable of Carbonate System: $U'(\text{DIC}) = 3\%$; $U'(\text{pCO}_2) = 7\%$

**Conclusions**

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**References**

Synthesis and photocatalytic application of novel diethylenetriamine modified titanate nanotubes for emergent pollutants degradation

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Introduction

Pharmaceuticals and personal care products (PPCPs) disposal has become very problematic nowadays. These emergent pollutants are resistant to conventional treatments and even at very low concentrations, they may impose toxicity at all biological hierarchy levels. Photocatalysis is attractive for several applications including for removal of pollutants from wastewater and/or air1. Here, new hybrid nanomaterials, were obtained through sensitization of titanate nanotubes (TNT) and titanium dioxide nanoparticles (TiO2) with diethylenetriamine (DETA) to produce DETA-TNT and DETA-TiO2 materials, respectively. The photocatalytic ability of the sensitized materials for the diclofenac degradation was evaluated. Secondary products were identified and quantified using LC-HR-ESI/MS. Reusability potential was evaluated in successive degradations using visible light. The sensitized samples demonstrated excellent catalytic reusability ability, without loss of chemical stability and photocatalytic performance.

Results and discussion

Pollutants photocatalytic degradation

By-products formation/degradation

UV-vis irradiation
- All the TNT and TiO2 samples show catalytic activity for diclofenac photodegradation;
- No significative differences were observed in TNT and TiO2 photocatalytic activity;
- All diclofenac (20 ppm) was degraded using DETA-TNT as photocatalyst, after 10 min of irradiation;
- All by-products were removed using DETA-TNT as catalyst after 60 min of irradiation.

Visible irradiation
- TNT and TiO2 samples show photocatalytic activity for diclofenac degradation;
- The best catalytic performance was achieved using DETA-TNT sample;
- All diclofenac has been degraded using DETA-TNT as photocatalyst, after 45 min of irradiation;
- After 60 min of irradiation, there are two by-products in solution, indicating that more time is required to complete the degradation under visible light.

Conclusions

- Nanocrystalline titanate nanotubes and TiO2 nanoparticles sensitized with DETA were successful prepared.
- The best catalytic results, for diclofenac photodegradation, were obtained using DETA-TNT, within 10 and 45 min of UV-vis and visible light irradiation, respectively.

References:
Thermal Stability of Choline Chloride-Ethylene Glycol Eutectic Mixtures: What DSC Tells Us

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Introduction
Deep Eutectic Systems (DES) have known a huge expansion in recent years1,2 as alternative solvents to conventional organic solvents, due to the simplicity of preparation, low melting points and low toxicities, which potentiate a wide variety of technological applications that span, among others, from the extraction and solubilization of some biomolecules to CO2 capture.

A deep eutectic solvent consists of two or more components that liquefy upon interaction through hydrogen bonding and Van der Waals interactions. At a molecular level, these physical interactions considerably lower the melting temperature of the mixture (relative to pure components) by stabilizing the liquid phase at room temperature.

In this work, the thermal behaviour of two compositions of the eutectic mixture choline chloride (ChCl)/ethylene glycol (eg) - 1:2 and 1:9 – was explored by differential scanning calorimetry (DSC) and, complementarily, also by hot stage microscopy (HSM) and nuclear magnetic resonance (NMR).

Results

Figure 1: Thermogram of heat flow (W/g) vs. temperature (°C) of a liquid sample from the eutectic mixture ChCl/EG 1:9.

Materials & Methods

DSC 2920 - TA Instruments
- ChCl/EG 1:9; Needles 1:2
  - TE[-130, 100] °C
- Bruker 400 MHz NMR, B-ACS 60, 400 UltraShield
  - ChCl/EG 1:9
    - TE[-50, -10] °C
- Olympus Microscope BX51
  - Needles of ChCl/EG 1:2
    - TE[-50, -10] °C

Conclusions

- 1:2 and 1:9 ChCl/EG eutectic mixtures were assessed in the temperature range -130 °C to 100 °C by DSC and also tracked by HSM using polarized light. The 1:9 mixture showed a reproducible metastable phase at low temperatures (at ~ -20 °C), as well as a glass-transition temperature (at ~ -115 °C) – Fig. 1. 1:2 needles registered a well-defined fusion temperature, at around +78 °C, and simultaneously a recrystallization temperature at ~ 60 °C observed upon cooling – Fig. 2.
- Preliminary 1H and 13C NMR experiments were also carried out (Fig. 3) to tentatively rationalize the observed thermal events detected during 1:9 DSC analysis, but no structural modification was perceived in the selected temperature range, unlike what is suggested by the calorimetric results (Fig. 1).
- HSM data confirmed the calorimetric analysis of the 1:2 needles with the observation of the progressive loss of crystallinity before the fusion process (Fig. 4).
- The results gathered, suggest the need for a systematic study of the thermodynamic properties of these systems at a molecular level over time.

References:
Synthetic Cathinones: Metabolite Profile by High Resolution Mass Spectrometry

Beatriz Teixeira Lopes1,2, Maria João Caldeira3, Helena Gaspar2, Alexandra M.M. Antunes1

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2University of Lisbon, Faculty of Sciences, BioISI – Biosystems & Integrative Sciences Institute, Campo Grande, CS 1749-016 Lisboa, Portugal
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Introduction

Synthetic cathinones are commonly abused new psychoactive substances (NPS).1 The rapid speed at which new NPS enter the market difficulties the response from authorities with toxicological studies and analytical methodologies suitable for the identification and quantification of parent NPS and their metabolites in biofluids.2

This work was aimed at characterizing by high resolution mass spectrometry (HRMS) the Phase I and Phase II metabolite profiles of several synthetic psychoactive cathinones (e.g. α-PVP and 4Cl-PVP) upon in vitro incubation in rat and human liver microsomes.

Methodology

**In vitro metabolism studies**

**Cathinone**
- Phase I co-factor: NADPH
- Phase II co-factor: UDPGA

**Aliquots**:
- 3 h
- 24 h

**Alamethicin-induced microsomes were used for identification of glucuronide metabolites.**

**Metabolite profile identification**

**HRMS Isotope cluster, tandem HRMS profiles and targeted search approaches were used for the identification of multiple metabolites.**

Results

**Scheme 1. Scheme of 4Cl-α-PVP metabolites identified in vitro.**

Multiple Phase I and II metabolite of 4-Cl-α-PVP were for the first time identified. This cathinone was recently introduced in the NPS market. Figure 1 displays the tandem HRMS spectrum obtained for one of the Phase I metabolites identified for this cathinone.

For α-PVP, it was consistent identified in rat and human microsome incubations one previously uncharacterized Phase II metabolite of this cathinone. The tandem HRMS of the protonated molecule of this new adduct presents fragment ions fully compatible with the structure ascribed (Figure 2).

Conclusion

Using this approach, not only a new Phase II metabolite of drug of abuse α-PVP was identified but also multiple Phase I and II metabolites of the new NPS, 4-Cl-α-PVP, were fully characterized. These metabolites are now available to be used as standards in a forensic context.
Modeling Preferential Solvation in Acetonitrile-Water Mixtures Using Kinetic Probes

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Introduction

- Acetonitrile-water (MeCN/water) mixtures are widely used for several physicochemical purposes and have been extensively studied using different methods.
- Our research group has been interested in the application of quantitative structure-property relationships to the study of tertiary alkyl halides’ reactivity in different media.
- We have studied the reaction of 3-Cl-3-methylpentane (Fig. 1) in MeCN/water mixtures and the obtained -log k vs. xwater curve revealed some interesting aspects (Fig. 2), most probably related to preferential solvation phenomena.
- Several models have been developed to explain/quantify preferential solvation, like the Bosch and Rosés’ model, originally applied to binary mixtures2 and later extended to ternary mixtures3, and the El Seoud’s model4.
- Both models consider the existence of preferential solvation phenomena in which solvent 1 (S1) can be replaced by solvent 2 (S2) or by a binary complex formed by both solvents (S1S2) – see equilibrium schemes.
- The preferential solvation is quantified considering 2 constants (derived from the models): f12/1 which quantifies the preferential solvation ability ratio of S2/S1 and f12/1, quantifying S1S2/S2 ratio.
- Bosch and Rosés’ model, postulates the formation of S1S2 only in the solution (I) cybotactic region.
- Conversely, El Seoud’s model, considers that S1S2 is formed only in the bulk mixture, throughout an equilibrium which is quantified outside the context of the studied process. In the case of MeCN/water binary mixtures, at 25.0 °C, K = 10.084.
- The observed property (Y), in our case -log k (proportional to ΔG), is considered to result from the sum of the Yi values (for S1, S2 and S1S2) multiplied by the respective molar fractions in the cybotactic region (x’i).

Bosch and Rosés’ Equilibria Equations

\[
\begin{align*}
I(S1)_m + mS2 & \rightleftharpoons I(S2)_m + mS1 \\
I(S1)_m + \frac{m}{2}S2 & \rightleftharpoons I(S1S2)_m + \frac{m}{2}S1
\end{align*}
\]

El Seoud’s Equilibria Equations

\[
\begin{align*}
S1 + S2 & \rightleftharpoons S1S2 \\
I(S1)_m + mS2 & \rightleftharpoons I(S2)_m + mS1 \\
I(S1)_m + mS1S2 & \rightleftharpoons I(S1S2)_m + mS1
\end{align*}
\]

Model Equation

\[ Y = Y_1x_1^* + Y_2x_2^* + Y_{12}x_{12} \]

Experimental Procedure

- Solvent mixtures were prepared by mass. Substrate concentration was 0.01 mol dm⁻³. Kinetic measurements were carried out on an automated conductance bridge. Reactions were followed, at 25.0 °C, up to 90% of the apparent plateau. Experimental values of -log k for 11 binary mixtures were determined using a previously designed spreadsheet5. Values for the pure solvents were calculated using a 3rd degree polynomial curve. Table curve 2D and 3D programs were used to perform the adjustments.

Results and Discussion

- The statistical figures of merit (s_fit, R² and F) show that both models are adequate to model the experimental data (Table 1).
- Bosch and Rosés’ model predicts a value of -log k_water-MeCN which corresponds to a ΔG = 99 kJ/mol (similar to the average result for a 1:1 mixture) and the corresponding value for El Seoud’s model is ΔG = 118 kJ/mol, representing an increase of about 22% regarding the average result for a 1:1 mixture.
- Bosch and Rosés’ model predicts a preferential solvation order (with an approximate relative magnitude) of water-MeCN (S) >> water (1) = MeCN (1).
- Results for El Seoud’s model lead to the following order: water-MeCN (10) ≈ water (2) > MeCN (1).

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References:

Table 1

<table>
<thead>
<tr>
<th>Statistics and properties</th>
<th>Bosch and Rosés’ model</th>
<th>El Seoud’s model</th>
</tr>
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<tbody>
<tr>
<td>s_fit</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>R²</td>
<td>0.9997</td>
<td>0.9988</td>
</tr>
<tr>
<td>F</td>
<td>7801</td>
<td>9361</td>
</tr>
<tr>
<td>-log k_water</td>
<td>0.47±0.03</td>
<td>0.74±0.03</td>
</tr>
<tr>
<td>-log k_MeCN</td>
<td>7.46±0.03</td>
<td>7.46±0.03</td>
</tr>
<tr>
<td>-log k'_water-MeCN</td>
<td>4.47±0.17</td>
<td>7.86±0.85</td>
</tr>
<tr>
<td>f_MeCN/water</td>
<td>0.03±0.33</td>
<td>0.41±0.07</td>
</tr>
<tr>
<td>f_water-MeCN</td>
<td>3.95±0.33</td>
<td>4.91±0.70</td>
</tr>
</tbody>
</table>
Green method for the production inverse spinels

Beatriz M. Santos,¹ Rute F. C. Faustino,¹ Ana P. C. Ribeiro¹

INTRODUCTION

Spinel is a common structural arrangement shared by many oxides of the transition metals with formula AB₂O₄. An inverse spinel is an alternative arrangement where the divalent ions swap with half of the trivalent ions so that the M(II) now occupy octahedral sites i.e. B(AB)O₄.

In this work, the preparation methods, materials characterization, and magnetic properties of inverse spinel materials, such as ZrFe₂O₄, NiFe₂O₄, by hydrothermal method.

The synthetic procedure includes the use of water and room temperature, and the purification is by thermal activation. The final materials are magnetic and can have potential applications in catalysis.

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Ln-based Compounds Applications in Magnetism and Optical Sensing

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Magnetism

The field of Ln-based single-molecule magnets (SMMs) is one of the hottest research areas in Molecular Nanomagnetism. Nevertheless, the study of the magnetic properties of Layered Lanthanide Hydroxides (LLHs) still remains largely unexplored, with the exceptions of our recent investigations in Dy layered compounds belonging to the Ln₃(OH)₂Cl₄nH₂O series (Figure 1). In this work, three LLHs, with the general formula Lnₓ(OH)₂Cl₄·nH₂O (Ln = Tb, Ho, Er), were prepared and magnetically characterized both as pure compounds and diluted within a yttrium diamagnetic matrix, LYHₓLn₄, LYH₀.044Tb, LYH₂₀.045Ho, and LYH₂₀.065Er.

As it can be observed in Figure 2, the χT curves can be successfully reproduced by using the Radial Effective Charge (RECO) model in the SIMPRE software package.

Optical Sensing

Methanol is extremely toxic so the development of a fast, efficient and low-cost methods for methanol quantification and detection in mixtures of ethanol/methanol is, therefore, pertinent to ensure food safety. Based on the interaction of trihexyltributylphosphonium cation ([P₆,₆,₆,₁₄][Eu(FOD)]) with the β-diketone (1,1,2,2,3,3-heptfluoro-7,7-dimethylecctane-4,6-dionate - FOD) of an Europium(III) complex, [P₆,₆,₆,₁₄][Eu(FOD)]₄, we present and discuss an equilibrium reaction with NaOPhMe₃ (Figure 4) with pronounced solvent effect between ethanol and methanol on Eu(III) luminescence.

A ratiometric method was used to calculate the ratio of the fluorescence intensities by adding different amounts of methanol in ethanol and correlate the methanol concentration with the normalized intensity of the ⁵D₀ → ⁷F₀ transition, Figure 5.

Highlight

The methanol-sensing studies showed that the resulting mixture of the reaction between [P₆,₆,₆,₁₄][Eu(FOD)]₄ and NaOPhMe₃ can be used as a sensitivity, highly reproducible, fast and low-cost ratiometric method to determine the methanol content in methanol/ethanol mixtures from as low as 15 % (w/w).

Figure 1. Lnₓ(OH)₂Cl₄·nH₂O unit with: Ln – purple, hydroxyls – grey, water oxygen – blue, chloride - green. The 8-fold dodecachowder and 9-fold monopodal square antiprism are in light green and purple, respectively

Figure 2. Experimental data (symbols) and theoretical simulation (lines) of the temperature dependence of the magnetic susceptibility of the LYHₓLn₄ compounds.

Figure 3. Plot of the temperature dependence of the relaxation time as 1/VT vs. T for Tbₓ(OH)₂Cl₄·6H₂O.

These results highlight the presence of significant interactions between the Ln centers. A clearer slow relaxation behavior is observed in the LYHₓLn₄ solid solutions. Semi-empirical calculations successfully allowed to access the Ln electronic configurations and the respective contributions to the slow relaxation behavior of these LLHs showing a diversity of magnetic behaviors.

Figure 4. Solvent dependent equilibrium with pronounced solvent effect on Eu(III) emission.

Figure 5. Calibration curve for methanol estimation in ethanol/methanol mixtures. χ molar fraction of methanol in ethanol.
Development of consolidation products to carbonate stones from built heritage

B. Sena da Fonseca, A.P. Ferreira Pinto, S. Piçarra, M.F. Montemor

**Introduction**

Carbonate stones are extensively present in monumental and non-monumental constructions having an outstanding cultural and architectural value. Conservation interventions, involving consolidation of stone, are often required due to their advanced state of degradation that threat the cultural value and significance of built heritage. However, the existing consolidation products, based in alkoxysilanes, present some limitations and often show a reduced efficacy or even potential to accelerate degradation phenomena. The most commonly cited drawbacks and the reasons behind their poor performance are:

- Tendency to crack
- Lack of chemical affinity with carbonate substrates

The project aims at developing new consolidation products with improved characteristics, particularly regarding these recognized weaknesses.

**Strategies**

<table>
<thead>
<tr>
<th>Optimized TEOS-based formulation</th>
<th>Flexible hydrophilic polymer (Lpfp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organically modified alkoxysilanes (LPam)</td>
<td>translucent ORMOSIL with low tendency to crack during gelling and aging steps</td>
</tr>
<tr>
<td>Organic acid solution</td>
<td>Tartaric acid (LPoa)</td>
</tr>
</tbody>
</table>

**Results**

<table>
<thead>
<tr>
<th>Xerogels</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPfp</td>
</tr>
<tr>
<td>Silicate material with low tendency to crack during gelling and aging steps (in relation to commercial consolidants)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calcite crystal / powder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated with calcite powder + Ultrasonic wave</td>
</tr>
</tbody>
</table>

**Efficacy (drilling resistance)**

Stone cohesion increments:

- All the formulations demonstrated potential to be applicable into porous carbonate stones and to increment their cohesion. Even so, the solutions with improved chemical affinity with the substrate caused the higher overall increment but still some tendency to create potentially harmful hard layers.

In the sequence of the promising results achieved, further improvements will be pursued by tailoring the reactional parameters of the formulations as well as to test other formulation paths.
CHARACTERIZATION OF ATMOSPHERIC AEROSOL OF A MEDIUM SIZE CITY IN BRAZIL

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\textsuperscript{3} Centro de Química Estrutural- Faculdade de Ciências da Universidade de Lisboa, C8 Campo Grande, 1749-016 Lisboa, Portugal

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References:
Evaluation of tannins as green corrosion prevention inhibitors in AA2024-T3 aluminium alloy used in aerospace industry

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Abstract

Corrosion is a major problem that affects many metals and alloys. The costs and consequences caused by corrosion are of such importance that justifies a comprehensive study in relation to its causes, mechanisms of identification, detection and development of methods of prevention and protection. The former conventional pre-treatment of AA2024-T3 aluminium alloy involves formulations containing chromium (VI) but REACH restricts the use of hexavalent chromium, due to the negative impact of these compounds in environment and human health. In recent years there has been an increased interest in developing new corrosion protection alternatives.

The objective of this study is to evaluate the anticorrosion character imparted by vegetable tannins, both hydrolyzable and condensed, in the AA2024-T3 alloy, and compare it with that obtained with tartaric acid based bath, which is used in the anodizing of this aluminium alloy widely used in aerospace industry (e.g. AIRBUS).

The corrosion resistance of the treated samples was monitored by potentiodynamic polarization assays and electrochemical impedance spectroscopy analysis.

Experimental

All the aluminium substrate panels (AA2024-T3) were submitted to the following sequence: cleaning, water rinsing, deoxiding, water rinsing, anodizing and sealed. The corrosion resistance of the treated samples was monitored by potentiodynamic polarization assays and Electrochemical Impedance Spectroscopy analysis.

<table>
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<tr>
<th>Electrolyte</th>
<th>Ecorr (V vs SCE)</th>
<th>Icorr (A/cm²)</th>
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<tr>
<td>AA2024-T3</td>
<td>-0.581</td>
<td>1.00 × 10⁻⁵</td>
</tr>
<tr>
<td>TA1</td>
<td>-0.594</td>
<td>5.1 × 10⁻⁹</td>
</tr>
<tr>
<td>TA2</td>
<td>-0.706</td>
<td>1.3 × 10⁻⁹</td>
</tr>
<tr>
<td>TA3</td>
<td>-0.552</td>
<td>5.0 × 10⁻⁸</td>
</tr>
<tr>
<td>TSA</td>
<td>-0.732</td>
<td>1.3 × 10⁻⁹</td>
</tr>
</tbody>
</table>

Bode plot for different green inhibitors, before anodising and sealed films in 0,5M NaCl.

Conclusion

The conversion coatings formed on the aluminium alloy revealed that the use of these tannins, despite the differences in their chemical structures, provide a good corrosion protection, making this pre-treatment a promising alternative for chromium (VI) based chemical conversion coatings. A discussion aiming to correlate the performance of these materials with their chemical class will be presented.

Acknowledgements

References:
Rationale

Platinum-group elements (PGE), i.e. platinum (Pt), palladium (Pd), rhodium (Rh), iridium (Ir), osmium (Os), and ruthenium (Ru), have low concentrations in the Earth’s crust (< 0.50 ng g⁻¹) and due to increasing concentrations in different environmental compartments, they are considered contaminants of emerging environmental concern, particularly in aquatic systems. Owing to their excellent properties, over the past years PGE worldwide demand and uses in a large variety of technology-based industries have increased. The automobile industry per se is responsible for nearly 50% of global demand and in turn resulting in one of the main sources of PGE to the environment, from degradation and abrasion of automotive catalytic converters. However, other source emissions, such as industrial catalysts and medical uses, cannot be disregarded. As a consequence, the widespread and increase of PGE in different environmental compartments have been observed. Their biogeochemical cycling in aquatic systems, namely in estuaries and coastal areas, remains unclear and potential hazardousness needs to be assessed.

Methods

Several analytical techniques have been proposed to quantify PGE in different matrices, such ICP-MS or AAS. Voltammetry has also been pointed out as a suitable technique for Pt and Rh determination, due to fast assay and being less expensive. Adoptive Cathodic Stripping Voltammetry (AdCSV) has been optimised and used for Pt and Rh quantification (Monteiro et al., 2017).

Additionally, a multi-method approach has been used to characterise ancillary parameters used in data interpretation.

Pt and Rh distribution in superficial sediments

Pt and Rh signature in WWTP

Ongoing and future work

Pt and Rh speciation under relevant environmental conditions

Modelling at a regional scale

(a) Future work

Pt and Rh in the water column under tidal influence

Estuaries are transition areas between the land and the ocean that can be greatly impacted with anthropogenic pressures. Therefore, the Tagus estuary is an ideal setting for PGE studies due to surrounding highly urbanised and industrialised areas, with considerably high traffic, as well adjacent to the Atlantic Ocean. Furthermore, the Tagus estuary is largely controlled by the hydrodynamic, which may affect distribution and fate of PGE at a regional scale.

Based on the Pt and Rh spatial distribution (Fig. 2), four sections were outlined (Fig. 3): (i) Background of Pt and Rh, comprising the stations considerably distant from potential sources (ii) Waste- and pluvial waters discharge sites from the northern margin (Lisbon region) (iii) Motorway bridges, in particular VG bridge (iv) Industrialised areas

References:

Carlos E. Monteiro and Margarida Correia dos Santos

Insights on the occurrence and transport of Pt and Rh in Tagus estuary region, SW Europe: from urban into the aquatic system.
Supported semiconductor nanocatalysts for environmental remediation and radiation sensing

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

Introduction
The modification of fibers has been widely explored towards the development of materials with specific and advantageous properties. This takes advantage from the possibility of imparting the properties of the NPs (or molecules) to the fibers, resulting in the preparation of a novel composite or hybrid material. Successful examples are the attachment of Ag, TiO_2, or BiOCl NPs to textile fibers for antibacterial, UV protection, self-cleaning and photocatalytic purposes, and the coating of fabrics with a hydrophobic layer (molecules or polymers) for water repellency and stain free fabrics. [1–4] In this work, several approaches for fibers modification are exploited towards the preparation of materials displaying photocatalytic and radiation sensing/protection responses.

Experimental details

In situ fibers modification

- PE fibers
- Carbon fibers
- Carbon/Co(1%)-TiO_2 fibers

Dye removal

- UV-Vis/NIR
- Photo-degradation
- Photo-degradation of Co(1%)-TiO_2

Photolysis

- Carbon/Co(1%)-TiO_2 fibers
- Carbon/TiO_2 fibers
- Co(1%)-TiO_2 fibers

Characterization

- XRD
- DRS
- FTIR

Optical response

- Photolysis of PE fibers
- Photolysis of Carbon fibers
- Photolysis of Carbon/Co(1%)-TiO_2 fibers

Pollutants removal

- Adsorption
- Photodegradation under UV-vis radiation

Conclusions
Polyester fibers were successfully modified with BiOCl NPs as shown by XRD and FTIR. Those NPs are crystalline and can be self-sensitised by light irradiation by oxygen vacancies formation. The degree of sensitisation depends on the conditions (e.g. wet/dry and radiation source [energy]), as well as the reversible process. Pristine TiO_2 NPs absorb in the UV range and show a good crystallinity with typical anatase phase. The cobalt doping did not affect the NPs crystallinity and those show absorption extended to the visible range. Although no NPs were detected on the Carbon fibers surface by the characterisation techniques, the good photocatalytic response obtained towards crystal violet degradation clearly shows that Co(1%)-TiO_2 NPs were immobilised on plasma-treated Carbon fibers.
Sulfalene: A Case Study on the Polymorphism of APIs
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Universidade de Lisboa, 1749-016 Lisboa, Portugal
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An active pharmaceutical ingredient (API) can crystallize in different packings – Polymorphism. Different polymorphs can have dissimilar physical properties (e.g., fusion point, solubility). Hence, each polymorph should be regarded as a unique material. Despite not being fully understood from a fundamental point of view, recrystallization from solution, is the election method to prepare and isolate an API. As consequence during this procedure unforeseen polymorphs can emerge, leading to dangerous health situations (e.g., Ritonovir [1]).

Sulfalene (SL, Figure 1) is an antibiotic and, until now, only one crystalline structure was identified [2].

**AIM:** Systematic study of crystallization in sulfalene to assess the existence of different solid forms.

### RESULTS

**Morphology**

Figure 2. Morphology of the sulfalene crystals obtained by recrystallization from solution from (a) methanol, (b) acetonitrile, and (c) ethanol. Scanning electron microscopy of the crystals obtained from (d) methanol and (e) acetonitrile.

**Solubility and Crystallization Curves**

Figure 3. Temperature versus concentration phase diagram of sulfalene in methanol. The blue and orange dots correspond, respectively, to the crystallization and solubilization curves. It is possible to distinguish two different zones in the solubilization curve, before and after 53 g·Kg⁻¹, which suggests that two different phases of SL could be prepared under those conditions.

**Crystalline Structure**

Figure 4. Diffractograms obtained by powder X-ray diffraction (PXRD) for the recrystallizations of Sulfalene (SL, in blue) from methanol (MeOH, in yellow), acetonitrile (MeCN, in grey) and ethanol (EtOH, in orange). The areas signaled in red highlight the 2θ values where the diffractograms present differences. All the diffractograms were normalized to the peak of highest intensity.

**Energetics**

Figure 5. Thermograms obtained by differential scanning calorimetry (DSC) for the recrystallizations of Sulfalene (SL, in blue) from methanol (MeOH, in yellow) and acetonitrile (MeCN, in grey). All thermograms were normalized relative to the mass of the sample used. No other thermal events were detected prior to the fusion of the samples.

### Conclusions

- Crystallization from several solvents leads to crystals with similar morphology (Figure 2), but the PXRD and DSC data suggest the preparation of different phases (Figures 4 and 5).
- Different polymorphs can be prepared from methanol by cooling crystallization, by changing the initial solution concentration (Figure 3).
Montelukast (MTK), a cysteine leukotriene receptor antagonist, is a drug used in asthma management in children and adults. Recently repurposed for other therapeutic applications (e.g., anti-inflammatory agent in the central nervous system, chemopreventive and adjuvant in cancer therapy and preventive agent in cardiovascular risk settings), MTK metabolism is poorly understood. To date, only five phase 1 and two phase 2 MTK metabolites have been identified and no association between metabolites and the adverse effects has been established. (1–4)

Taking into account the potential new applications of MTK, our initial goal was to evaluate the in vitro metabolism of MTK.

**METHODOLOGY**

Different incubations were performed at 37°C and different incubation times were tested. Products were analyzed by high performance liquid chromatography coupled to high-resolution electrospray ionization tandem mass spectrometry – QqToF.

**RESULTS**

Biologically relevant thiol radicals is plausible in vivo, with NO NEED FOR BIOACTIVATION.

**FINAL REMARKS**

- With the exception of CYP2D6, all the biological systems were responsible for MTK metabolism.
- The metabolic ability of other human fractions will be tested to access the metabolite profiles in other organs.
- Further studies with MTK plus cofactors and other biomolecules will be conducted.
- Potentially reactive MTK metabolites will be explored and characterized.
A WORKFLOW FOR DRUG METABOLISM MS STUDIES WITH DATA-INDEPENDENT ANALYSIS

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BACKGROUND AND OBJECTIVE

Drug metabolism studies involve repetitive experiments where the target compounds are incubated with enzymes/cells/tissues of interest in order to understand their metabolic profile. An exhaustive study of possible metabolites must thereafter be performed, and a metabolite database created and updated using proprietary software such as Bruker’s TASQ (Target Analysis for Screening and Quantitation), that is designed for metabolomics and not for drug metabolic profiling. However, with the advancement of IT tools, new software has been developed to help in data processing based on metabolite databases. Software as MZmine 2 [1] and TASQ are two examples of how automation can help users in expedite data processing.

We present here the workflow for a complete identification of drug metabolites by HRMS using data-independent acquisition and data-independent processing.

WORKFLOW

REACTION MIX INCUBATION

HRMS DATA ACQUISITION

Manual Chromatogram Extraction & Peak Picking

AUTOMATIC DATA PROCESSING

AUTOMATIC PROCESSING

MANUAL DATA PROCESSING

RESULTS

MANUAL DATA PROCESSING

AUTOMATIC DATA PROCESSING

FINAL REMARKS

OTHER PROS OF AUTOMATED PROCESSING

CONS OF AUTOMATED PROCESSING

Funding:
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References:

 Manuel Chromatogram Extraction & Peak Picking

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</table>

- Manual peak isotope profile confirmation
- Automatic mass detection (above specified noise level)

- Automated chromatogram extraction for all detected masses (above minimum height with minimum RT span and maximum 0.005 ppm m/z tolerance)

- Paired peak list

- Paired peak list

- Paired peak list

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- Paired peak list
SOLVENT-FREE SYNTHESIS OF COPPER BENZENE-1,3,5-TRICARBOXYLATE 
\[ \text{Cu}_3(\text{BTC})_2(\text{H}_2\text{O})_3.10\text{H}_2\text{O} \] AND 
\[ \text{Cu}_2(\text{OH})(\text{BTC})(\text{H}_2\text{O}).2\text{H}_2\text{O} \] 
BY BALL MILLING

Célia Aissani 1,2,*, Elisabete C. B. A. Alegria 1,3, Ana P. C. Ribeiro 1

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2 Chemistry department, Faculty of Sciences and Engineering, Sorbonne Université, Paris, France
3 ADEQ-ISEL-Instituto Politécnico de Lisboa, Lisbon, Portugal

* Corresponding author : celia.aissani@etu.upmc.fr

Introduction
Making compound synthesis easier and less energy consuming is possible with ball milling, representing a fundamental perspective for a greener and sustainable chemistry. However, modifying some parameter in ball milling experiments [1] tend to show their potential influence on the obtained substances. A systematic study was made to investigate the effect of various ball milling conditions on the production of two MOFs, \( \text{Cu}_3(\text{BTC})_2(\text{H}_2\text{O})_3.10\text{H}_2\text{O} \) and \( \text{Cu}_2(\text{OH})(\text{BTC})(\text{H}_2\text{O}).2\text{H}_2\text{O} \). The number of spheres, the rotation per minute (rpm) and initial mass of starting materials were found to be determining for the structure of the final compounds.

A solvent-free synthesis is possible by ball milling. The process will be investigated in the future for the production of MOFs based on other transition metals.

In future work, the produced MOFs will be complexed with TiO2 and tested in photo-catalysis (Figure 4).

Keywords
Ball milling, mechanochemistry, metal organic framework, green chemistry

References

Fundings
Centro de Química Estrutural is funded by Fundação para a Ciência e Tecnologia – projects PTDC/QUI-QIN/29778/2017, UID/QUI/00100/2019 and PTDC/QEQ-ERQ/1648/2014.
Erasmus + also contributed to this project.

All the samples were observed with a microscope (Figure 2) and analyzed by ATR (Figure 3). Compounds A, B and C, have been synthesized. A was obtained by samples 1, 3, 5, 13, 14 and 15 ; B from 2, 4, 6, 8, 10 and 12 ; C from 7, 9 and 11.

A comparison with the reported spectra [1] has lead to an attribution of 2 of the 3 compounds (Figure 3). Product C has probably an intermediate structure.

Hence, the stirring time had no effect on the final compound. Only the number of spheres, the rotation per minute and the starting mass of materials had an influence on the obtained compound.

Results

A solvent-free synthesis is possible by ball milling. The process will be investigated in the future for the production of MOFs based on other transition metals.

In future work, the produced MOFs will be complexed with TiO2 and tested in photo-catalysis (Figure 4).
Ionic composition and balances of seawaters from different locations, assessed by Ion Chromatography

C. M. Oliveira, Bárbara Anes, R.B. Silva, M. F. Camões

Accurate characterization of the composition of seawater is required to understand chemical changes occurring in the ocean and their impact on marine ecosystems. The different concentration ranges of major and minor ions represent a big challenge to the analysis of seawater samples by ion chromatography.

**EQUIPMENT**

**SAMPLING SITES**

**ION MASS CONCENTRATION IN THE ANALYSED SAMPLES**

<table>
<thead>
<tr>
<th>Ion</th>
<th>Atlantic Ocean</th>
<th>Baltic Sea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>11.04 ± 0.33</td>
<td>11.01 ± 0.35</td>
</tr>
<tr>
<td>K⁺</td>
<td>0.41 ± 0.12</td>
<td>0.42 ± 0.15</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>1.28 ± 0.13</td>
<td>1.31 ± 0.17</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>0.433 ± 0.063</td>
<td>0.416 ± 0.081</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>19.7 ± 1.9</td>
<td>19.5 ± 2.2</td>
</tr>
<tr>
<td>Br⁻</td>
<td>0.066 ± 0.026</td>
<td>0.067 ± 0.026</td>
</tr>
<tr>
<td>SO₄²⁻</td>
<td>2.73 ± 0.15</td>
<td>2.65 ± 0.15</td>
</tr>
</tbody>
</table>

| Salinity  | 35.6%o         | 35.4%o      | 35.6%o       | 7.4%o         | 7.3%o        |
| Hardness (g L⁻¹) | 6.33 ± 0.56  | 6.42 ± 0.63 | 7.00 ± 0.56  | 1.34 ± 0.14   | 1.27 ± 0.14  |
| Mg²⁺ / Ca²⁺ | 2.94 ± 0.52  | 3.14 ± 0.74 | 3.18 ± 0.54  | 2.44 ± 0.48   | 2.46 ± 0.51  |

**IONIC BALANCE PARAMETERS FOR EACH SEAWATER SAMPLE**

<table>
<thead>
<tr>
<th>Ionic balance/ meq L⁻¹</th>
<th>Atlantic Ocean</th>
<th>Baltic Sea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Port of Lisbon</td>
<td>617 ± 18</td>
<td>128 ± 4</td>
</tr>
<tr>
<td>Cabo Espichel</td>
<td>618 ± 21</td>
<td>128 ± 15</td>
</tr>
<tr>
<td>Sesimbra</td>
<td>673 ± 19</td>
<td>128 ± 15</td>
</tr>
<tr>
<td>Position 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Position 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Port of Lisbon</td>
<td>613 ± 54</td>
<td>126 ± 18</td>
</tr>
<tr>
<td>Cabo Espichel</td>
<td>607 ± 62</td>
<td>126 ± 18</td>
</tr>
<tr>
<td>Sesimbra</td>
<td>668 ± 62</td>
<td>126 ± 18</td>
</tr>
<tr>
<td>Position 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Position 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charge balance</td>
<td>4.2 ± 57</td>
<td>1.8 ± 19</td>
</tr>
<tr>
<td></td>
<td>10.5 ± 66</td>
<td>-1.2 ± 15</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

- The principle of constant proportions was observed for the tested samples.
- Results of seawater samples from the Portuguese Coast match the expected values for seawater hardness (≥ 6 g L⁻¹), having the characteristics of very hard water. The low total hardness of Baltic Sea water can be explained by the relevant influence of river discharges.
- Mg²⁺ / Ca²⁺ ratios found for all the Portuguese Coast samples are very similar and slightly larger than those of Baltic Sea.
- A small but consistent “excess” of positive charges in the ionic balance can be explained by the presence of, not quantified, HCO₃⁻ and CO₃²⁻.
The ciliopathy-involved protein KIAA0753 functional interactions with the regulator of centrosome positioning TBCCD1

Ferreira DC1,2, Carmona B1,2,3, Nolasco S1,4, Mariño HS1,2 and Soares H1,2,3
1 Centro de Química Estrutural, Faculdade de Ciências da Universidade de Lisboa; 2 Centro de Química e Bioquímica, Faculdade de Ciências da Universidade de Lisboa; 3 Escola Superior de Tecnologia da Saúde de Lisboa, Instituto Politécnico de Lisboa; 4 Centro de Investigação Interdisciplinar em Sanidade Animal (CISfA), Faculdade de Medicina Veterinária, Universidade de Lisboa

Background

Cilia are slender protruberances found in eukaryotic cells, consisting of a microtubule (MT)-based ciliary axoneme, which confer motility and sensory functions. These organelles have a centriole/basal body, which can be derived from the centrosome and that nucleates/assembly the ciliary axoneme. Centrosomes are composed of a pair of centrioles, surrounded by the pericentriolar matrix, and are the major microtubule organizers in animal cells, participating in a variety of processes.1 Centriolar satellites are cytoplasmic granules located around the centrosome. These structures play essential roles in centrosome assembly and primary cilium formation, through the delivery of centriolar/centrosomal components from the cytoplasm to the centrosome.2 Mutations in genes encoding centrosome and/or centriolar satellite components and regulators lead to various human disorders, such as microcephaly and ciliopathies.

Ciliopathies are a group of rare diseases, typified by often overlapping clinical manifestations, such as infertility, brain and skeletal developmental problems and blindness. Previous work from our group, using a BioID approach, characterized the interactome of a new centrosomal TBC domain-containing human protein (TBCCD1) involved in correct positioning of the centrosome and cilia biogenesis. Among the identified proteins, there were several well-known proteins encoded by ciliopathy genes, e.g. centrosomal and centriolar satellites protein KIAA0753 (also known as OFIP and Moonraker). The ofip gene is mutated in the Joubert syndrome and related disorders, a heterogenous group of ciliopathies defined by hypotonia, developmental delay, abnormal eye movements and breathing abnormalities.3

Objectives

Our main objective is to study the role of the protein Moonraker, in association with the proteins TBCCD1 and OFD1, in the development of primary cilia. Additionally, we will also investigate if TBCCD1 interacts with this protein for being a component of the OFD1/Moonraker/FO20 complex or if the interaction with these proteins involves another mechanism.

Results

1. Depletion of KIAA0753 in centrosome and MT cytoskeleton

In hTERT-RPE-1 cells, knockdown of KIAA0753 affects the centrosome by increasing the distance between the centrioles (shown in the figure below).

2. KIAA0753 localization in ciliated RPE1 cells

KIAA0753 accumulates in the proximal region of primary cilia.

3. Impact of TBCCD1 levels in KIAA0753 and PCM1

Knockdown and overexpression of TBCCD1 affects the levels of KIAA0753, as well as its localization at the centrosome. The depletion of TBCCD1 also causes an alteration of the PCM1-containing pericentriolar satellites pattern next to the centrioles.

4. Impact of TBCCD1 overexpression in cilia biogenesis

TBCCD1-GFP-RPE-1 has more difficulty producing primary cilia, doubling it’s size when they do (shown in the figure below).

Conclusion

These results support KIAA0753’s role in cytoskeleton organization and ciliogenesis, which implicates it in ciliopathies. They also point to a new functional interaction between TBCCD1 and KIAA0753, as it’s suggested that TBCCD1 plays a role in the recruitment of KIAA0753 to the centrosome, and strongly support that tbccd1 is a new ciliopathy gene.
Diclofenac sustained release using an LbL coated silicon-based hydrogel

Diana Silva, Hermínio C. de Sousa, Maria Helena Gil, Carmen Alvarez-Lorenzo, Ana Paula Serro and Benilde Saramago

1. CQE, Instituto Superior Técnico, Universidade de Lisboa, Lisboa, Portugal
2. CIEPQF, Departamento de Engenharia Química, Universidade de Coimbra, Coimbra, Portugal
3. Departamento de Farmacología, Farmacia y Tecnología Farmacéutica, R+D Pharma Group (GI-1645), Facultad de Farmacia and Health Research Institute of Santiago de Compostela (IDIS), Universidade de Santiago de Compostela, Santiago de Compostela, Spain
4. CIIEM, Instituto Universitário Egas Moniz, Caparica, Portugal.

Introduction

Although eye drops remain the primary dosage form for ocular therapy due to their easiness of administration by the patient himself, they provide low drug bioavailability. Soft contact lenses (SCLs) have raised great interest as potential drug vehicles for ocular therapy due to their biocompatibility and prolonged contact time with the eye. Nevertheless, they usually lead to an initial burst and a fast drug release.

Methods

I. Drug release

The coating leads to a decrease in the initial drug burst and ensures a controlled drug release in sink conditions.

II. Optical Irritation

Hen’s Egg Test – Chorioallantoic Membrane (HET-CAM) Test Method

The coating was stable, and did not adsorb lysozyme (tear fluid protein), showing antifouling properties.

III. Characterization

The main objective of this work was to develop LbL coated therapeutic lenses loaded with the anti-inflammatory drug diclofenac (DCF).

Results

Physical and chemical properties of coated silicon-based hydrogels

Conclusions

- The coated hydrogel presents adequate characteristics to be used in therapeutic contact lenses.
- DCF release was significantly enhanced by the presence of the coating.
- The coated hydrogel shall not induce optical irritation.
Sustainable Iron(II) scorpionate for the synthesis of cyclic carbonates

Erivaldo J.C. Lopes, Ana Paula C. Ribeiro, Luísa Margarida D.R.S. Martins

Introduction

The climate change issue is one of the main concerns nowadays. Carbon dioxide has a significant contribution in this problematic, so, in order to reduce the release of carbon dioxide to the atmosphere, processes that use CO₂ as chemical feedstock, such as the one depicted in Sch. 1, have been developed.

\[ \text{CO}_2 + \text{NH}_2\text{NH}_2 \rightarrow \overset{\circ}{\text{O}} \overset{\circ}{\text{O}} \]

Sch. 1: Process to produce a cyclic carbonate by reacting CO₂ and epoxide.

Recently, other processes have been developed, see Sch. 2. They don’t use CO₂ directly; CO₂ is required to treat the side product NH₃ to recycle the initial urea used in the process.

\[ \overset{\circ}{\text{O}} \overset{\circ}{\text{O}} + \overset{\circ}{\text{O}} \overset{\circ}{\text{O}} \rightarrow \overset{\circ}{\text{O}} \overset{\circ}{\text{O}} \overset{\circ}{\text{O}} \]

Sch. 2: Process to produce cyclic carbonate by reacting urea with 1,2-diol.

This poster presents selected results of these processes catalyzed by the iron(II) scorpionate \([\text{FeCl}_2(\text{pz})_3]\) (pz = pyrazolyl) complex.

Procedure

The process uses temperatures from 80 to 150 ºC during several hours.

Table 1. Selected substrates and corresponding products for the cycloaddition of CO₂ to epoxides (Sch. 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Epoxide</th>
<th>Product</th>
<th>Yield /%</th>
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<td>1</td>
<td></td>
<td></td>
<td>6.5</td>
</tr>
<tr>
<td>2</td>
<td></td>
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<td>6.1</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>5.3</td>
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</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield /%</th>
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<tbody>
<tr>
<td>1</td>
<td>80 ºC</td>
<td>6 h</td>
<td>12.3</td>
</tr>
<tr>
<td>2</td>
<td>150 ºC</td>
<td>6 h</td>
<td>26.2</td>
</tr>
<tr>
<td>3</td>
<td>150 ºC</td>
<td>24 h</td>
<td>34.8</td>
</tr>
</tbody>
</table>

Substrates tested

For the production of a cyclic carbonate by reacting urea with a 1,2-diol, the chosen substrate was 1,2-cyclohexanediol.

Future work

- Test other substrates.
- Improve the tested procedures.
- Mechanistic studies.
- Assessment of the CO₂ utilization.

References:

Polymorphism Study in Fumaric Acid
Filipa Bernardes, Carlos E. S. Bernardes
Centro de Química Estrutural, Faculdade de Ciências Universidade de Lisboa, 1749-016 Lisboa.

Scope

- Fumaric acid (FA, Scheme 1) is a compound widely used in the food industry, in medicine, and as starting material in several chemical processes [1].
- Almost no energetic and structural studies are available in the literature for this compound. A search at the Cambridge Crystallographic Data Centre (CCDC) reveals four communications reporting its single crystal structure of FA, published between 1925 and 1966.
- Until now, two polymorphs (i.e. materials where the packing of FA molecules is different) were identified, but a recent study [2], revealed that the X-ray powder pattern (XRPD) predicted based on the known single crystal structures does not correspond to the experimentally observed for the compound.

AIM

Investigate the polymorphism in fumaric acid based on recrystallization studies, and characterization of the precipitated materials by X-ray diffraction and differential scanning calorimetry (DSC).

Results

![Single crystal structure](image)

Figure 1. Single crystal structure of the two polymorphs of FA: (a) form α (redetermined in this work); (b) phase β (CCDC).

![XRPD comparison](image)

Figure 2. Comparison of the XRPD predicted for FA based on the single crystal data of form α and β, with the patterns found for the compound after recrystallization acetone, water, THF:Cyclohexane mixture, and by sublimation.

![Thermograms](image)

Figure 3. (a) Thermograms obtained by Differential Scanning Calorimetry (DSC), for a sample of FA form α, submitted to a sequence of heating and cooling runs. (b) Comparison between the predicted XRPD for the polymorphs of FA with that found for a sample heated to 500 K.

Conclusions

- Recrystallization of FA from acetone leads to the precipitation of form α, while a mixture of THF:Cyclohexane produces a mixture of phases α and β. A pure sample of form β was only obtained by sublimation (Figure 2).
- When water is used as a solvent, two diffraction peaks between 10 and 15 °2θ, are observed. This suggests that, besides crystals of phase α, a new polymorph was obtained (Figure 2).
- To the best of our knowledge, two previously unreported phase transitions at 440 K and 470 K, were observed in the DSC traces (Figure 3a). The thermal event at 470 K was assigned to a transition to the β phase (Figure 3b).
Targeting Epigenetics in Cancer: Design and biological evaluation of EZH2 inhibitors

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3Inte:Ligand Software Developments und Consulting, Mariahilferstrasse 748, 1070 Vienna, Austria;
4Department of Pharmaceutical Chemistry, Faculty of Life Sciences, University of Vienna, Althanstraße 14, A-1090 Vienna, Austria;
5Fraunhofer IME-SP, Schnackenburgallee 114, 22525 Hamburg, Germany;
6Hovione Farmacência SA, Sete Casas, 2674-506, Loures, Portugal

INTRODUCTION

- Enhancer of Zest Homolog 2 (EZH2) is the catalytic subunit of PRC2;
- Some cancer types with poor prognosis are related to overexpression and gain of function mutations of EZH2.
- Thus, the inhibition of EZH2 appears as an opportunity for anticancer therapy.

METHODS/RESULTS

PHARMACOPHORE GENERATION

99 models generated

PHARMACOPHORE USAGE

VIRTUAL SCREENING

DE NOVO DESIGN

BIOLOGICAL EVALUATION

EZH2 INHIBITION
ALPHALISA
H3K27me3 Cell imaging assay
HIGH CONTENT SCREENING
- Quantification of total H3
- Quantification of H3K27me3
- Quantification of nucleus (n° of cells)

METABOLISM
CYP450
- CYP2C9
- CYP2C19
- CYP2D6
- CYP3A4
- CYP1A2

OFF-TARGET KINASE
- AURORA B
- PDE4C
- ERG
- SRT7
- HDA4
- HDA6
- HDA8
- HDA9

TOXICITY
- MC7
- hTERT
- OCT-1 y 19
- Hep G2
- U-2 OS
- HEK 293

CONCLUSIONS

- Promising EZH2 inhibitors with clean and safe off-target and ADME-Tox profiles were found;
- Pharmacophore models were shown to be helpful in finding new small molecule inhibitors of this target;
- Additionally, computational methods proved to be important in designing new scaffolds of EZH2 inhibitors.
Evaluation of the vapor pressure of deep eutectic solvents for desulfurization applications

Filipa Lima1,2,3, Armando Silvestre2, Luís Branco3, Isabel Marrucho1
1ISTA, Universidade de Lisboa; 2CICECO-Universidade de Aveiro; 3Solchemar Ltda

FRAMEWORK

In recent years, Deep Eutectic Solvents (DES) have attracted a lot of attention due to their potential in green chemistry combined with their easy and simple preparation. In addition, the wide range of available compounds for their preparation has boosted the application of DES in various fields. Removal of sulfur and nitrogen compounds from fossil fuels is one of those applications, since emissions of SOx and NOx represent one of the main current concerns related to air pollution. Over the last years, DES have been intensively explored as alternative solvents to remove those sulfur- and nitrogen-containing compounds from fuels [1,2].

Regarding separation technology, there is an important feature that stands out, which is the vapor pressure of the extractant (in this case – DES), and should be as low as possible. During the last years, DES have been largely compared to ionic liquids, which are known for their negligible vapor pressure. However, in the case of DES, depending on its constitution, it is to be expected that this is not always the case.

In this work, the vapor pressure of several DES was accessed through head-space gas chromatography mass spectrometry (HS-GC-MS).

DES VAPOR PRESSURE

1) Vapor pressures of pure compounds VERSUS Partial pressure of the DES constituents:
- The partial vapor pressure of each DES constituent is lower than the vapor pressure of each pure compound;
- Our DES is less volatile than sulfolane.

![Figure 1: Vapor pressures of pure tetrabutylammonium bromide (TBPB) and pure sulfolane (Sulf) and partial vapor pressures of TBPB and Sulf in the DES TBPB:Sulf (1:4), determined by HS-GC-MS, between 40 °C and 100 °C.](image)

2) Ideal mixture behavior? No!
- The calculated vapor pressures using the Rout’s law [P = xPm^i] are over predicted for both DES constituents, indicating that TBPB:Sulf (1:4) DES is a non-ideal mixture;
- As the measured vapor pressures are lower than the ideal pressures, the activity coefficients will be lower than 1, which means that the interactions between HBA-HBD are more attractive than the interactions between HBA-HBA or HBD-HBD.

![Figure 2: Partial vapor pressures of the DES TBPB:Sulf (1:4) constituents. Experimental data determined by HS-GC-MS (symbols); calculated vapor pressure using Rout’s law for ideal mixture behavior (lines).](image)

3) Total vapor pressure of TBPB:Sulf at different molar ratios, at 60 °C:
- The increase in the amount of TBPB present in the DES leads to the decrease of the total vapor pressure of the DES, as expected;
- Interestingly, this effect was very noticeable in a specific mole fraction of TBPB (0.1). This is coincident with the eutectic point of our DES.

![Figure 3: Total vapor pressure of TBPB:Sulf at different molar ratios.](image)

![Figure 4: SLE diagram of TBPB:Sulf predicted by PC-SAFT.](image)

FINAL REMARKS
- The total vapor pressure of TBPB:Sulf DES is lower than the vapor pressure of pure sulfolane;
- The TBPB:Sulf (1:4) DES is not an ideal mixture;
- The interactions between HBA-HBD in the DES are more attractive than the HBA-HBA and HBD-HBD interactions.
Tuberculosis (TB) is still one of the top 10 causes of death worldwide and the main cause of mortality from a single infectious agent, the *Mycobacterium tuberculosis* (*Mtb*) bacillus. Treatment misuse has led to the upsurge of multidrug-resistant tuberculosis (MDR-TB), taken as resistance to at least isoniazid (INH) and rifampicin (RIF), first-line antituberculars, and to extensively drug-resistant TB (XDR-TB), a form of TB that answers to even fewer drugs.

**Results from previous projects**
- Synthesis of 5 new compounds more active than INH against *H37Rv Mtb*
- From these, 3 are more effective than INH against the most frequent mutation conferring INH resistance, *katG* S315T
- Top compound is an INH derivative with a C_{10} alkyl chain (INH-C_{10})

**So far**
- Quantum mechanics calculations to assess the ability of INH derivatives to spontaneously form the INH radical (formed in the first step of INH activation in KatG), have been carried out and suggest that compounds INH-A2 and INH-B facilitate the formation of the radical by comparison with INH
- MD simulations of permeability rates of compounds INH-A1 (= INH-C_{10}) & INH-A2, as well as of higher order INH-B1, lead to permeability rates significantly higher than that of INH

**References:**

**Funding:**
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**So far**
- Only 2 new drugs have received conditional approval for treatment of MDR-TB

**Goals**
To develop a new drug lead against MDR-TB, through in silico design of compounds, structurally similar to those that scored higher against S315T *Mtb*, followed by synthesis, and *in vitro* studies to assess their potential as anti-TB drug candidates

**Team**
Multidisciplinary, with a wide range of backgrounds spanning from machine learning techniques to organic synthesis, interfacial chemistry, biophysics and microbiology

**Problem**
- *Mtb* has become increasingly resistant to INH and attempts to develop INH-based compounds to by-pass the problem and improve drug activity have failed

**Fact**
- Isoniazid (first synthesized in 1952) is one of the two most effective drugs to treat TB and is part of all WHO multidrug recommended regimens

**Challenge**
Is it possible to develop new, QSAR-oriented INH derivatives, rationally modified to upturn INH activity and, simultaneously, circumvent MDR-TB?

---

**A Challenge, a Team, a Project: TARGTUB**

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Dye sensitized solar cells based on porphyrins

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Abstract: Dye sensitized solar cells (DSSC, Figure 1) have been representing a new promising method for the conversion of visible light, in a wide range of light in indoor and outdoor conditions, enabling the conversion of both artificial and natural lights into electrical energy to powered a broad range of electric devices.1 This technology demands two main requirements: a) efficient charge generation at the semiconductor-dye interface; and b) efficient charge transport by the semiconductor and the electrolyte reduction ability.1 The selected semiconductor for the photoelectrode is mostly being titanium dioxide (TiO2) due to its availability, low cost and non-toxic properties. In terms of dyes, there is the possibility of modifying its optical properties and consequently their corresponding DSSC’s conversions/efficiencies. This can be done by simple dye structural modifications. At the same time, carriers transport properties can be improved by optimizing the semiconductor and the electrolyte composition.2

In the present work we are using free-base and metal coordinated porphyrins due to their unique optical properties and large possibility of structural modifications. These compounds are macrocycles with a highly conjugated aromatic system, which allow strong absorptions. They have been applied in natural and synthetic structures, being studied in different fields, such as: medicine, sensing and electron transfer applications.3,4 The last application has drawn their use in light-harvesting devices.5,6

Evaluation of the photosensitizer properties of TPPCOOH and TriPyCOOH

Table 1 – Measurements of the efficiency of dye synthesized solar cells after the deposition of the dye in methanol.

<table>
<thead>
<tr>
<th>Photosensitizer</th>
<th>Voc (V)</th>
<th>η (%)</th>
<th>Jsc (mA/cm²)</th>
<th>FF</th>
</tr>
</thead>
<tbody>
<tr>
<td>N719</td>
<td>0.55</td>
<td>3.94</td>
<td>10.68</td>
<td>65.58</td>
</tr>
<tr>
<td>H2TPPCOOH</td>
<td>0.22</td>
<td>0.1</td>
<td>0.9</td>
<td>52.82</td>
</tr>
<tr>
<td>NiTPPCOOH</td>
<td>0.23</td>
<td>0.035</td>
<td>0.32</td>
<td>45.91</td>
</tr>
<tr>
<td>H2TriPyCOOH</td>
<td>0.22</td>
<td>0.044</td>
<td>0.42</td>
<td>45.09</td>
</tr>
<tr>
<td>ZnTriPyCOOH</td>
<td>0.4</td>
<td>1.75</td>
<td>7.33</td>
<td>57.8</td>
</tr>
</tbody>
</table>

Depending on the type of dye used, the overall efficiency of the DSSCs may vary:

The modification of substituents in porphyrin decreases efficiency and the Jsc.

- Decrease of efficiency as result of the metalation with Ni, probably due to the decrease of the capacity of the injection of electrons and low energy level of LUMO.
- Increase of efficiency as result of metalation with Zn; also improving the Jsc and Voc.

Conclusions

- It was possible to see that the different structure of porphyrins influences the results of the DSSC. Exposure of DSSC to light appears to have a catalytic effect on ZnTriPyCOOH.
- The insertion of Zn in the porphyrin’s nucleus influences the results obtained in a positive way. But, on the other hand, Ni negatively influences cell results when compared to free base porphyrin.
- In certain cases, even when the light has been turned off, the cell behaves in the same way as under light exposure. For this reason, and due to technical limitations, it would be interesting to develop further work on the characterization of these DSSC to better understand the results obtained.
M.C.M. Sequeira¹, H. M. N. T. Avelino¹², F.J. P. Caetano¹³, J. M. N. A. Fareleira¹

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Studying the PEG family

Realisation of experimental measurements of thermophysical properties of a homologous series of ethylene (DiEG, TriEG, TeEG) and polyethylene glycols (PEG 600, PEG 400 and PEG 200) and the development of correlation methods.

Influence of molecular mass in density at constant pressure

Influence of molecular mass in viscosity at constant pressure

Influence of molecular mass in viscosity when the pressure increases at constant temperature

Hard-Spheres Correlation of series of ethylene (DiEG, TriEG, TeEG) and polyethylene glycol (PEG 400)

Viscosity of PEG 400 at high pressures

09 MET

References:


Work in progress:

- Viscosity and density measurements of PEG 200 at high pressure
- Self-diffusivity measurements of DiEG, TriEG and TeEG.
- Analyse the relation of the present results with those obtained before for CO₂ saturated PEG mixtures. Aim: to predict the viscosity of the mixtures.
- Determination of the pressure-viscosity and temperature-viscosity coefficients - important to characterize lubricants.
The use of treated water from Wastewater Treatment Plants (WWTP) for irrigation presents challenges that need to be clarified and then overcome. One of the challenges is the use of treated water from WWTP for the irrigation of vegetables. The use of treated water for lawn watering of gardens and golf courses poses the challenge of the proliferation of microorganisms that can cause diseases in humans and domestic animals. However, the use of treated water for gardening raises the question of the contamination of vegetables by toxic metals and other harmful compounds to humans [1].

In this study, our concern is about the contamination of vegetables by toxic metals, namely cadmium, chromium, nickel and lead. Regarding this concern, our group implemented a research project in which synthetic treated water was used for controlled irrigation of cabbage (Brassica oleracea) and lettuce (Lactuca sativa).

### INTRODUCTION

#### Cultivation Conditions

<table>
<thead>
<tr>
<th>Metals</th>
<th>Concentration:</th>
<th>1/3 ELV</th>
<th>2/3 ELV</th>
<th>ELV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cd</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cr</td>
<td></td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Ni</td>
<td></td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Pb</td>
<td></td>
<td>10</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>ALL</td>
<td></td>
<td>13</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Ø</td>
<td></td>
<td>16</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

Synthetic waters with 1/3 ELV, 2/3 ELV and ELV (Emission Limit Value) were used for irrigation.

ELV is the maximum discharge concentration of the metals allowed in the legislation, DL 236/98.

#### Microwave extraction

- **Microwave extraction parameters:**
  - Temperature: 80 ºC
  - Power: 100 W;
  - Total time: 3min;
  - Solvent: Methanol (2 mL/g sample)

- **CEM SP Discover**

#### DPPH free radical scavenging method

To each microplate well add:

- Sample: 30 µL lettuce extract solution + 270 µL DPPH solution 100 µM;  A blank and control reaction was done
- **Absorbance λ=515nm** (BIOTek Synergy 2).

#### DPPH Cabbage Leaves results

<table>
<thead>
<tr>
<th>Concentration:</th>
<th>DPPH expressed as Trolox equivalent antioxidant capacity (TEAC) in µg TEAC/mg FW (Fresh Weight - Extract)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/3 ELV</td>
<td>87,26</td>
</tr>
<tr>
<td>2/3 ELV</td>
<td>67,47</td>
</tr>
<tr>
<td>ELV</td>
<td>57,24</td>
</tr>
<tr>
<td>Ni</td>
<td>59,90</td>
</tr>
<tr>
<td>Pb</td>
<td>30,54</td>
</tr>
<tr>
<td>ALL</td>
<td>48,24</td>
</tr>
<tr>
<td>Ø</td>
<td>57,24</td>
</tr>
</tbody>
</table>

• In what the efficiency of the microwave extraction it concerns it was concluded that it was equivalent for all cabbage samples with and without contamination (~1.7%).
• On the other hand, the obtained results showed that, in fact, the antioxidant capacity of the studied samples increases when they are irrigated with contaminated solutions of the individual metals (with respect to the blank samples).
• This evidence may be due to the vegetables metabolism reaction in the presence of heavy metals, with the respective increase in antioxidant capacity.
• Additionally, the most significant response was obtained when the samples were irrigated with cadmium synthetic solutions.

### References


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Introduction

Cu-containing complexes represent an interesting class of compounds capable of functionalizing C–H bonds in rather inert substrates such as alkanes. Considering the growing interest in the development of effective and single-step protocols for the oxidative transformation of saturated hydrocarbons, the main objectives of the present work were the synthesis and characterization of new multicopper(II) coordination compounds using Hbes as a primary N,O ligand source, and the catalytic application of the obtained compounds in the mild oxidation and carboxylation of alkanes to form value-added products. Due to its structure with three different functionalities, versatile multidentate nature, stability, and aqueous solubility, N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (Hbes) was selected as main building block.

Results (Synthesis)

Three novel tetracopper(II) coordination compounds namely [Cu₄(µ-Hbes)(µ-Hbes)(µ-ba)]·2H₂O (1), [Cu₄(µ-Hbes)(µ- Hbes)(µ-hba)]·2H₂O (2) and [Cu₄(µ-Hbes)(µ-Hbes)(µ-thba)]·2H₂O (3) were easily generated from Cu(NO₃)₂, a trifunctional aminoalcohol sulfonic acid (Hbes) as a principal building block, and a benzene carboxylic acid as a supporting ligand (i.e., benzoic (Hba), 4-hydroxybenzoic (Hhba), or 3- hydroxybenzoic (Hthba) acid). The obtained microcrystalline products, were isolated and fully characterized by FTIR (Fourier-Transform Infrared Spectroscopy), elemental analysis, ESI-MS (Electrospray Ionisation Mass Spectrometry), and single-crystal X-ray diffraction methods (Figures 1 and 2).

Results (Catalysis)

The obtained tetracopper(II) complexes 1–3 were applied as efficient and versatile homogeneous catalysts in the oxidative C–H functionalization of alkanes (propane and cycloalkanes) by aqueous H₂O₂ in acidic MeCN/H₂O medium at 50°C, showing a remarkable level of activity. Two different model reactions were explored: (1) mild oxidation of alkanes with hydrogen peroxide to give alcohols and ketones, and (2) mild carboxylation of alkanes in the presence of carbon monoxide, water, and potassium peroxodisulfate to give carboxylic acids. For these reactions, effects of different parameters (acid promoter effect, catalyst amount, loading of substrate, oxidant and acid catalyst, substrate scope, and effect of water), as well as mechanistic and selectivity characteristics, were studied (Figures 3, 4 and 5). The maximum product yields up to 46% were obtained.

References:

A New Calorimetric Cell for Studies of Co-Crystals Energetics

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CONTEXT
- Co-crystals are substances containing two or more different molecules (AₙBₘ).
- The use of cocrystals has emerged in recent years as a very attractive strategy to tune the properties of new APIs and improve the performance of existing ones.
- A key aspect is to assess the stability those co-crystals relative to their co-formers.
- A good indicator of that stability is the standard molar enthalpy, Δ_rH_m, of reaction:
  \[ nA(cr) + mB(cr) \rightarrow A_nB_m(cr) \]

A new cell has been developed for determination of Δ_rH_m with small amounts of sample.

PERFORMANCE

Quality of the calorimetric signal

Sensitivity of the calorimetric system

Dissolution tests: KCl and Theo2·Oxa

Funding:
Centro de Química Estrutural is funded by Fundação para a Ciência e Tecnologia – project UID/QUI/00100/2019. This work was supported by Fundação para a Ciência e Tecnologia – project PTDC/QUI-OUT/28401/2017 (LISBOA-01-0145-FEDER-028401) and UID/MULTI/00612/2013.

References
For leading references see:

CONCLUSION
- The baseline noise is an order of magnitude smaller than that of a previous existing cell.
- The calibration constant was found to be stable if power P > 10⁴ W.
- Validation through Δ_dissH_m (KCl, cr) measurements showed excellent accuracy and better precision than recommended reference data.
- Tests with Theo₉·Oxa showed excellent performance of the new cell for co-crystal stability studies with small amounts of sample.
Lighting the mitochondria with Two-photon red-emitting cationic molecules

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A set of fluorescent mitochondria target molecules based on dipolar and quadrupolar quinolizinium and benzimidazolium cations were developed. (Fig. 1) Some of the dipolar compounds could be excited in the Near-infrared due to a high two-photon brightness while exhibiting emission in the red part of the visible spectra (600-700 nm). Interaction with the mitochondria in living cells leads to an unexpected blue-shift of the emission of these compounds.

Fig. 1 - General structure of push-pull systems based on either the quinolizinium (Q and Qe) or benzimidazolium (B and Be) cations. Ten charged compounds where prepared by combining the different electron acceptor core with different electron donor groups.

Fig. 2 – Absorption (left) and emission (middle) spectra for the Quinolizinium (top) and Benzimidazolium (bottom) compounds in DMSO; CIE 1931 colour space chromaticity diagram for their emission (right top) and TPA cross-section (n2) against the full width at half maxima (FWHM) of the two-photon induced emission band for all the compounds.

Fig. 3 - Fluorescence microscopy images of HEK 293 T cells co-stained with the compounds Q2, Q3, Qe2, Qe3 and B4 (green), the MitoTracker Red (red) and the Hoechst 33342 (blue) and the overlay of the isolated channels showing the co-localization of the selected compounds with the MitoTracker. Scale bar common in all images: 10 µm.

Fig. 4 - Emission spectra of Q2, B2 and Qe3 in HEK 293T cells and in PBS at pH7 solution (top left) and solvatochromic studies for the red emitting Q2 (top right) and B2 (bottom left) showing the blue-shift in emission in low polarity solvent. The photograph shows emission of a film of B2 changing from orange to green while it dries.

References:
INTRODUCTION

Metal catalysts supported by carbon materials\(^2\)–\(^9\)

- Reduced catalyst loading
- Improved efficiency and recovery
- High surface area
- Porous surface
- Thermal stability

Synthesis of 1,2,3-triazoles\(^1\)–\(^8\)–\(^9\)

Highly valuable organic scaffolds

Use of inexpensive Cu-catalyst

OBJECTIVES

- To subject different carbon materials to pre-treatment methods (i.e., C-ox and C-oxNa).
- To immobilize Cu(I) complexes to commercially available and pre-treated supporting matrices (i.e., charcoal, carbon nanotubes).
- To synthesize disubstituted triazoles using carbon supported Cu(I) complexes.
- To compare catalytic efficiency of supported catalysts versus the homogeneous counterparts.

METHODOLOGY

1. Cu(I) complexes preparation\(^1\)
2. Carbon materials preparation\(^2\)–\(^7\)
3. Immobilization of Cu(I) complexes to carbon materials
4. Synthesis of 1,2,3-triazoles

RESULTS

- Figure 1. Yield of 1,2,3-triazole from MW-assisted three-component CuAAC click reaction.
- The figure above (Fig. 1) shows the comparison between the yields obtained from homogeneous versus supported catalysts.
- Higher yields were observed upon immobilization of Cu(I) complex and greatly increased upon the use of CNT (carbon nanotube) materials as support.

CONCLUSION

Carbon supported Cu(I) complexes were used as catalyst for the synthesis of 1,2,3-triazole. The immobilized catalysts show higher TONs as compared to the homogeneous counterpart. Moreover, the reaction was performed under MW irradiation for 15 min at lower temperature (80 °C) with very low catalyst loading of 0.067 mol %.
In the last few years, an alternative static microextraction technique, bar adsorptive microextraction, was proposed for trace analysis of polar to nonpolar analytes in aqueous media. This analytical approach, based on the floating sampling technology enrichment process, presents several advantages, including the possibility of selecting the most convenient sorbent coating (e.g. activated carbons (ACs), polymers (Ps), etc.) according to the target compounds involved, which has already shown high effectiveness in many applications [1-3].

In order to maximise the microextraction efficiency, several parameters used to be optimised, including sorbent selectivity, equilibrium time, agitation speed and matrix properties, such as, pH, polarity and ionic strength. Nevertheless, the matrix pH may have a significant influence on the recovery yields, once it decides the overall charge of the ionic compounds in the matrix and can also affect the surface charge of the sorbent phases.

While the interactions between the matrix pH, sorbent phase and compound polarity (Fig. 1) were never truly studied in detail by BAμE. The present contribution aims the evaluation of the performance of BAμE prior to high-performance liquid chromatography-diode array detection to understand the mechanisms behind those interactions by using several organic analytes with distinct polarity and pKa values as model compounds and different sorbent phases.

By mixing some sorbent phases, better recovery conditions the less favourable are for both the microextraction and back-extraction stages; the compounds polarity seems to have a strong influence on the enrichment process; the matrix pH may have a significant influence on the recovery yields, once it decides the overall charge of the ionic compounds in the matrix and can also affect the surface charge of the sorbent phases.

In general, the more alkaline are the matrix pH, the less favourable are for both the microextraction and back-extraction stages; the compounds polarity seems to have a strong influence on the enrichment process; the matrix pH may have a significant influence on the recovery yields, once it decides the overall charge of the ionic compounds in the matrix and can also affect the surface charge of the sorbent phases.

The sorption mechanism of organic compounds in aqueous media using activated carbons and polymers is a very complex task; the main parameters involved are the polarity of the compounds, the physico-chemical characteristics of the sorbents as well as, the matrix pH; in general, the more alkaline are the matrix conditions the less favourable are for both the microextraction and back-extraction stages; the compounds polarity seems to have a strong influence on the enrichment process; by mixing some sorbent phases, better recovery yields are observed for some particular compounds.

![Figure 2](image-url) - Schematic of the procedure for the microextraction methodologies.

![Figure 3](image-url) - Chromatogram of a standard mixture of the four compounds (250 mg/L) obtained by HPLC/DAD at 254 nm. 1. Caffeine; 2. 2,2',4,4'-tetrahydroxybenzophenone; 3. Atrazine; 4. Anthracene.

![Figure 4](image-url) - Chromatogram of a standard mixture of the four compounds (5 mg/L) obtained by HPLC/DAD at 226 nm. 1. 2,2', 4,4'-tetrahydroxybenzophenone; 7. Prazepam; 8. Caffeine

![Figure 5](image-url) - Average recovery following back-extraction, from ultrapure-water and non-extracted from BAμE device using AC1 as sorbent phase. 24BP: 2,2',4,4'-tetrahydroxybenzophenone; 3BP: 3-hydroxybenzophenone; CLO: clofibric acid; PRA: prazepam; IBU: ibuprofen.

![Figure 6](image-url) - Chromatogram of a standard mixture of the four compounds (250 mg/L) obtained by HPLC/DAD at 226 nm. 1. 2,2',4,4'-tetrahydroxybenzophenone; 2. 3-hydroxybenzophenone; 3. Clofibric acid; 4. Prazepam; 5. Ibuprofen.

### Experimental Procedure

**BAμE procedure:**
- Equilibrium time: 16 h
- Stirring rate: 1000 rpm
- Microliquid desorption
- Sorbent selectivity: 30 min under sonification

**Back-extraction:**
- Equilibrium time: 16 h
- Microliquid desorption
- Stiring: 100 µL MeOH
- 10 min under sonification

**Analysis:**
- Injection vial

### Results

- **Recovery (%)**
  - AC1
  - AC2
  - Mixture AC1/AC2
  - P1
  - P2
  - Mixture P1/P2
  - BAμE AC1
  - BAμE AC2
  - BAμE Mixture AC1/AC2
  - BAμE P1
  - BAμE P2
  - BAμE Mixture P1/P2

### Conclusions

- The sorption mechanism of organic compounds in aqueous media using activated carbons and polymers is a very complex task;
- The main parameters involved are the polarity of the compounds, the physico-chemical characteristics of the sorbents as well as, the matrix pH;
- In general, the more alkaline are the matrix conditions the less favourable are for both the microextraction and back-extraction stages; the compounds polarity seems to have a strong influence on the enrichment process;
- By mixing some sorbent phases, better recovery yields are observed for some particular compounds.

### References

Camphor complexes with antimicrobial and/or cytotoxic properties: design, synthesis and assessment of biological activity

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Introduction

This project aims at find new camphor derived complexes with antibacterial, antifungal and/or cytotoxic properties that may overcome the increasing fungi and bacteria resistance to antimicrobials in use. A particular focus is made in the search for active molecules that combine anti-cancer and antimicrobial properties to fight opportunistic infections during anti-cancer treatment.

The strategy is to design and synthesize camphor derivatives that react with metals to produce biological active complex. The variety of ligands provides different electronic and steric properties that can be tuned according to the applications by changing the mono or bicapmor character and the substituents (Y or 2) at the imine group. Initially, the metal precursor chosen was silver nitrate. Good to excellent antifungal results were obtained although the toxicity of nitrate was a drawback that is tentatively being faced by using acetate or chlorate silver salts. The biological activity of all compounds was evaluated by calculation of MIC values.

Currently the project was extended to synthesis and biological assessment of Au(I) camphor derived complexes. Other metals of groups 10 and 11 will be screened.

Metal | Ligand | Complex
--- | --- | ---
Ag(OAc) | L1: Y=PhCH2 | [(Ag(OAc)µ-O)]
L2: Z=CH2 | [(Ag(OAc)µ-O)]
L3: Z=Ph | [AgCl]2
AgCl | L1: Y=PhCH2 | [(AgCl)µ-O]
L2: Z=Ph | [AgCl]2
Ag(NO3)2 | L1: Y=Zn-C6H4 | [Ag(NO3)µ-O]
L2: Z=Ph | [Ag(NO3)µ-O]
L3: Z=Ph | [Ag(NO3)µ-O]
KAu(CN)2 | L1: Y=PhCH2 | [K(Au(CN)µ-C2H2)2]
L2: Y=Zn-C6H4
L3: Y=Zn-C6H4

Antimicrobial activity

The MIC values of silver and gold compounds were calculated in order to assess their antimicrobial activities. The silver compounds showed excellent antifungal (C. albicans, C. glabrata, C. parapsilosis and C. tropicalis) and antibacterial (S. aureus Newman, B. contaminans IST408, E. coli ATCC25922, P. aeruginosa 477) activities. Preliminary results from gold compounds point to low or no activity.

Cytotoxic activity

Selected complexes were probed through evaluation of the cytotoxic properties (IC50) towards A2780 and A2780cisR cell lines.

- **Conclusions**
  - High active antifungal and antibacterial silver complexes were synthesized by design of the camphor ligands.
  - The electronic and steric characteristics of the ligands are tuned through choice of the imine substituent (Y) at the camphor imine ligand. Such choice drives the biological activity towards fungi or bacteria and in some cases also combining cytotoxic activity.
  - Preliminary results show that silver camphor imine complexes perform much better than the corresponding gold complexes in what concerns antimicrobial activity.
  - Preliminary results show that applications in the area of medicinal materials are feasible.
NEW SELECTIVE COPPER(I) COMPLEXES FOR PROSTATE CANCER CELLS

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INTRODUCTION
Prostate cancer is the second most common cancer in men (1.3 million new cases in 2018). Platinum-based drugs are one of the most used anticancer agents, however they show severe side effects and drug resistance.1 Copper complexes are emerging as potential alternatives, as they are likely to be equally effective, less toxic, overcome platinum resistance, and be less expensive to produce.2

Recently, our group has been developing novel copper(I)-phosphine complexes for cancer therapy, showing higher cytotoxicity than cisplatin against ovarian and breast cancer cells.3,4 Herein, we report the synthesis, characterization and evaluation of the anticancer activity of a new family of complexes of general formula [Cu(PP)(LL)][BF4], in which PP represents several bi/monodentate phosphines and LL different N,O-heteroaromatic ligands (Scheme 1).

STRUCTURAL CHARACTERIZATION
NMR analysis are in good agreement with the proposed structures for all the compounds. In general, upon coordination of the ligand, deshielding is observed from the 1H NMR spectrum (Figure 1). No significative shift is observed for the 31P resonance. Broad signals are characteristic of coordination with Cu(I).

SYNTHESIS
[Cu(I) complexes were synthesized according to Scheme 1, with 34 to 96 % yields.]

ULTRAVIOLET-VISIBLE SPECTROSCOPIC STUDIES
The complexes show an intense absorption band in the UV region with maximum circa 240-270 nm (n→π* transitions of the aromatic fragments) and a second broad less intense band between 350 and 470 nm (metal to ligand charge transfer band).

CONCLUSIONS
❖ A new family of 16 complexes of formula [Cu(PP)(LL)][BF4] (PP = phosphines; and LL = N,O-heteroaromatic ligands) was synthesized with high purity.
❖ All complexes were structurally characterized by elemental analysis, FT-IR, UV-Vis and multinuclear NMR techniques.
❖ 9 structures were determined by single crystal X-ray diffraction studies.
❖ All complexes are stable over 24 h in aqueous and organic solution.
❖ The complexes showed high activity against prostate cancer cells (LnCap).
❖ All complexes are selective with therapeutic index values ranging from 10 to 70.

References:
A Metabolomics-based Workflow to Identify Protein Covalent Modifications

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Introduction

Identification of protein covalent modifications (covalent adducts) is a challenging task mainly due to the lack of data processing approaches for Adductomics studies. Despite the huge technological advances in mass spectrometry (MS) instrumentation and bioinformatics tools for proteomics studies, enabling the identification of several thousands of proteins in a single injection analysis, these methodologies have very limited success on the identification of low abundant covalent protein adducts.1

Our Approach

Herein we present a novel strategy to identify protein covalent modifications inspired in metabolomics workflows that consists on LC-MS data pre-processing using the open source software MZmine followed by statistical analysis. Our workflow involves three steps: 1) data acquisition in full scan mode to maximize the sensitivity; 2) LC-MS data preprocessing followed by statistical analysis to reveal those ions (adducts) that differentiate negative samples from positive samples (non-exposed vs exposed or healthy vs disease); and 3) targeted MS/MS acquisition of the statistically significant ions for adduct identification.

Results

Table 1. Comparison of results obtained by our novel metabolomics-inspired strategy and the standard Adductomics strategies.

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Glycidamide-modified peptide</th>
<th>m/z (in ppm) [Charge]</th>
<th>Protein</th>
<th>Adduct Onset</th>
<th>Adduct MS/MS</th>
</tr>
</thead>
</table>

Using our novel metabolomics-inspired approach we were able to identify more glycidamide-modified peptides than the commonly used methodologies in proteomics studies.

Conclusions

We present a new metabolomics-inspired data processing approach for the identification of covalently-modified peptides that is fast, sensitive and allows to perform any statistical analysis. This methodology will increase the possibility of identifying low abundant adducted proteins in biological samples and, thereby, enhancing the chances of identifying new biomarkers of exposure to carcinogens.
Introduction

Food irradiation is a widely used technique for improving the safety and shelf-life of foods, including most spices. However, growing concerns by the consumers about this technique require further investigation on the effects of radiation, both on the safety of the food and on its organoleptic properties.

Cloves of diverse origins were submitted to different irradiation doses in a $^{60}$Co source. Trapped radicals and their decay were assessed by EPR spectroscopy. The volatile bioactive composition and the clove oil were evaluated before and after irradiation GC-TOF-MS.

Results and Discussion

The central EPR line appears in most spices that were not exposed to radiation, and is due to semiquinone radicals produced by oxidation of phenolic groups in polyphenols or lignin. The weak triplet with a 30 G coupling constant arises from a C(5) carbon-centered cellulose radical, and these are the lines used to prove irradiation. These radicals decay fast and 120 days after irradiation they are practically undetectable by EPR.

Change of the volatile and liquid (in the oil) composition relative to eugenol (100 in all) with the dose of irradiation:

1) caryophyllene contributes more to the clove aroma than its content in the oil would predict.
2) decrease of caryophyllene and an increase in caryophyllene oxide with the irradiation, although the latter is still a minor component.

Conclusions

Gamma irradiation is a clean technique for clove decontamination, since no significant change in the aroma or oil compositions was found and low levels of trapped paramagnetic species, after the initial decay period, were detected upon irradiation. Furthermore, irradiation doses higher than the legally allowed are equally safe.
Mixed valence radical anions of 4,4”-dinitro-p-terphenyl and its aza-derivatives as models for electronic communication in conducting polymers

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Introduction
Poly(p-phenylene) (PPP) is an aromatic polymer that is interesting in various areas of material science, such as conducting materials, molecular composites, nonlinear optics, or electroluminescence.\(^1,2\)

The Mixed Valence radical anions of 2, 3 and 4 were prepared as models for electron conductance in poly(p-phenylene) polymers, to study how the increasing electron-accepting bridges influence their electronic properties.

Results and Discussion
Optical spectra of 2 (0: neutral) upon reduction with Na (Hg) to the radical anion (-1) and dianion (-2) in NMP. (Inset: relative concentrations of the three species in equilibrium). Due to disproportionation, the NIR wide band of the radical anion is superimposed with the dianion. To have the NIR spectra of the “pure” radical anion, a fraction of the dianion spectra was subtracted from the maximum of radical anion.

Marcus-Hush analysis of the charge-transfer band allows the calculation of the reorganization energy (\(\lambda\)) and the electronic coupling (\(H_{ab}\)), the latter being a measure of the conductivity of the bridge. Contrary to 2, radical anion of 4 has a delocalized charge in THF, and so a smaller \(H_{ab}\). 3 has an intermediate behavior (not shown).

Conclusions
Rate of electron transfer (by EPR) and electronic coupling \(H_{ab}\) in the order 2 < 3 < 4. Inclusion of pyrazine or pyridazine units in poly-p-phenylene polymers may result in enhanced electrical properties and better conductivity due to a lower band gap and increased planarity.

References:
1 V. Cimrová et al., Adv. Mater. 8 (1996) 146-149.
Gas-Phase Ion Chemistry Studies with \( p \)-, \( d \)- and \( f \)-Elements

Joaquim Marçalo, Bernardo Monteiro, João P. Leal, Joaquim B. Branco, José M. Carretas, Leonor Maria, Sandrina Oliveira

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Introduction

For some years, we have been using FTICR and QIT mass spectrometry to examine the gas-phase ion chemistry of the lanthanides from La to Lu (except Pm), the actinides from Th to Cm, and several \( d \) transition elements. We revealed new species, determined thermodynamic properties of neutral and ionic molecules, and, in the case of the actinides, probed the role of 5f electrons in bonding and the issue of covalence. Recently, we have also focused our attention on the chemistry of the noble gases, particularly of Kr and Xe as a prelude to future experiments with highly radioactive and scarcely studied Rn.

Experimental details

The QIT-MS experiments were performed using a Bruker HCT equipped with an ESI interface and with \( MS^n \) collision induced dissociation (CID) capability. Stock solutions of \( \text{MNO}_2(\text{H}_2\text{O})_2 \) \((M = Sc, Y, Ln)\), \( \text{ThNO}_3(\text{H}_2\text{O})_3 \) and \( \text{UO}_2(\text{NO}_3)_3(\text{H}_2\text{O})_3 \) in water were diluted with ethanol to prepare \( 10^{-3} \text{M} \) solutions for ESI. The \( \text{Cu} (\text{CH}_3\text{COO})_2 \cdot \text{H}_2\text{O} \) solution was prepared in \( \text{CH}_3\text{OH} \). The metal solutions were directly injected into the ESI source using a syringe pump. The helium buffer gas pressure in the trap was constant at \( \approx 10^{-4} \text{Torr} \). The background air and water pressure in the ion trap is estimated to be on the order of \( 10^{-6} \) Torr. Neutral reagents were introduced into the mass spectrometer through a leak valve to pressures on the order of \( 10^{-5} \) Torr. The \( MS^n \) capabilities of the QIT were used for isolation of ions with a specific \( m/z \) and subsequent CID of mass-selected ions, using helium buffer gas as the collision partner.

The FTICR-MS experiments were performed in an Ettre/Finnigan FTMS 2001-DT 3 Tesla spectrometer with an "internal" source design. The instrument was controlled by a system developed by BridgePoint (Portugal), based on National Instruments units and LabVIEW software. The reagent gases were introduced in the spectrometer through leak valves to pressures on the order of \( 10^{-4} \) Torr. The studied noble gases were Kr and Xe and as oxidizing and fluorinating agents, we used \( \text{N}_2 \) and \( \text{SF}_5 \), respectively. The reagent ions were produced by electron ionization (EI) and mass spectra were acquired at various reaction time delays.

Results and discussion

\( d \)- and \( f \)-Elements

CID of \([\text{MNO}_2]^{+} \) gave rise to oxide nitrate anions, \([\text{M} (\text{NO}_3)]^{+} \), that result from \( \text{NO}_3 \) elimination. CID in the presence of ethene (Fig 1), ethane and benzene showed the formation of \([\text{M} (\text{OR}) (\text{NO}_3)]^{+} \). These \( C-H \) activation reactions were also observed for \([\text{ThN}_2]^{+} \) (anions (Fig. 2), which similarly to the case of the \( \text{RE} \), are formed by CID of \([\text{ThNO}_3]^{+} \). Other reactive oxide nitrate anions can be obtained by nitrate CID, including for uranyl with starting the precursor anion \([\text{UO}_2(\text{NO}_3)]^{+} \).

\( p \)- and \( d \)-Elements

The reaction of \( \text{Kr}^{+} \) with \( \text{SF}_5 \) gave rise to the formation of \( \text{SF}_5^{+} \) as well as to a \( \text{KrSF}_5^{+} \) species at \( m/z \) 211 (Fig. 4). The origin of this species was confirmed by reacting isolated \( \text{SF}_5^{+} \) with neutral Kr up to 5 s, with no observation of \( \text{KrSF}_5^{+} \). These reactions were not observed with \( \text{Xe}^{+} \), as shown in Fig. 5. In the reaction of \( \text{Kr}^{+} \) with \( \text{N}_2 \) only electronic transfer to yield \( \text{N}_2^{+} \) was observed, while for \( \text{Xe}^{+} \) no reaction occurred.

Concluding remarks

We obtained experimental evidence that highly reactive rare earth and actinide oxide nitrate anions are capable of attacking hydrocarbons in the gas phase. These ongoing experimental studies bear interest in the long-standing search for systems that are capable of activating methane. For the reactions involving the noble gases, evidence was obtained for the formation of an interesting \( \text{KrSF}_5^{+} \) species. This result indicates that new gas-phase chemistry for the noble gases, including Rn, can be expected using these \( MS^n \) techniques.
Rare Earth Elements (REEs; lanthanides (Ln), scandium and yttrium) have become an important raw material in the industry, playing an essential role in modern electronic technologies, industrial and medical products and innovative environmental technologies. REEs are considered as being highly relevant for societal needs but there exists a significant risk of supply for actual demand. Therefore, the development of selective, efficient, economical and environmentally friendly separation processes of REEs from different materials is under intense development.\(^1\) In our current work, ionic liquids (ILs) with only CHON elements in their composition, both already existent or newly synthesized, are being used for separation of REEs from other metals, as an alternative to more traditional methods.\(^2\)

The experiments involved the combination of aqueous solutions of several lanthanides (Ln) in acidic media, at different pHs, with toluene solutions of ILs, in various molar ratios IL:metal and several extraction times. Metal concentrations in the aqueous phases, before and after extraction, were assessed by ICP-MS.

Tetraoctylammonium oleate (IL1)\(^3\), 1-butyl-3-methylimidazolium-di(2-ethylhexyl)-oxamate (IL2)\(^4\), and the new tetraoctylammonium dicytldiglycolamate (IL3) and tetraoctylammonium di(2-ethylhexyl)-oxamate (IL4) were the ILs under investigation. IL1 and IL4 displayed a significant differentiation between lanthanides and are adequate to selectively extract Ln among them. Results for IL1 are presented in Fig 4. In certain conditions, IL2 was able to separate Ln from other metals, as Fe(III) was partially extracted while Ln were not (Fig 5). Work is in progress for optimizing a selective extraction of REEs in the presence of other metals and an effective separation along the lanthanide series.
Non-iridescent tunable spherical colloidal photonic pigments

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

Overview

Synthetic colloidal photonic crystals consist of periodically arranged nanoparticles originating repeating regions of low and high dielectric constants that can be used to control the propagation of light. Their shining structural coloration arises from the modulation of electromagnetic waves by means of Bragg reflection from photonic band gaps. They can be used as waveguides in optoelectronic and photovoltaic applications, as sensors or in structural color.

Experimental details

Colloidal building blocks

Soft- lithography

Microfluidic W/O emulsification followed by PNP assembly

Optical characterization of spherical photonic pigments

FCC packing of PNP

Angle-resolved reflectance measurements

Conclusions

- Microfluidics yields highly monodispersed and homogeneous spherical photonic pigments;
- Spherical confinement breaks long range-order originating non-iridescent structural color;
- Vibrant and bright structural color from photonic pigments obtained using 170 - 333 nm diameter PNP, covering the entire visible light range.

References:

Novel Corrosion Inhibition Strategy for Mild Steel

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Abstract
Efficient corrosion protection strategies are of great importance for most industries today, especially smart self-healing coating systems. In this work, microcapsules containing isocyanate-based polymerizable agent in their core were used in combination with cerium-based pH-sensitive corrosion inhibitor. The synergistic effect of both these additives was investigated. The barrier properties were studied using Electrochemical Impedance Spectroscopy (EIS). To assess the self-healing potential, Localized Electrochemical Impedance Spectroscopy (LEIS) was used. Results showed improved protection of the underlying mild steel substrate when the additive-modified coating system was used.

Experimental
EIS was performed during sample immersion in 0.05 M NaCl, using SCE as reference electrode. LEIS measurements were performed at 10 Hz, over artificial defect, during immersion in 0.005 M NaCl.

Results

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image1.png}
\caption{FEG-SEM images of corrosion inhibitor (a) and self-healing microcapsules (b).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image2.png}
\caption{Bode plot of coating modified with mixed additive-MCs system, applied on mild steel (a); and evolution of high frequency impedance modulus with the immersion time for coatings modified with the mixed additives, and coatings modified with each additive (corrosion inhibitor or MCs) (b).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image3.png}
\caption{LEIS maps obtained for coated samples with an artificial defect: coating with mixed additive-MCs system after 5 h and 100 h of immersion in 0.005 M NaCl.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image4.png}
\caption{Evolution of admittance for coated samples with an artificial defect: coating with self-healing microcapsules, and coating with mixed-additive-MCs system.}
\end{figure}

Conclusions
In this work, the synergistic effect of two coating additives (corrosion inhibitor and self-healing microcapsules) was studied. The mixed coating system showed good barrier properties and a synergistic effect was found. Furthermore, the mixed coating system was able to continuously suppress the intensification of corrosion activity and its propagation. Thus, this work represents an important step towards the development of autonomous corrosion protection strategies.

Acknowledgements
Sherwin Williams for providing the model coating formulation; Shell Qatar (and Dr. Nick Laycock) as partner in the project SmartCoat (NPRP 9); L. M. Calado acknowledges FCT for PhD grant SFRH/BD/127341/2016 and M. J. Carmezim for scientific supervision.

Funding
This work was made possible with the funding granted by SmartCoat project (NPRP 9) – Grant no. 080-02-039 funded by QNRF. Centro de Química Estrutural is funded by Fundação para a Ciência e Tecnologia – project UID/QUI/00100/2019.
NON-AQUEOUS URANIUM COORDINATION CHEMISTRY: URANIUM COMPLEXES SUPPORTED BY HYDROBIS(MERCAPTOIMIDAZOLYL)BORATES

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INTRODUCTION

Compared to d-block metals, uranium chemistry is less developed, and uranium-ligand bonding and reactivity remain puzzling and unpredictable. Insight into the fundamental chemistry of this f-element is crucial in many aspects of nuclear technology and in determining its mobility in the environment, as well as in the search for new applications. The oxidation of a metal is a well-suited reaction to study the influence of the supporting ligand on reactivity. Since trivalent uranium has a high reducing power, its complexes are extremely reactive with oxidizing substrates. As such, studies of U(III) redox chemistry have been reported using diverse U(III)-systems leading to unprecedented transformations and structures, demonstrating the chemical potential and unique properties of uranium.1

Hydrobis(mercaptoimidazolyl)borate ligands are mono-anionic soft chelates, analogues to the [N,N]-donor hydrobis(pyrazolyl)borate ligands, that provide [S,S]-donor ligands. Previous results obtained by us demonstrated that the bis(mercaptopimidazolyl)borate ligands [H(R)B(timM)]2 are able to stabilize uranium(III) cationic complexes.2 Revisiting our studies with these [S2]-donor chelators, we verified that the neutral U(III) complex [U\((k^3-H,S,S',H-Ph)B(timM)_2\)]2 can be used as an U(III) precursor in electron-transfer reactions to access new tetravalent and hexavalent uranium complexes supported by soft bis(azolyl)borate ligands.3

SYNTHESIS AND CHARACTERIZATION

Oxidation of the U(III) complex [U\((k^3-H,S,S',H-Ph)B(timM)_2\)]2 with the one-electron oxidants AgBPh₄ or I₂ lead to the formation of the cationic U(IV) compounds [U\((k^3-H,S,S',H-Ph)B(timM)_2\)][X] (X = BPh₄, I). The more sterically crowded U(IV) complexes probably resulted from ligand redistribution of the unstable U(IV) cation, [U\((k^3-H,S,S',H-Ph)B(timM)_2\)]+. The uranium complexes were characterized by multinuclear NMR, IR and UV-vis/NIR spectroscopies and by X-ray diffraction analysis.

The reaction of the U(III) neutral precursor with O-atom transfer reagents, such as pyridine N-oxide led to the formation of the uranyl complex [U\((k^3-\cdot-H,S,S',O)B(timM)_2\)]2(O₂)2 and of [U\((k^3-H,S,S',H-Ph)B(timM)_2\)][O].

CONCLUDING REMARKS

We have demonstrated that the soft donor ligand [HPhB(timM)]1 is able to stabilize the +3, +4 and +6 uranium oxidation states. Oxidation reactions of the U(III) precursor allowed to isolated tetravalent and hexavalent uranium complexes. The U(III) and U(IV) complexes were stabilized by additional U-H-B three-center two-electron interactions.3
Co-Crystals of Fumaric Acid Esters with Aminoacids

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Scope
Fumaric acid esters are one of the most commonly used active pharmaceutical ingredients (API) in the treatment of psoriasis vulgaris.¹ The low solubility of fumaric acid esters in aqueous media poses significant limitations to the development of pharmaceutical formulations with high bioavailability. An interesting strategy to improve this is based on the formation of co-crystals, multi-component substances combining two or more molecules in the same crystal lattice.

AIM
Produce co-crystals of methyl fumarate, ethyl fumarate and dimethyl fumarate through mechanochemistry with amino acids as co-formers, to increase the solubility of the APIs

Method

Results

Table 1. Results for the compound mixtures utilized for the mechanochemical grinding. Every test was made with a 1:1 stoichiometry.

<table>
<thead>
<tr>
<th>Compound</th>
<th>D-Alanine</th>
<th>L-Cysteine</th>
<th>DL-Serine</th>
<th>DL-Arginine</th>
<th>D-Aspartic Acid</th>
<th>L-Glutamic Acid</th>
<th>L-Phenylalanine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl fumarate</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Ethyl fumarate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Reaction occurred
- Reaction did not occur
- Partial reaction occurred
- Untested Mixture

Conclusions:
- Out of all the tested systems, 4 achieved a complete reaction, yielding co-crystals.
- Formation of co-crystals was also suggested from the XRPD data for 6 mixtures. This, indicates that complete co-crystal formation may be achieved if the reaction conditions are changed (e.g. stoichiometry, type/quantity of solvent, and reaction time).

References:
The **Supercritical Antisolvent precipitation (SAS)** is a semi-continuous process that uses a supercritical fluid, or a compressed gas, as an antisolvent. The compound of interest to be precipitated is dissolved in an organic solvent and is fed to the precipitator, alongside the supercritical fluid that is, generally, CO₂ due to its characteristics (non-flammability, low toxicity, low cost, abundant, with a critical point readily accessible: T=31.2°C and P=7.38 MPa).

### References:

In order to complete the studies, precipitated compounds must be very well characterised. Besides the morphology analysis using SEM images, others techniques are required like infrared spectroscopy, X-ray diffraction, thermogravimetry or isothermal adsorption.

![Fig. 5. Example of thermogravimetry analysis comparing the calcium acetate micronized and the commercial](image)

This is a versatile and environmental friendly technique. Through this, is possible to tune the physical characteristics of the materials by changing the operation conditions. The applicability of this technique is huge, with tested products from the pharmaceutical industry to the catalysts field, crossing the polymers area.
C-dots based nanocomposites materials for the photodegradation of organic pollutants

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INTRODUCTION

Although a wide variety of semiconductor materials have been studied as potential photocatalysts for the photodegradation of organic pollutants, the low efficiency of this class of materials in the visible region has been obstructing their largescale application. A possible way to achieve the foreseen visible-light-active photocatalysts with high efficiency can be addressed by hybrid nanostructured materials in which two or more units are combined together into a single nanocomposite material. This work involves the development of visible-light-active carbon dots (C-dots) based nanocomposites for the photodegradation of caffeine, being silica the inert matrix used. The C-dots were obtained using cork industry and olive mill wastewaters as C sources aiming at the valorization of these industrial wastes.

EXPERIMENTAL

• Synthesis of SiO₂ microparticles (Stöber method)

• Synthesis of C-dots/SiO₂

RESULTS AND DISCUSSION

Caffeine photocatalytic degradation under UV-vis radiation

The Attenuated Total Reflection (ATR) spectra indicates the immobilization of the C-dots nanoparticles in the SiO₂ surface.

The absorption spectrum of C-dots/SiO₂ confirms the immobilization of C-dots in the matrix surface.

After C-dots incorporation, the nanocomposite starts to absorb in the visible range.

CONCLUSIONS

• New C-dots/SiO₂ nanocomposite materials were successfully prepared;
• The C-dots/d-SiO₂ were not photocatalytic for caffeine degradation using UV-vis radiation, probably due to the degradation of C-dots;
• New applications for these C-dots/SiO₂ hybrid materials are currently in study.
The coordination chemistry of Cu(II) is very interesting. It exhibits a rich variety of distorted coordination geometries including tetragonal, tetrahedral, square planar, and trigonal bipyramidal. Due to the presence of single unpaired electron and flexible coordination behavior, Cu(II) complexes are widely explored for magnetic studies, with a growing interest on the synthesis of polynuclear complexes and clusters and their application in molecular magnetism.[1]

In this work, we are presenting the syntheses, characterizations and the catalytic activity of three trinuclear Cu(II) arylhydrazone complexes towards mild hydrocarboxylation of linear and cyclic alkanes into carboxylic acids in water/acetonitrile medium. The complexes 1–3 are shown to act as good catalytic precursors for the hydrocarboxylation of linear and cyclic C5–C8 alkanes, leading to carboxylic acid yields up to 26% based on the starting alkane.[2]

The three complexes 1–3 exhibit good catalytic activity towards the alkane hydrocarboxylation, leading to carboxylic acid yields up to 26% based on the starting alkane. The achieved herein activity is quite considerable taking into account the high inertness of alkanes and the rather mild reaction conditions (60 °C, 4 h, aqueous medium). In general, the highest activity is shown by complex 1, followed by 3 and 2.

A free-radical mechanism of alkane hydrocarboxylation is proposed. Sulfate radicals SO4•− derived from thermolysis of K2SO2 react with the alkanes, resulting in the formation of alkyl radicals R•. These rapidly react with CO forming the corresponding acyl radicals RCO•. The catalytic role of the Cu-complex consists in the oxidation of these acyl radicals RCO• to acyl cations RCO+ via the CuII/CuI redox couple. The RCO+ is further hydrolyzed with water to form the carboxylic acid RCOOH.

CONCLUSIONS

Three different hydrazone Schiff base ligands have been synthesized by condensation reactions of 2,3-diarylhydrazine benzaldehyde separately with 2-hydroxybenzonic acid, 2-aminobenzoic acid and benzaldehyde. The complexes 1–3 are shown to act as good catalytic precursors for the hydrocarboxylation of linear and cyclic C5–C8 alkanes, leading to carboxylic acid yields up to 26% based on the starting alkane. The achieved herein activity is quite considerable taking into account the high inertness of alkanes and the used rather mild reaction conditions (60 °C, 4 h, aqueous medium).
Green methodologies in the preparation of new photoactive MOFs for energy applications

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• This communication presents a new sustainable approach for the preparation of metal-organic frameworks (MOFs) with semiconductor behaviour. A large number of structural features makes these hybrid materials good candidates for energy conversion in electroluminescent devices [1].

• The novelty is to introduce ligands and co-ligands with improved light harvesting properties in MOFs, and for that, the reactivity of unexplored functional ligands: diphenyl anthracene (DPA), naphthalene diimides (NDIs) and perylene diimides derivatives (PDIs).

Methods

Mechanosynthesis: Ball Mill Approach

Solid State Characterization

Variable-temperature Powder X-Ray Diffraction

FT-IR Spectra

Thermogravimetric Studies

On going studies

Conclusions/Future Work

- A new, simple and sustainable synthetic route to obtain CPO-5 was developed, as well as its 1D MOF precursor.
- The obtained small particles are predictably advantageous to engineer these materials in the active layer of electroluminescent devices.
- Future studies to be performed on these materials include photoluminescent properties as well as cyclic voltammetry.
- Expand the methodology to other photoactive ligands (NDIs, PDIs).

References:
Viscosity measurements of compressed ionic liquid EMIM OTf

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Background:
Properties for several Ionic Liquids such as viscosity, density, electrical conductivity have been measured by our group [1–5]

1. Ethyl-3-methylimidazolium bis[trifluoromethyl]sulfonylimide ([C2mim][OTf])
2. Ethyl-3-methylimidazolium ethyl sulfate ([C2mim][EtSO4])
3. Ethyl-3-methylimidazolium trifluoromethanesulfonate ([C2mim][OTf])
4. Hexyl-3-methylimidazolium bis([trifluoromethyl]sulfonylimide ([C6mim][OTf])

Vibrating-wire viscosity measurements – the sensor has a tungsten wire subjected to a magnetic field (>4000 Gauss). A lock-in amplifier is used to apply a current through a range of frequencies and measure the potential drop across the vibrating-wire.

New and sustainable achievements
1-ethyl-3-methylimidazolium trifluoromethanesulfonate ([EMIM] [OTf])

Electrical conductivity, \( \kappa \), measurements of the ILs

\[
\eta = 6.035 \times 10^{2} \left( \frac{1}{T} \right)^{2} \exp \left( \frac{0.003}{T} \right)
\]

Experimental density data of EMIM OTf at temperatures: 298K, 313 K, 328 K, 333 K, 343 K, 353 K, 363 K

The root mean square deviation of the fitting is 0.008 % and the bias is essentially zero

\[
\left| I \right| = R_{m} + b \times f^{-1/2}
\]

Deviations of the viscosity, \( \eta \), of EMIM OTf obtained with a vibrating-wire viscometer, from correlation: 298K, 313 K, 328 K, 333 K, 343 K, 353 K, 363 K

Outcomes:
• High quality determination of properties: (1) viscosity at high temperatures and high pressures; (2) electrical conductivity, of the ionic liquid (EMIM) [OTf].
• Vibrating-wire viscosity technique may be applied to ILs without any loss of its high accuracy.
• As far as the authors are aware these are the only IL frequency-dependent electrical conductivity measurements, extrapolated to infinite frequency, applied to ILs.
NMR in Strategic Areas of CQE’s Research

Maria João Ferreira, José R. Ascenso

Acknowledgements: The NMR spectrometers are part of the National NMR Network (PTNMR) and are partially supported by Infrastructure Project No 022161 (co-financed by FEDER through COMPETE 2020, POCl and PORL and FCT through PIDDAC). Further financial aid comes from the FCT institution (Project number UID/QUI/00100/2019).
A UNIFIED pH SCALE FOR ALL SOLVENTS
Meaning and assessment of pH in solvents other than water

Filomena Camões,
Bárbara Anes, Cristina Oliveira, Ricardo Silva

The concept of pH is very well defined and routinely evaluated by means of potentiometric measurements valid in dilute aqueous solutions.

\[ \text{pH} = -\log \left( a_{H^+} \right) \]

Values of pH in different media are related through the proton Gibbs free energy of transfer between solvents

\[ \Delta G / n = \mu^* + R T \ln a \]

\[ \mu(H^+) = \mu^0(H^+) + R T \ln a(H^+) = \mu^0(S) - R T \ln 10 \times pHS \]

The introduction of the unified acidity concept, pH_{abs}, based on the proton chemical potential, \( \mu(H^+) \), has enabled comparability of pH values between all phases.

\[ \mu_{abs}(H^+, \text{solv}) = \Delta_{\text{solv}} G^0(H^+ + S) - R T \ln 10 \times \mu_{S} \]

Concept of a unified Bronsted acidity scale pH_{abs} defined on the basis of the chemical potential of the proton, \( \mu(H^+) \)

It is practical to link the acidity scale to the aqueous pH scale via the Gibbs free energy of solvation of the proton in water

\[ \Delta G = -W - n F E = E - R T \ln a \]

\[ \Delta H_{\text{abs}} = \Delta_{\text{abs}} G^0(H^+, H_2O) - 193.5 \text{ pH at } 25 \text{ °C} \]

\[ \text{Indicator electrode (Ind 1) } | \text{ Solution 1 (S1) } | \text{ Bridge solution (B) } | \text{ Solution 2 (S2) } | \text{ Indicator electrode 2 (Ind 2)} \]

\[ \Delta E = E(\text{Ind 2}) - E(\text{Ind 1}) = \frac{-RT}{nF} \left[ \text{pH(S2)} - \text{pH(S1)} \right] \]

\[ \Delta E = \Delta E_{\text{measured}} + \Delta E(\text{B, S1}) - \Delta E(\text{B, S2}) \]

\[ \text{pH}_{\text{abs}} = \mu_{\text{abs}} + \Delta_{\text{abs}} G^0(H^+, H_2O) \]

Glass electrode 1 \( \text{Sol. A } \parallel \) Pt in IL \( \text{Sol. B } \parallel \) Glass Electrode 2

All solid state
Glass electrode 1
All solid state
Glass electrode 2

Capillary filled with Ionic Liquid (IL) N225 mF2

References:
Identification of Contaminants of Emerging Concern (CEC) in surface waters

CEC (as human and veterinary pharmaceuticals, pesticides, and various industrial additives) belong to the most important chemical contaminants currently found in the environment. These analysis is really challenging because of the diversity in chemical properties, the complexity of matrices, and generally the very low concentrations at which CEC are found.

- An in-house accurate mass library was constructed for 64 standards plus 650 suspected substances (drugs and pesticides and care).
- Screening using finf Compounds-Chromatogram via SigmaFIT™ with Target Analysis Software (Bruker).
- Values with a mass deviation lower than 5 ppm and nitrogens lower than 100 [match factor between the measured isotopic pattern and theoretical pattern for a given chemical formula] were considered acceptable postive confirmation (m/z <100 acceptable, <50 good, and <25 excellent).
- After screening with the Target Analysis software the results were manually validated, using the Data Analysis software (accurate mass, isotopic and MS/MS profiles).

MS in Strategic Areas of CQE’s Research

Maria da Conceição Oliveira
Development of an Analytical Method for the Determination of 6 Tricyclic Antidepressants in Biological Matrices

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Introduction
Depression affects around 300 million people globally. It substantially impairs people’s life. It can even lead to suicide. Antidepressants are used as an effective form of treatment1. Patients with a record of depressive disorders, dementia and anxiety disorders in Portugal have increased over recent years2. Tricyclic antidepressants (TCAs) are an important class of psychoactive drugs, however they can dangerously lead to an overdose due to the TCAs’ relatively narrow therapeutic/toxic index. The determination of TCAs in biological matrices is compulsory for emergency toxicological screening, drug abuse testing, forensic medical examinations for probable fatality caused through overdose, therapy monitoring, and for pharmacokinetics studies3. In this contribution, we propose an analytical methodology for the determination of 6 common TCAs (figure 1) using bar adsorptive microextraction4 followed by microliquid desorption in combination with large volume injection-gas chromatography coupled to mass spectrometry operating in the selected-ion monitoring acquisition mode (BAµE-µLD/LVI-GC-MS(SIM)).

Experimental Procedure

Sampling flask
Solvent + IS (100 µL)
Injection vial
BAµE device
Teflon magnetic bar
5 mL of urine sample

Figure 1 - Chemical structures of the studied TCAs.

Instrumental Analysis

GC conditions
• Gas Chromatograph: 6890 Agilent Technologies System
• Column: Zebrob 25-5 (30 mm x 0.25 mm x 0.25µm) (Phenomenex)
• Software: MSD ChemStation (version C.00.00).
• Injection Mode: Splitless injection (10 µL)
• Injector Temperature: 250 °C
• Oven Temperature: 40°C (0.5 min) to 280 °C at a rate of 50 °C min⁻¹

MS conditions
• Mass detector: 5973N Agilent Technologies
• Transfer Line: 280 °C
• Quadrupole: 150 °C
• Ion source temperature: 230 °C
• Ionization mode: Electronic ionization (70 eV)

Results

Method optimization

Table 1 - Validation data obtained for the present study, including average recovery yields, limits of detection (LOD), lower limits of quantification (LOQ), linear range and determination coefficients (R²), obtained by BAµE-µLD/LVI-GC-MS(SIM), under optimized experimental conditions.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Recovery yields ± RSD (%)</th>
<th>LOD (µg/L)</th>
<th>LOQ (µg/L)</th>
<th>Linear range (µg/L)</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMT</td>
<td>103.0 ± 6.8</td>
<td>0.1953</td>
<td>12.5</td>
<td>12.5 - 100.0</td>
<td>0.9991</td>
</tr>
<tr>
<td>MIA</td>
<td>93.0 ± 1.2</td>
<td>0.1953</td>
<td>1.6</td>
<td>1.6 - 100.0</td>
<td>0.9994</td>
</tr>
<tr>
<td>TRI</td>
<td>94.6 ± 2.0</td>
<td>0.1953</td>
<td>12.5</td>
<td>12.5 - 100.0</td>
<td>0.9989</td>
</tr>
<tr>
<td>IMP</td>
<td>97.3 ± 5.7</td>
<td>0.1953</td>
<td>12.5</td>
<td>12.5 - 100.0</td>
<td>0.9987</td>
</tr>
<tr>
<td>MIR</td>
<td>99.7 ± 4.4</td>
<td>0.3906</td>
<td>1.6</td>
<td>1.6 - 100.0</td>
<td>0.9997</td>
</tr>
<tr>
<td>DOT</td>
<td>100.9 ± 4.9</td>
<td>1.5625</td>
<td>1.6</td>
<td>1.6 - 100.0</td>
<td>0.9976</td>
</tr>
</tbody>
</table>

The linear model proved to be suitable for the analysis of the 6 target TCAs from urine samples (R² > 0.99).

Conclusion

A novel methodology (BAµE(C18)-µLD/LVI-GC-MS(SIM)) is proposed for trace analysis of six TCAs in urine matrices.

The analytical data shows remarkable performance, indicating it to be a good alternative over other established microextraction techniques.

References:
NEW DONEPEZIL MIMETIC HYBRIDS AS POTENTIAL MULTI-TARGET ANTI-ALZHEIMER’S DISEASE AGENTS

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Introduction

Alzheimer’s Disease (AD)

- AD is a complex neurodegenerative disorder characterized by progressive deterioration in memory, cognition, and behavior.
- Main pathological hallmarks of AD brains: Amyloid plaques; Neurofibrillary tangles; Cholinergic deficit
- Current symptomatic treatment (no cure)
- Inhibitors of AChE; NMDA receptor antagonist
- AD Multifactorial nature- Multi-target approach [1];
- Inhibition of AChE; Inhibition of Aβ aggregation; Control of ROS ; Modulation of metal dyshomeostasis.

Scheme 1. Donepezil (DNP) and design of hybrid DNP mimetics

Aims. To pursue our interest on the engineering of new multitargeting drug candidates [2,3], aimed to combat both the symptoms and the causes of Alzheimer’s disease (AD). Donepezil (DNP) templates (for cholinesterase inhibitory capacity) are hybridized with hydroxymethylbenzimidazole-based units to provide the conjugates with other important pharmacological responses, namely through the inhibition of Aβ aggregation and the control of related features as metal dysregulation of AD patient brains.

Methods. The polyfunctional compounds are firstly designed on the basis of computational simulation and then selected compounds are prepared by standard methods of organic synthesis. The new compounds are evaluated in aqueous solution for their biological activity, namely for the inhibition of AChE and Aβ aggregation, under the effect of metal ions, using standard spectroscopic techniques. Effects of these compounds in cell viability and neuroprotection are also assessed in neuroblastoma cells after Aβ(1-42) induced toxicity.

Fig. 1. Docking models of ligands superimposed with DNP (IOCDC, green) within the AChE active site [2,3].

Inhibition of Aβ aggregation

Scheme 2. Structural parameters of the hybrid DNP mimetics: Benzylpiperazine-Benzimidazole (PP-BIM) and Benzylpiperazine-Benzimidazole (PZ-BIM). Calculated log P and log BB (iDProp prog.)

Funding:
This work was supported by FCT/MEC financing CQEE (FCT UID/QUI/0100/2019) from IST-ID and also Erasmus Programs (F.R., R.J.).

References:
[4] RCSB Protein Data Bank (PDB, entry 1DGC).

Conclusions

- The compounds present a moderate-high (11-75%) Aβ-aggregation inhibition with apparent dependence both on the intercalating ability of the compound inside the fibrils and on its copper chelating capacity due to the BIM chelating moiety. For the benzylpiperazine-bonding hybrids (PP-BIM), the positional isomerization in the BIM moiety is not determinant for activity, in opposition to the PZ moiety for which the para position is favored. Regarding the benzylimidazole hybrids (PZ-BIM), there is dependence on the BIM substituent with best activity for the nitro-derivative (less lipophilic).

- The AChE inhibition showed activity in low micromolar range, evidencing some structure-activity relationships, mostly supported by docking simulations. The PP-BIM hybrids present better activity than the corresponding PZ-BIM analogues (1/2, 6/8), the positional isomers of PP-BIM hybrids evidenced activity increase with the distance between amine group of piperidine (1, 3, 4) and also of benzimidazole (3, 5]) and the corresponding carbon of derivatization. Substitution on the BIM unit affects the AChE inhibitory activity; the best (+) effects were found for the fluoro-derivatives (4/1 and 9/2), while a (-) effect was observed for the nitro-derivative (7/2).

- The neuroprotective effects were accomplished for a selection of PP-BIMs (3,4) by preventing Aβ-induced cell toxicity, but the cell protection from Aβ-induced oxidative stress was not evidenced (preliminary results).
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SYNTHESIS AND CHARACTERIZATION OF LOW-COST ADSORBENT MATERIALS FROM GLYCEROL

INTRODUCTION

In the search for alternative fuels to petroleum, biodiesel has gained expression in the market and its production has been increasing steadily. Sustainable biodiesel production requires optimization of the production process and drastic increase in the utilization of glycerol, the principal by-product of the process. With the introduction of large volumes of glycerol coming from biodiesel production, it is imperative to find new applications for this chemical, otherwise the economic feasibility of the biodiesel as a renewable fuel can be impaired. Recent studies report the use of glycerol for the production of char.4,5

This present study focuses on the characterization of glycerol-based activated carbons via a two-step: (1) procedure involving carbonization and (2) chemical activation or thermal activation.

Chemical activation of acid carbonized glycerol allowed the preparation of an activated carbon with a developed micropore network. Regardless the temperature used, thermal activation promoted a smaller porosity development, composed practically only by micropores. SEM micrographs show that the materials are constituted by interconnected spheres with diameters of ∼1-2 μm. The FTIR and pHZC data reveal the acidic nature of the surface functional groups, which is in line with the high amounts of sulfur and oxygen detected in the elemental analysis.

Considering all the above facts, glycerol-derived activated carbons will be tested as adsorbent materials. Moreover, the high acidity of the samples allows us to foresee their use as catalysts.

REFERENCES

In-situ electrochemical and fiber-optic micro-sensors: traditional and novel applications, limitations, challenges

Maryna Taryba, Alberto Adán-Más, M.F. Montemor

Equipment:

- a) vibrating probe;
- b) 2D vibrating linkage (preamplifier);
- c) 3D computerized stepper-motors system;
- d) movable holder;
- e) video camera, with a long-distance lens, providing magnification up to 400 times;
- f) two pin set of reference electrode and ground electrode;
- g) 3D micro-manipulator, used for calibration or probe positioning in advanced multi-electrode setup;
- h) SVET preamplifier

Advanced sensors combinations, examples:

Assembled cell for triple simultaneous measurements:

Tools/Techniques:

SVET measures the potential difference between extreme points of the probe vibration. The measured potential difference is being converted into current density using cedvictivity/resistivity of the immersion solution. The probe is vibrating in the vertical (Z) and horizontal (X) planes. →Current density distribution is registered.

SIET: Potentiometry with microprobes. Glass-capillary ion-selective microelectrode are prepared using the silanized capillaries that are tip-filled with a selective membrane and back-filled with an inner reference solution (membrane length ~ 60 μm). →ion (e.g. pH) distribution is registered.

SPET: Various sensors can be used as micro-amperometric probes:
(1) Pt disk probes (d=5-100) μm. Disadvantage - fast fouling
(2) Boron doped nanocrystalline diamond (B-NCD) amperometric microsensor (radius > 100 nm) [1]. Calibration of microsensor is recorded using N2 and air saturated solutions. →Dissolved oxygen distribution is registered.

Energy storage

pNa measurements during charge-discharge of mixed Ni-Co hydroxide electrodes in 0.05M Na2SO4

Correlation between pH, pNa and dissolved O2 distributions and cyclic voltammetry provided relevant information concerning the charge-discharge reaction mechanism. Results reinforce the solid-state proton diffusion model and confirms the effect of oxygen evolution reaction as parasitic reaction [2].

Examples

Corrosion studies

Simultaneous current density, pH and dissolved oxygen monitoring of the epoxy-coated steel substrate with 2 artificial defects during 24h of non-stop immersion in 0.05M

DO: distinguishing cathodic activity and flow of negatively charged species from the coating in absence of cathodic activity

Conclusions

- Micro-scale processes of different nature can be assessed employing micro-sensors with various principles of detection.
- Quasi-simultaneous data acquisition allows for obtaining highly reliable correlations
- Complementation of the results obtained using localized techniques with physico-chemical analysis can provides additional information for confirmation and clarification of the proposed clues (mechanisms, reactions involved, corrosion products formed)
- The process of oxygen reduction can show important signs of degradation for both, energy storage and corrosion science applications. Such signs sometimes are not detectable by other techniques.
- Localized electrochemical and fiber-optic micro-sensors successfully demonstrate their efficiency for already known applications (i.e. corrosion science, physiology) and for integration into new challenging fields with extreme importance for modern society (e.g. energy storage)
Natural Deep Eutectic Mixtures-Based Aqueous Biphasic Systems For Extraction Of Virus-Like Particles

Mateusz Marchel, Ana S. Coroadinha, Isabel M. Marrucho

Introduction

Due to their unique properties, virus-like particles (VLPs) have been portrayed as a promising high-value biopharmaceutical in VLP-based vaccination and cancer therapy. Nevertheless, due to the limited physical and economical capabilities of the current downstream processing of VLPs, their production is still difficult and seen as major problem that needs to be tackled.

Aqueous biphasic systems (ABS) have shown to be an alternative operation in purification of various biomolecules, because they are versatile, biocompatible and easy to scale-up. Especially the introduction of adjuvants, such as ionic liquids (ILs), in ABS implementation showed that it is possible to fine tune the properties of the aqueous phases in equilibrium, offering new separation schemes characterized by high effectiveness, high yield and high purity degree [1]. In the last years, deep eutectic solvents (DES) have emerged and gained a lot of attention in several fields and different applications, including the ABS implementation, where they have been proposed as a cheaper, versatile and very often more readily biodegradable substitute of ILs [2].

Results

Phase diagrams of PPG 425 + carbohydrate or DES + H₂O

T=25°C

T=37°C

Sucrose > Glu:Suc = Fru:Suc > Glu:Fru:Suc > Glucose > Glu:Fru = Fructose

Decreasing trend order of the ability of studied carbohydrates and DES to promote a biphasic system

Thermoreversible ABS

Increase in binodal phase diagram with increase of temperature

Representation of the binodal curves as a function of carbohydrate concentration

Decrease of concentrations of carbohydrates needed for the liquid-liquid demixing

Cytotoxicity profile:

- Good biocompatibility of all tested carbohydrates and DES for HEK 293 cells
- Low concentrations of fructose and Fru:Suc increase cell viability in HEK 293 cells

Conclusions

- Novel thermoreversible ABS composed of carbohydrates and its deep eutectic mixtures were developed and characterized
- The use of DES leads to a decrease of concentrations of compounds needed for the liquid-liquid demixing, when compared with systems composed by only one of the DES components
- The studied carbohydrates and DES show good biocompatibility for the cells and therefore their use in ABS implementation for extraction of VLPs is very promising
Ionic Liquids Incorporating Nitrogen Units as Novel Lubricants or Oil Additives

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Introduction
Lubrication of microelectromechanical and nanomechanical systems are in high demand since the rise of the development of this kind of materials and the need to improve its efficiency. [1] Ionic Liquids (ILs) have been studied for this purpose in Si substrates.

In the present study, the ILs [(C4SO4H)MIM][TfO][2], [C2MIM][S-CSA], [C2MIM][R-CSA], [C2-3-pic][MeSO4], [C2MIM][TfO][3], and [C2MIM][EtSO4][4] were characterized as 2% wt additives to commercial lubricant PEG 200 while the ILs [C2-3-pic][MeSO4] and [C2-3-pic][EtSO4][4] were characterized as pure lubricants. Also, the application of Deep Eutectic Solvents (DES as formed by combination of Hydrogen bond donors and acceptors) as lubricants have been tested (DES based on [C2-3-pic][MeSO4]:PEG 200 (1:4) and [C2MIM][S-CSA]: PEG 200 (1:4)).

Synthesis of ILs

Contact Angles and Viscosity

- Higher Yields and Purity levels
- NMR and FTIR Characterization
- Sustainable Synthesis

ANIONS
[C2MIM][EtSO4]
[C2MIM][MeSO4]
[C2MIM][CSA]
[C2MIM][TfO]

CATIONS
\[\text{R}1=\text{Me}:[\text{C}1-3-\text{pic}];\
\[\text{R}1=\text{Et}:[\text{C}2-3-\text{pic}];\
\[\text{R}1=\text{Me}:[\text{S}3-\text{pic}];\
\[\text{R}1=\text{Et}:[\text{S}3-\text{pic}];\
\[\text{R}1=\text{Et}:[\text{TfO}];

Tribological tests
Friction coefficient (CoF) as a function of sliding velocity

Pure ILs
Pure DES
ILs AS ADDITIVES

All lubricants led to similar or smaller CoFs than PEG 200, whose values are between 0.15 and 0.26.
The CoF values of the ILs based on the cation ([C2MIM][CSA]) and similar, independently of the anion.
Furthermore, the similar CoF values of 0.11-0.08 obtained with pure [C2-3-pic][EtSO4][4] and [C2-3-pic][MeSO4] demonstrate that increasing the length of the alkyl group in the cation and the anion had no significant effect. The CoF lubricant [C2-3-pic][MeSO4], in its pure and additive 2% form, are similar.
The DES showed very good results, with a CoF of 0.11-0.05.

Legend 1 - PEG; 2:[S] [C2MIM] [CSA]%; 3:[R] [C2MIM] [CSA]%; 4:[C2-3-
Bu][MeSO4]%; 5:[C2-3-pic][MeSO4]%; 6:[C2MIM][CSA]; 7:[C2-
MIM][TfO]%; 8:[C2MIM][EtSO4]%; 9:[C2MIM][EtSO4]; 10:[S3MIM][CSA];
PENG 200; 11:[C2-3-pic][MeSO4]; PEG 200

Conclusions
✓ Novel RTILs based on pyridinium and methylimidazolium cations have been developed.
✓ In general, ILs additives showed lower or similar contact angles on Si surfaces than PEG (commercial model lubricant) without significant viscosity variation as well as lower CoF values (good lubrication attributed to strong interaction between the IL and the surface).
✓ Pure ILs and DES are effective as lubricants with promising performances.
Characterization and interaction with Albumin of 3-hydroxyl-2-naphthoylhydrazones oxidovanadium(IV) complexes

Nádia Ribeiro, Filipa Ramilo-Gomes, Adelino M. Galvão, Clara Gomes, João Costa Pessoa, Isabel Correia

INTRODUCTION

The use of metallo-drugs has been a subject of interest for several years, especially after the discovery of powerful anti-cancer agents. It is known that metal ions play crucial roles in the living organisms and, therefore, biology has found control mechanisms by developing dedicated biomolecules to transport and store these elements, namely proteins. In the last decades, there was an increasing need for developing techniques and assays that provide insight over the metallo-drugs-proteins relationships, for it is known that this phenomena can help explain experimental results. Biospeciation is an emergent area of research and spectroscopic techniques associated with computational studies are indispensable tools for a bioinorganic chemist.

In this work we have synthesized and characterized three ligands and their oxidovanadium(IV) complexes, as well as several spectroscopic experiments which provided us with an overview of how they interact with albumins. Computational docking studies were used to validate the experimental results. Aroylhydrazones have already proven their value on the pharmaceutical application, as well as vanadium compounds and therefore were chosen for biological evaluation.

SYNTHESIS AND CHARACTERIZATION

Scheme 1 – Synthetic pathway for the ligands and corresponding V\(^{IV}\)/O complexes.

SPECTROSCOPIC TECHNIQUES

Spectroscopic techniques were used to follow the interaction of the compounds with BSA. Far UV-Vis circular dichroism (CD) experiments showed an increase in the α-helix content of BSA, due to H-bonding interactions of BSA with the free hydroxy groups of the compounds; UV-Vis absorption revealed strong interaction with the protein, mainly affecting the aromatic amino-acid residues. Fluorescence quenching experiments also revealed the interaction of the compounds within the hydrophobic binding site I where Trp213 is located.

Figure 1 – First derivative X-band EPR spectra of the V\(^{IV}\)/O complexes measured at ca. 100 K in DME: Concentration ca. 3 mM.

Figure 2 – DFT optimized structures of H\(^{L}\)/I and its V\(^{IV}\)/O complex based on the obtained structure for the ligand using single crystal X-ray diffraction.

DOCKING STUDIES

Figure 6 – Superimposed chains of Bovine Serum Albumin and Human Serum Albumin. BSA (PDB-ID:4JK4-A) is represented in green and HSA (PDB-ID:3LU6-A) represented in blue. Zoom of Binding site I of sub-domain IIA for BSA (green) and HSA (blue), superimposed. The amino acids represented in sticks are the most relevant for interactions with the ligands.

Figure 7 – A. Proposed interaction of VO[L\(^{2+}\)] inside the pocket of BSA (PDB-ID: 4JK4). B. Proposed binding mode of VO[L\(^{2+}\)] with HSA (PDB-ID: 3LU6).

Figure 8 – Docking binding modes for HL\(^{2-}\) and HL\(^{2+}\) with BSA (PDB-ID:4JK4) where a stacking with Trp213 is observed. Similar results were obtained for HL\(^{2+}\).

Figure 9 – Docking binding modes for HL\(^{2-}\) and HL\(^{2+}\) with HSA (PDB-ID: 3LU6) where a stacking with Trp214 is observed. Similar results were obtained for HL\(^{2+}\).

CONCLUSION

Three new V\(^{IV}\)/O complexes were prepared from naphthophthalazones ligand precursors with a ML\(_2\) stoichiometry, all presenting a distorted square pyramidal geometry, also predicted by DFT theoretical calculations. Spectroscopic studies conducted with bovine serum albumin showed strong interactions with all compounds, resulting in high conditional binding constants, an increase of the α-helix content of the protein and aromatic amino-acid residues exposure, also corroborated by molecular docking studies for both bovine and human serum albumins.
Exploring the catalytic behavior of hierarchical BEA zeolite in Friedel-Crafts Acylations

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Introduction

Friedel-Crafts acylation is an organic synthesis widely used reaction to acylate compounds. However, this reaction requires, in general, the use of non-reusable and environmentally harmful catalysts. In the last 20 years several studies have been reported in which zeolites replace classical catalysts, making it easier the regeneration and separation processes, while leading to less toxic and corrosive residues.

In the sequence of a previous work, we present here some preliminary results of the systematic study of the catalytic behavior of hierarchical BEA zeolite (Fig. 1), modified by alkaline treatment followed by acid leaching, in Friedel-Crafts acylations using environmentally friendly reaction conditions.

Methodology

Substrates (Fig. 2) (0.0105 mol) and acetic anhydride (0.0529 mol) were mixed and subsequently a zeolite sample (150 mg) was added.

The mixture was stirred and heated at 60 °C or 120°C on a heating and stirring plate (Fig. 3).

The samples were removed using a hypodermic syringe and filtered using a Millipore Swinnex to separate the catalyst from the remaining reaction mixture.

The reaction progress was analyzed by gas chromatography on a Perkin Elmer GC, equipped with a DB-5MS capillary column and a flame ionization detector (Fig. 4).

Results and Discussion

Figure 1

Equation 1

Langmuir-Hinshelwood simplified model equation

\[
\text{Rate} \approx k \frac{[A][S]}{[A]+[S]+K_p[P]^2} 
\]

\[ [A] \text{- concentrations of acetic anhydride} \]
\[ [S] \text{- concentrations of substrate} \]
\[ [P] \text{- concentrations of acylated product} \]
\[ k \text{- rate constant} \]
\[ K_p \text{- ratio between the adsorption equilibrium constants.} \]

The simplified model (Eq. 1) was applied to all kinetic data (Fig. 5) and results are summarized in Table 1.

- In the case of furan, the increase in temperature leads to a significant increase in the rate constant. At 60 °C, the rate constant remains approximately unchanged when the zeolite suffers only desilication (BEA_D) but shows a major increase upon acid treatment (BEA_D_AT).
- On the other hand, with benzofuran the acylation rate constant, even after desilication and acid treatment at 60 °C, is rather low, which is probably related with its chemical structure (bigger size and fewer acylation positions). However, when the temperature is doubled, a 30-fold increase in the rate constant is observed.
- As regards to pyrrole and indole, additional experiments are needed to compare the substrates’ behavior under different zeolite treatment conditions. However, indole shows already a very small reactivity at 60 °C which might render further analysis pointless.
- The analysis of the equilibrium constants shows that when the zeolite suffers desilication, \( K_p \) increases significantly, suggesting an accumulation of products inside the pores, but this result is much less important or even slightly reversed upon acid leaching due to pores obstruction by Si debris.
- As a final note, one can say that, in the case of furan, desilication + acid treatment increase both rate and equilibrium constants, whereas for benzofuran this effect is only observed in \( K_p \).

Table 1

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Substrate</th>
<th>Temp. (°C)</th>
<th>k (mmol min⁻¹ g⁻¹)</th>
<th>( K_p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEA</td>
<td>Furan</td>
<td>60</td>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>BEA</td>
<td>Furan</td>
<td>120</td>
<td>132</td>
<td>2</td>
</tr>
<tr>
<td>BEA_D</td>
<td>Furan</td>
<td>60</td>
<td>58</td>
<td>12</td>
</tr>
<tr>
<td>BEA_D_AT</td>
<td>Furan</td>
<td>60</td>
<td>164</td>
<td>14</td>
</tr>
<tr>
<td>BEA</td>
<td>Pyrrole</td>
<td>60</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>BEA</td>
<td>BenzoFuran</td>
<td>60</td>
<td>1.34</td>
<td>26</td>
</tr>
<tr>
<td>BEA</td>
<td>BenzoFuran</td>
<td>120</td>
<td>39</td>
<td>53</td>
</tr>
<tr>
<td>BEA_D</td>
<td>BenzoFuran</td>
<td>60</td>
<td>0.31</td>
<td>240</td>
</tr>
<tr>
<td>BEA_D_AT</td>
<td>BenzoFuran</td>
<td>60</td>
<td>1.15</td>
<td>201</td>
</tr>
<tr>
<td>BEA</td>
<td>Indole</td>
<td>60</td>
<td>Conversion &lt; 1.5%</td>
<td></td>
</tr>
</tbody>
</table>

BEA : Commercial Beta zeolite ; BEA_D : NaOH desilicated zeolite ; BEA_D_AT : NaOH desilicated zeolite + acid treatment.

References:
INTRODUCTION

In this work different electrochemical biosensors, with potentiometric and conductometric transductions, were developed aiming at the determination of toxic amides, such as acrylamide and formamide, in foodstuff [1] as well as in drinking water and wastewater [2]. The biological recognition element consisted of whole cells of Pseudomonas aeruginosa containing intracellular amylace (EC 3.5.1.4) activity. The biosensors’ detection mechanism relied on the monitoring of the potential difference or conductivity changes due to the formation of ammonium and hydroxide ions, resulting from acrylamide hydrolysis catalyzed by amylace, either using an ammonium ion selective electrode, or several interdigital conductometric devices developed by our group. These interdigital devices were constructed with different designs and electrode materials, namely graphite, silver, aluminum and gold. The electrodes were deposited by inkjet printing or from metallic vapor consisting of different interdigital fingers and relative distance, thus resulting in different sensitive areas (0.1 ± 0.01 cm², 0.16 ± 0.17 cm² and 0.21 cm²). One of the most important aspects regarding the development and assembly of a biosensor, relies on the procedure and materials used for the immobilization of the biological recognition element or bioreceptor. An adequate immobilization of the biological material may have a crucial impact on the overall analytical performance of the biosensor [3-5]. In the present study, the biosensor was immobilized on the surface of several types of polymeric membranes, such as polyethersulphone, polycarbonate, nylon, polyvinylidene fluoride, nitrocellulose, cellulose acetate and biocellulose, using glutaraldehyde as a crosslinking agent or physically confined. As an alternative to the use of polymeric membranes, several biosensor immobilization matrices were tested, based on natural polymers, such as gelatin and agarose, crosslinking agents, such as glutaraldehyde and bovine serum albumin, charge exclusion polymers, such as nafion and encapsulation media such as inorganic and organic sol-gel. Several figures of merit as well as other biosensors performance characteristics arising from these several immobilization procedures were evaluated.

Comparative results

TABLE 1: Preliminary evaluation of the different membranes

<table>
<thead>
<tr>
<th>Membrane</th>
<th>Incubation time (min)</th>
<th>Attachment to the transducer (M)</th>
<th>Typical response (mV)</th>
<th>Membrane regeneration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyethersulphone</td>
<td>30 min</td>
<td>suitable</td>
<td>120 – 140</td>
<td>45 min</td>
</tr>
<tr>
<td>Nylon</td>
<td>30 min</td>
<td>suitable</td>
<td>80 – 100</td>
<td>50 min</td>
</tr>
<tr>
<td>Polyvinylidene fluoride</td>
<td>&gt; 60 min</td>
<td>not suitable</td>
<td>n.d</td>
<td>n.d</td>
</tr>
<tr>
<td>Nitrocellulose</td>
<td>&gt; 60 min</td>
<td>not suitable</td>
<td>n.d</td>
<td>n.d</td>
</tr>
<tr>
<td>Polycarbonate</td>
<td>&gt; 60 min</td>
<td>suitable</td>
<td>100 – 120</td>
<td>25</td>
</tr>
<tr>
<td>Cellulose Acetate</td>
<td>&gt; 60 min</td>
<td>not suitable</td>
<td>n.d</td>
<td>n.d</td>
</tr>
<tr>
<td>Biocellulose</td>
<td>*</td>
<td>suitable</td>
<td>80 – 90</td>
<td>10 min</td>
</tr>
</tbody>
</table>

* Biocellulose membrane preparation was approx. 2 days corresponding to the cells growth period; n.d. = not determined.

Analytical performance

<table>
<thead>
<tr>
<th>Figures of merit</th>
<th>Polyethersulphone membrane</th>
<th>Polycarbonate membrane</th>
<th>Biocellulose membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear response interval (M)</td>
<td>4.89 ± 1.10E-4</td>
<td>4.63 ± 1.10E-4</td>
<td>5.10 ± 1.10E-4</td>
</tr>
<tr>
<td>Sensitivity (mV/mM)</td>
<td>46.04 ± 1.10E-4</td>
<td>48.04 ± 1.10E-4</td>
<td>38.05 ± 1.10E-4</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.988</td>
<td>0.988</td>
<td>0.988</td>
</tr>
<tr>
<td>Typical response (mV)</td>
<td>120 – 140</td>
<td>120 – 120</td>
<td>60 – 80</td>
</tr>
<tr>
<td>Limit of detection (M)</td>
<td>4.90 × 10⁻⁵</td>
<td>2.29 × 10⁻⁵</td>
<td>5.28 × 10⁻⁵</td>
</tr>
<tr>
<td>Limit of quantification (M)</td>
<td>5.60 × 10⁻⁴</td>
<td>4.03 × 10⁻⁴</td>
<td>1.05 × 10⁻³</td>
</tr>
<tr>
<td>Immobilization regeneration time (min)</td>
<td>45</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>Response time (min)</td>
<td>3.46 ± 0.2</td>
<td>3.36 ± 0.2</td>
<td>3.06 ± 0.2</td>
</tr>
<tr>
<td>Incubation time (min)</td>
<td>30</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>Half-life time (days)</td>
<td>30</td>
<td>14</td>
<td>12</td>
</tr>
</tbody>
</table>

In what the alternative immobilization materials concerns, the use of glutaraldehyde as an immobilization matrix exhibited the most suitable results. Almost all the materials were able to produce biosensors with significant physical consistency. However only glutaraldehyde and TEOs resisted well to solution agitation, where the former exhibited a higher response and a significant reduction in the biosensor regeneration time. When comparing materials it can be seen that the use glutaraldehyde as an immobilization matrix allowed the development of biosensors with better figures of merit, namely sensitivity, limits of detection and quantification and half-life time, thus increasing its reusability.

Polymeric membranes

In fact, the biosensor assembled with the polycarbonate membrane exhibited lower limits of detection and quantification and higher sensitivity; however the device using polyethersulphone membrane showed a higher response, a lower incubation time and a longer period of reusability, thus allowing a reduction in costs, bearing in mind effective savings resulting from the reduction of cells suspension and polymeric membrane utilization.

REFERENCES:
[3] In this work different electrochemical biosensors, with potentiometric and conductometric transductions, were developed aiming at the determination of toxic amides, such as acrylamide and formamide, in foodstuff [2]. The biological recognition element consisted of whole cells of Pseudomonas aeruginosa containing intracellular amylace (EC 3.5.1.4) activity. The biosensors’ detection mechanism relied on the monitoring of the potential difference or conductivity changes due to the formation of ammonium and hydroxide ions, resulting from acrylamide hydrolysis catalyzed by amylace, either using an ammonium ion selective electrode, or several interdigital conductometric devices developed by our group. These interdigital devices were constructed with different designs and electrode materials, namely graphite, silver, aluminum and gold. The electrodes were deposited by inkjet printing or from metallic vapor consisting of different interdigital fingers and relative distance, thus resulting in different sensitive areas (0.1 ± 0.01 cm², 0.16 ± 0.17 cm² and 0.21 cm²). One of the most important aspects regarding the development and assembly of a biosensor, relies on the procedure and materials used for the immobilization of the biological recognition element or bioreceptor. An adequate immobilization of the biological material may have a crucial impact on the overall analytical performance of the biosensor [3-5]. In the present study, the biosensor was immobilized on the surface of several types of polymeric membranes, such as polyethersulphone, polycarbonate, nylon, polyvinylidene fluoride, nitrocellulose, cellulose acetate and biocellulose, using glutaraldehyde as a crosslinking agent or physically confined. As an alternative to the use of polymeric membranes, several biosensor immobilization matrices were tested, based on natural polymers, such as gelatin and agarose, crosslinking agents, such as glutaraldehyde and bovine serum albumin, charge exclusion polymers, such as nafion and encapsulation media such as inorganic and organic sol-gel. Several figures of merit as well as other biosensors performance characteristics arising from these several immobilization procedures were evaluated.
On the preparation of metallic Co foams based nanocomposites as electrodes for energy storage devices

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Obtention of Co foams

Highly porous Co nanofoams were prepared by using the Dynamic Hydrogen Bubbling Template (DHBT) method. This process is based on the application of high negative potentials to simultaneously propitiate both hydrogen evolution and the reduction of Co²⁺ ions contained in the electrolyte. Metallic cobalt deposition is influenced by hydrogen release, which acts as a template, leading to a porous material that is controlled by the bubbles’ shape and pathway.

<table>
<thead>
<tr>
<th>Electrolyte: CoCl₂ 0.1 M NH₄Cl 2 M</th>
<th>Counter electrode: Pt</th>
<th>Applied current = -1.8 A cm⁻²</th>
</tr>
</thead>
</table>

![Stainless steel (SS) substrate](image)

Number of pores | Average pore area / µm² | Median pore area / µm² |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3617</td>
<td>229.55</td>
<td>188.16</td>
</tr>
</tbody>
</table>

Functionalization of foams: NiCo(OH)ₓ@Co

Co nanofoams were used as improved substrates for the deposition of Ni-Co hydroxide, used as positive electrode for energy storage devices. To prove the enhancement of its electrochemical response, a thin-film of the same material was directly deposited onto stainless steel and is electrochemical response evaluated in KOH 1M.

<table>
<thead>
<tr>
<th>Electrolyte: Co(NO₃)₂ 0.1 M Ni(NO₃)₂ 0.1 M</th>
<th>Counter electrode: Pt</th>
<th>Pulsed deposition: -1.1V/0V for 1s/1s during 200 cycles</th>
</tr>
</thead>
</table>

Ni-Co(OH)ₓ thin-films have been electrodeposited on top of Co foams prepared by using DHBT method. The introduction of a cobalt-based porous structure leads to a 22% improvement of capacitance when compared to the analogous thin-film obtained under the same conditions. This result can be directly correlated to a larger active area caused by the porous microstructure.

Conclusion

| Co foam: | 21 mA·h·g⁻¹ |

<table>
<thead>
<tr>
<th>Ni-Co(OH)ₓ thin-film:</th>
<th>204 mA·h·g⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cycles:</td>
<td>1000</td>
</tr>
<tr>
<td>Capacitance:</td>
<td>56.8%</td>
</tr>
</tbody>
</table>

References:
Inducing the activity of NK cells with NKp30 small organic ligands

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Centro de Química Estrutural – Instituto Superior Técnico
iMed.UL Instituto de Investigação do Medicamento – Faculdade de Farmácia

NATURAL KILLER CELLS AND IMMUNOSURVEILANCE

Natural killer (NK) cells are a type of cytotoxic lymphocyte critical to the innate immune system. NK cells provide rapid responses to viral-infected cells and respond to tumor formation as they can kill tumor cells without previous sensitization.

NK-mediated cancer immunosurveillance is prompted by the recognition of surface ligands on tumor cells that trigger the activation of cytotoxic responses. In humans, NKp30, NKp44, and NKp46 are major activating NK receptors.

Amongst the known natural cytotoxicity receptors (NCRs), NKp30 is the one for which a ligand (B7-H6) has been identified and whose structure has been resolved in both free and bound forms. B7-H6 is selectively expressed on tumor cells and its interaction with NKp30 results in NK cell activation.

The comparison between the two 3D structures revealed important conformational changes that may be a key-factor for the NK-response activation by B7-H6.

However, tumor cells employ many strategies to evade immunosurveillance by NK cells through over-expression of histocompatibility receptors or by suppressing the expression of NK-activation receptors, masking the malignant cells.

By building an artificial NK-activation ligand it should be possible to induce the cytotoxic activity of these cells against a desired target.

A combined computational docking and molecular dynamics approach was used to screen a wide library of ligands to find the ones establishing stronger interactions with the NKp30 ligand bay in its bound form (PDB 3PV6).

AutoDock Vina was used in docking routines, using several restriction boxes centered in the ligand bay, to dock ligand structures obtained from ChemBank. The results were filtered, by selection of the best candidates for refining using GROMACS in molecular dynamics simulations. Finally, all the hits were docked against NKp30’s unbound conformation (PDB 3N0), proving the ability of the designed ligands to interact with the native protein.

This yielded a family of ligands for the NKp30 receptor.

SYNTHESIS AND TESTING OF THE ARTIFICIAL NKp30 LIGANDS

Fifteen new molecules were obtained from the same core structure. These were fully characterized by NMR and MS.

Binding affinity towards the NKp30 receptor (recombinant protein) was determined by an MS-based technique. Six of the 10 ligands tested showed positive interaction with the receptor.

The ligation of ligand 05 with the recombinant receptor was confirmed by NMR.

ACTIVATION OF NK CELLS WITH LIGAND 05

Human peripheral blood mononuclear cells (PBMCs) were isolated from 5 healthy donors and exposed for 24h to Ligand 05. Secretion of the cytokines TNF-α and IFN-γ was determined by ELISA.

The capacity of Ligand 05 to induce the cytotoxic responses of NK cells was also probed. A culture of target cells (HepG2 cell line) was exposed to PBMCs isolated from 3 donors in the presence or absence of 10 µM of Ligand 05. After 24h the viability of the target cells was determined.

The cytotoxicity of Ligand 05 was tested in the same target cells (HepG2) and no evidence of cell death was found after 24h of exposure.

CONCLUSIONS

Ligand 05 is a non-toxic potent NKp30 agonist that induces cytotoxic response of NK cells. New experiments are being designed to further characterize the responses elicited by this molecule. Future work will aim at directing the triggered activity towards cancer cells as part of a new therapeutic strategy.
Theoretical Study of Low Temperature Solid-Solid Phase Transitions in 4’-Hydroxyacetophenone

P. Tomaz Melo, C. E. S. Bernardes, M. E. Minas da Piedade
Centro de Química e Bioquímica e Centro de Química Estrutural, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016, Portugal

Funding:
Centro de Química Estrutural is funded by Fundação para a Ciência e Tecnologia – project UID/QUI/00100/2019. This work was supported by Fundação para a Ciência e a Tecnologia (FCT), Portugal through Projects PTDC/QUIOUT/28401/2017(LISBOA-01-0145FEDER-028401) and UID/MULTI/00612/2013. A Post-Doctoral grant from FCT is also gratefully acknowledged by C. E. S. Bernardes (SFRH/BPD/101505/2014).

References:

Scope

Polymorphism, the ability of a substance to crystallize in more than one lattice arrangement, is currently a major concern for the manufacture of organic products, since each crystal form can exhibit significant differences in physicochemical properties (e.g. fusion temperature, solubility/dissolution rate).

4’-Hydroxyacetophenone (HAP; Figure 1) is a compound with significant commercial applications and additional potential end uses. Two polymorphs of HAP (Form I and Form II) have been reported up to now [1].

A new phase transition in both polymorphs at ~79 K was recently identified from adiabatic calorimetry studies [2].

Figure 1. Molecular structure of 4’-Hydroxyacetophenone (HAP)

Results

Figure 2. Single crystal X-ray structures of HAP exhibiting one and two molecules in the unit cell asymmetry unit of HAP in form I and II, respectively.

Figure 3. Resonance vibration frequencies of the crystal simulation box computed for (a) Form I and (b) Form II, as a function of the temperature.

Figure 4. Probability distribution of the HAP dihedral angle O=C‒C‒H as a function of temperature, determined to the different molecules in the asymmetric unit of the two polymorphs of HAP.

Conclusion

• A modulation effect seems to occur in the case of HAP Form II around 60 K (Figure 3).
• The MD simulation results suggest that the experimentally observed phase transition at ~79 K may be related to a variation in the mobility of the HAP methyl group with temperature (Figure 4).
• The activation process for the rotation of the methyl groups is different in both polymorphs, and in the case of form II, is different in the two molecules in the asymmetric unit.
Adaptation to nutrient-limited media remains accurate at the cost of an increased energy dissipation

R. N. Bento, C. E. S. Bernardes, M. E. Minas da Piedade, F. Antunes

Scope

Adaptation is a fundamental biological process by which organisms adjust internal molecular mechanisms to achieve a better fitting to environmental conditions, having implications in health and disease, underlying processes such as acquired resistance to antimicrobials. Recently the existence of a trade-off between the energetic resource usage for adaptation and the speed and accuracy of the adaptive process has been proposed (ESA), supported by the observation that (1) a high energy dissipation is necessary for an accurate and fast adaptation response and (2) when the energy source in the medium decreases, the speed of adaptation of E. coli to a chemical stress also decreases with little effect on the accuracy of adaptation. But while the speed and accuracy of adaptation were experimentally determined, energy dissipation was estimated.

Aim

Aim: Understand how the energy cost of adaptation is affected by nutrient availability.

Approach: Use of microcalorimetry to follow metabolic activity of Saccharomyces cerevisiae (S. cerevisiae) cells in real time during growth in Yeast Petone Dextrose (YPD) and Synthetic Complete (SC) media, which are nutrient rich and poor media, respectively.

Calorimetric data is coupled with results from cell concentration and other auxiliary measurements.

Results

1. Adaptation is faster in the poorer medium, but its accuracy is similar in the poor and rich media

![Graph showing adaptation speed and lag phase duration]

2. Energy dissipation increases to compensate for nutrient limitations in the poor medium

![Graph showing specific power and optical density]

Conclusions

- 60% higher energy dissipation in the nutrient-limited (Synthetic Complete) medium during the lag phase compensates for the nutrient constraint to maintain the adaptation accuracy (measured by the maximal proliferative rate) and increases the adaptation speed (measured by the duration of the lag phase).

- This work provides the experimental evidence necessary to validate the ESA hypothesis.

- The detection of an enhanced energy dissipation is a potential biomarker for metabolic deficiencies.
Emulsions Based on Hydrophobic Eutectic Mixtures

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Introduction
Up until recently, the study of eutectic solvents has been mostly focused on hydrophilic mixtures. However, mixtures composed of hydrophobic components such as terpenes, organic acids, and ammonium salts, among other classes of compounds, have been shown to have eutectic ratios as well, and thus can also be used as solvents. Being hydrophobic, these mixtures present excellent dissolution properties for added value hydrophobic compounds such as pharmaceuticals, for example. Thus, the study and understanding of hydrophobic eutectic solvents surface properties is of utmost importance for these applications.

Surface tension
• Measure of the liquid-air interface energy.
• Typical values for hydrophilic eutectic systems: 40 to 65 mN·m⁻¹
• Values for studied hydrophobic eutectic systems: 20 to 30 mN·m⁻¹
• Linear trend with temperature

Emulsions
Typical case:
• Two unmixable phases
• Addition of surfactant leads to micelle formation
• Micelles dispersed in one of the phases
• Stability controlled by temperature: heat leads to separation.

Ouzo effect¹:
• Uses a third solvent
• Exploits solubility of both phases in the third solvent.
• Three possible stages: solution, emulsion and microemulsion
• Stability controlled by temperature: cold leads to separation.

Conclusion
Hydrophobic eutectic solvents have the potential to be used extraction of pharmaceuticals, drug delivery and cosmetics. In addition to being cheap to prepare, their low surface tension, as well as low viscosity, makes them easy to use in an industrial setting.
Extracting more information from research in chemistry: The multidisciplinary evaluation of data uncertainty

Ricardo Bettencourt da Silva (rjsilva@fc.ul.pt)

All research in chemistry involves comparing and/or reporting qualitative and/or quantitative chemical information. The quality of the research depends on the quality of the information and of their interpretation. The sciences of qualitative and quantitative chemical analysis are Examininology and Metrology in Chemistry, respectively. When small trends or differences of chemical systems need to be distinguished, it is necessary to manage all evaluation steps and effects that affect the result to guarantee information will be fit for the intended use. If qualitative and quantitative information is reported with uncertainty, it can be quantified the probability of their interpretation being correct. For instance, the presence of trace-levels of a compound in a urine sample can be reported with a probability of 99.993 % of being correct and the reduction of a contaminant in the water of a river after improving wastewaters treatment can be determined with a risk of 0.03 % of wrongly concluding that the reduction is meaningful. Our research group have been developing novel strategies for extracting objective and more information from complex and vast chemical systems and is willing to collaborate in new challenges for producing sound chemical information.

We recently developed strategies for evaluating the uncertainty of kinetic constants that quantify the efficiency of photodegradation catalysts, strategies for the objective detection of trends of vast environmental areas, and reliable criteria for identifying trace levels of compounds in complex matrices by GC-MS/MS or LC-MS/MS. All these achievements are supported on publications in the highest impact factors journals.

**Determination of kinetic constants with uncertainty:**

The first assessments of kinetic constants uncertainty were applied to the determination of methylene-blue photodegradation by UV/Vis spectroscopy. Methylene-blue is a frequently used photodegradation marker. This publication aimed at discussing how calibrators quality and the lack of linearity of the instrumental response can affect the uncertainty of kinetic constants quantification. At this moment, a flexible tool for determining the uncertainty of kinetic constants have been developed that can be used regardless of calibrators uncertainty value. Monte Carlo simulations were implemented in a user-friendly spreadsheet to allow the evaluation of kinetic constants uncertainty by non-experts in metrology.

**Determination of environmental pollution trends:**

One of the more demanding challenge in environmental chemistry research is the objective assessment of the status or trends of a vast environmental compartment. Our research group developed an innovative tool for estimating the mean value of a chemical parameter, and the respective uncertainty, in a vast environmental compartment by modelling the available information of the spatial distribution of the parameter. The modelling considers the uncertainty of the GPS coordinates and of the estimated chemical parameter on analysed samples. This modelling allows the optimization and objective determination of small trends of the environmental system.

**Reliable identification of trace-levels of compounds:**

The false identification of trace levels of compounds in complex matrices by low-resolution GC-MS/MS or LC-MS/MS is frequent due to the inadequate interpretation of the analytical data. Our research group develop statistically sound criteria for identifying compounds using these instrumental methods of analysis that proved official doping analysis are affected by high rates of false negative results. That technology can be used in many other research fields.
Conformational Polymorphism in Molecular Organic Crystals: 4’-Hydroxyvalerophenone, as a Case Study

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Scope
• Many compounds can crystallize in more than one solid structure, a phenomenon known as polymorphism.
• Different polymorphs often display different properties (e.g. melting point, solubility), and thus represent a challenge for the production of solid materials with highly reproducible properties.
• Polymorphic studies in families of structurally related molecules can offer insights into how small variations in the molecular structure can lead to alterations in the packing architecture and relative stability of different crystals.
• In this work, the polymorphic behavior of 4’-hydroxyvalerophenone (HVP, Figure 1) was analyzed. This molecule is part of a family of compounds with the general formula (HOC₆H₅C(O)R, with R=H, n-alkyl), and where conformational and packing polymorphism have previously been identified [1,2].

Table 1. Crystal data for the two polymorphic forms of HVP.

<table>
<thead>
<tr>
<th></th>
<th>Form I</th>
<th>Form II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Space group</td>
<td>P2₁/c</td>
<td>C2/c</td>
</tr>
<tr>
<td>Crystal System</td>
<td>monoclinic</td>
<td>monoclinic</td>
</tr>
<tr>
<td>a (Å)</td>
<td>9.990(2)</td>
<td>8.4860(16)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>10.454(2)</td>
<td>14.976(3)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>9.882(2)</td>
<td>12.045(13)</td>
</tr>
<tr>
<td>β (°)</td>
<td>107.46(3)</td>
<td>111.054(13)</td>
</tr>
<tr>
<td>Z/Z</td>
<td>4/1</td>
<td>8/1</td>
</tr>
<tr>
<td>ρ (g·cm⁻³)</td>
<td>1.202</td>
<td>1.145</td>
</tr>
</tbody>
</table>

Figure 2. Crystal structures of HVP Forms I and II. Molecular chains (above) and the crystal packing (below).

Figure 3. Differential scanning calorimetry (DSC) thermogram of HVP Form I. Temperature program: cooling to 153 K, heating to 453 K (black line), cooling to 212 K, heating to 453 K (red line). The heating/cooling runs were conducted at 10 K·min⁻¹.

Conclusions:
The crystal structure of a new polymorph of HVP was determined, and compared with the previously published form [3]. The molecular conformation was different in the two structures (Z in Form I and E in Form II, Figure 2), revealing a case of conformational polymorphism in this compound.
The melting temperature and enthalpy of fusion determined for Form II ($T_{m}=324.3±0.2$K, $Δ_H^{m}=18.14±0.18$ kJ·mol⁻¹), was significantly lower than what was observed for Form I ($T_{m}=335.6±0.7$K, $Δ_H^{m}=26.67±0.04$ kJ·mol⁻¹), as seen in Figure 3, while changes to the space group, cell parameters and density of the crystals were also noted between the two polymorphs (Table 1). The decrease in density and the DSC results suggest that Form II is less stable than Form I, and that the system is monotropic.
Synthesis of half-sandwich ruthenocarboran complexes incorporating N-donor ligands as eminent candidates for Boron Neutron Capture Therapy

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INTRODUCTION

One of our newer approaches in the design of novel antitumor agents involves the replacement of the monoanionic cyclopentadienyl ([η⁵-C₅H₅]⁻) moiety by a highly boronated dianionic nido-carborane cluster ([C₅B₆H₉]²⁻) in order to amplify the action of our ruthenium-based complexes (Figure 1). This rationale modification would amplify the antitumoral potential of our Ru compounds since a combinatorial therapy can be envisaged this way (traditional chemotherapy and Boron Neutron Capture Therapy, BNCT).

Therefore, in this communication, we reveal the synthesis and characterization of a new family of ruthenocarboranes complexes of general formula \([3\text{-}C\text{O}-3,3\text{-}(\text{OH}_2)-4,4\text{-R}_2-2,2\text{-}(\text{NC}_3\text{H}_5)_3\text{-closo}-3,2,1\text{-Ru}_2\text{B}_6\text{H}_{14}\text{-}3\text{-}2\text{-}3\text{-}3\text{-}3\text{-}\text{Ru}_1\text{B}_6\text{H}_{14}\text{]}\) comprising 2,2'-bipyridyl ligands. All complexes were screened against the highly metastatic human melanoma cell line (A375) and human primary glioblastoma cell line (U87) and the irradiation reaction of the boron cluster conjugate is currently under evaluation.

Conclusions

- Three new ruthenocarboranes complexes with bipyridyl ligands were successfully synthesized and proposed for BNCT;
- Ru1-Ru3 were the first complexes of Ru-carboranyl-bipyridyl conjugates that have been biologically evaluated. All compounds showed promising cytotoxic profile against the A375 and U87 cancer cell lines for BNCT reaction;
- The irradiation with neutrons of Ru1-Ru3 is currently ongoing to further explore the potential of these compounds in BNCT.

SYNTHESIS AND STRUCTURE

Figure 1. Scheme for Boron Neutron Capture Therapy (BNCT). BNCT is based on non-reactive isotope ¹⁰B atom that absorbs low energy neutrons and disintegrates into a particle and ⁷Li nucleus causing nonreparable damages to the cell where they were generated while sparing the healthy tissues.

Figure 2. ¹H and ¹³B(¹H) NMR spectrum of Ru1 in acetone-d₆.

Figure 3. Absorption spectrum of Ru1 in CH₂Cl₂ (−−−) and DMSO (−−−).

Figure 4. Cyclic voltammogram of Ru1 in CH₂Cl₂ at scan rate of 200 mV s⁻¹.

Figure 5. IC₅₀ values (half-inhibitory concentrations) of Ru1-Ru3 against human melanoma cell line (A375) and human primary glioblastoma cell line (U87) within a period of exposure of 24 h (left) and cellular distribution of Ru1-Ru3 in A375 cells determined by ICP-MS analysis (right).

Ru1 and Ru3 show low cytotoxic activity in both cancer cell lines studied;
Ru2 presents moderate cytotoxic activity against highly aggressive A375 and U87 cancer cell lines;
Different mechanisms of action for Ru1 and Ru3 vs Ru2, leading to different IC₅₀ values and intracellular distribution.
Exploring Solvent Properties of Hydrophobic Eutectic Mixtures

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Introduction

Kamlet-Taft parameters (α, β, and π*) which are a measure of solute-solvent interactions, are usually determined through solvatochromic probes (A to E – Fig. 1) resorting to some known mathematical relations – Fig. 2. In some cases, however, probe A characteristic band, which allows the calculation of α, can appear partially or fully masked by other bands, making its determination by UV-Vis hard or even impossible. On the other hand, it has been shown that rate constant for tertiary alkyl halides solvolyses correlate well with Kamlet-Taft parameters1, in pure organic solvents. For the solvolysis of t-BuBr, the correlation is as follows:

$$\log k = 6.91\pi^* + 3.39\alpha + 0.67\beta - 12.48$$

Thus, by using this correlation, it is possible to extract α for a given system if β, π* and k are known.

In recent years, there has been a growing interest in hydrophobic eutectic mixtures that can be used in various water sensitive applications2. Yet, for these mixtures it is often difficult to determine α by spectrophotometry. In this work, a kinetic-based approach was used to compute α for DL-menthol:octanoic acid and octanoic acid:dodecanoic acid eutectic mixtures - Table 1.

![Solvatochromic probes used](image1)

**Figure 1** Solvatochromic probes used

**Table 1** Composition of the studied eutectic mixtures

<table>
<thead>
<tr>
<th>Systems</th>
<th>HBA</th>
<th>HBD</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES1</td>
<td>DL-Menthol</td>
<td>Octanoic</td>
<td>1:1</td>
</tr>
<tr>
<td>DES2</td>
<td>Octanoic</td>
<td>Dodecanoic</td>
<td>3:1</td>
</tr>
</tbody>
</table>

**Table 2** Results obtained for α using both approaches

<table>
<thead>
<tr>
<th>Systems</th>
<th>π*</th>
<th>β</th>
<th>k×10^4 /s^-1</th>
<th>α_probes</th>
<th>α_kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES1</td>
<td>0.70</td>
<td>0.63</td>
<td>2.64</td>
<td>1.07</td>
<td>1.04</td>
</tr>
<tr>
<td>DES2</td>
<td>0.71</td>
<td>0.20</td>
<td>8.13</td>
<td>1.25</td>
<td>1.29</td>
</tr>
</tbody>
</table>

Conclusion

This work validates the use of a combined spectroscopic and kinetics approach to determine the value of α, in cases where the use of probe A is not possible, thus extending the span of log k vs. (α, β, and π*) correlation from pure solvents to hydrophobic eutectic mixtures.
Hydrogen transfer reactions of nitro compounds using MoS$_2$ / titanate nanotubes as catalyst

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Introduction

It is known that nitroarenes are vital chemicals for living organisms and environment. Not only nitro compounds, but also their reduction products, like amino compounds are essential in several industries such as dyes, pigments, agrochemicals, herbicides, pharmaceuticals, rubber manufacturing, chelating agents and textile. $^1$

This work focused on the synthesis of nanostructured titanate nanotubes (TNT) modified with molydenum disulfide nanoparticles (MoS$_2$/TNT) and its application in catalytic reduction reactions of nitro compounds. The titanate nanotubular sample was prepared by a hydrothermal approach, using an amorphous precursor. $^2$ Using the same method, the molydenum disulphide nanoparticles were produced in the presence of the TNT particles. $^3$

Hydrogen transfer reactions of several nitroarenes were studied to evaluate the MoS$_2$/TNT catalytic activity. The results indicate that the reaction is only possible in the presence of the MoS$_2$/TNT and the obtained reaction products were the wanted amino compounds.

Catalyst synthesis & characterization

The results indicate that the hydrogen transfer processes are only possible in the presence of the MoS$_2$/TNT and the obtained reaction products were the expected amino compounds. All substrates were successfully reduced, being methyl-$p$-nitrobenzoate and $p$-nitrotoluene the fastest ones.

References:
Mercury cycling in a Portuguese mesotidal ecosystem, Tagus estuary: Water column chemistry and transport

Rute Cesário¹*, João Canário¹, Marta Nogueira²

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Introduction and aims

The data set emphasizes the importance of examining the complex site-to-site variation within a system, in order to understand estuary wide mercury (Hg) and methylmercury (MMHg) dynamics, and demonstrates that processes driving MMHg fate may be distinct in different regions of the same system. Six sampling campaigns were performed bimonthly during one year covering the North Channel (NC) and the adjacent areas of Tagus estuary to better understand transport and fate of mercury species in the water column. The association of Hg species with organic matter and the evaluation of other processes that govern Hg methylation were also studied.

Study Area

Sampling strategy and Analysis

Samples were collected enclosed different tide conditions and also a tidal cycle of 13 hours was made with samples collected hourly. Mercury species (Hg, MMHg), organic carbon in both dissolved and particulate fractions (POC, DOC), suspended particulate matter (SPM), salinity and other interpretative parameters were determined.

Major Findings

Final Remarks

- The MMHg export from NC is clearly influenced by tidal excursion.
- The transport of mercury species is mainly associated with SPM.
- Sediments are important sources of MMHg to the water column, although phytoplankton bloom may also play a role.

Future Perspectives

- MMHg production and transport in this estuary must be clarified MAINLY IN THE DISSOLVED FRACTION. A detailed hydrodynamic modeling to study methylmercury speciation would be useful.
- Determination of residence times in specific regions to obtain an accurate mass balance between MMHg loading from the water column and from the sediment will also be necessary.
- Application of Hg stable isotope techniques to evaluate simultaneously the methylation/demethylation rates in the water column should be performed.

Funding:

- Centro de Química Estrutural is funded by FCT.
- Rute Cesário PhD grant (SFRH/BD/86441/2012) funded by the Portuguese Foundation for Science and Technology (FCT)
- Projects financed by FCT:
  I. PROFUX - Processes and fluxes of mercury and methylmercury in a contaminated coastal ecosystem, Tagus estuary, Portugal (PTDC/MAA/115798/2009).
  II. PLANTA - Effect of salt-marsh plants on mercury methylation, transport and volatilization to the atmosphere (PTDC/AAC-AMB/115798/2009).

* The MMHg export from NC is clearly influenced by tidal excursion.
• The transport of mercury species is mainly associated with SPM.

MMHg inside the NC

MMHg in the BC

MMHgOD in the EZ stations

THgD → CV-AFS
HgD → CV-AAS
MeHgD, MeHgD → GC-CV-AFS
DOC → HTCO
POC → E.A.
High Throughput Bar Adsorptive Microextraction (HT-BAµE) – Application for monitoring nicotine and cotinine in large number of urine samples

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Introduction
Tobacco consumption is the leading cause of cancer death worldwide. Nicotine (the main component of tobacco) poses several health hazards [1]. For this reason, there is a need to monitor levels of nicotine and its main biomarker (cotinine) in biological fluids, e.g., urine.

In this contribution, A simple, effective, convenient and environmentally friendly methodology using high throughput bar adsorptive microextraction (HT-BAµE) [2] with microliquid desorption (µLD) in combination with large volume injection-gas chromatography–mass spectrometry operating in the selected-ion monitoring acquisition mode (LVI-GC-MS(SIM)) was applied for the determination of nicotine and cotinine in urine samples. The target compounds were extracted in a HT-BAµE apparatus, which allows for simultaneous microextraction and subsequent back-extraction of up to 100 samples, resulting in a sample preparation time of 1.8 min/sample, with average recovery yields of 61.7–67.5 % and 53.9–57.8 % for nicotine and cotinine, respectively. The developed methodology was applied for the analysis of 86 samples, belonging to various volunteers having different smoking habits, where the target compounds were quantified in the ranging from 23.6 to 2612.6 μg L⁻¹.

Experimental procedure
1. HT-BAµE extraction procedure (Sorbent selectivity, Stirring rate, Equilibrium time, Matrix pH, Organic modifier, Ionic strength)
2. Back-extraction step (Solvant type, Sonification time)
3. Method validation (linearity, accuracy, precision, recovery, matrix effects, limits of detection and quantification)
4. Application to real urine samples

Results

Method development

Table 1 – Optimized experimental conditions using HT-BAµE-µLD/LVI-GC-MS(SIM).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Desorption solvent</th>
<th>Back extraction time</th>
<th>Equilibrium time</th>
<th>Matrix pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimized parameter</td>
<td>MeOH (100µL)</td>
<td>30 min</td>
<td>2.5 h</td>
<td>11.0</td>
</tr>
</tbody>
</table>

Application to real samples

There were 86 subjects, ages 18-53, which were divided in three groups: non-smokers and not exposed to ETS for at least a week before sampling (n=1; group #1), non-smokers and exposed to ETS in the week of sample collection (n=64; group #2), and smokers (n=6; group #3).

Conclusions

- Method successfully optimized, validated and applied for the analysis of nicotine and cotinine in urine samples using a convenient HT-BAµE apparatus.
- The proposed HT-BAµE-µLD cycle proved to be simple, cost-effective and environmentally friendly, without compromising performance.
Photoimmunoconjugates to treat Cancer and Age-related Macular Degeneration by Photodynamic Therapy

Sandra Beirão,1,2,3 Sara R. G. Fernandes,1,4,5 Bruno Sarmento,4,5,6 Rosa Fernandes,2,3 João P. C. Tomé∗

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A key component of the Photodynamic Therapy (PDT) is a photosensitizer (PS) and its choice is critical for a successful PDT treatment.

Since the approval of the PDT, several photoactive molecules of the first and second generation, such as porphyrin, chlorin and phthalocyanine derivatives are promising PS candidates for the PDT treatment to various medical diseases and conditions.3 This strategy has been widely studied for the treatment of various types of tumors4 and, more recently, for the treatment of Age-related Macular Degeneration (AMD), a painless eye condition that affects the macular region of the retina.5

Targeted PhotoDynamic Therapy (tPDT) appeared as a more selective PDT approach and uses third generation PSs to reduce the side effects.6 The design strategy of these compounds includes the conjugation of first or second generation PSs with a biomolecule or a targeting agent, for example antibodies (Abs), which selectively bind to target cell receptors and improve the selectivity and efficiency of the photobioconjugates (Figure 1).7

The main objective of these two works is the synthesis of new PSs (Figure 2) for the preparation of PICs to target tumor cells and endothelial cells of choroidal neovessels and their validation in photodynamic activity.

References
Structure-based virtual screening toward Hexokinase 2 inhibitors: targeting metabolism and apoptosis signaling in cancer cells

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Background

Glucose metabolism is a potential target pathway to be explored for cancer treatment. Hexokinase 2 (HK2) is overexpressed in different types of cancer cells1. HK2 is involved in the first and most determinant step of glycolysis, as well as in mitochondria-induced apoptosis. HK2 binds to voltage-dependent anion channel (VDAC) blocking the action of pro-apoptotic proteins (e.g. Bax). Inhibition of the HK2 catalytic pocket has shown to be effective in both reducing glycolysis and detaching HK2 from VDAC, reducing the main source of energy to cancer cells and enhancing apoptosis2,3.

Aim

Finding hit compounds for HK2 inhibition:
- Defining an accurate molecular docking protocol to be used for structure-based virtual screening (SBVS)
- Screening different databases to find hit compounds

Molecular Docking calculations

Defining the protocol

- Available 3D structures
- Protein’s energy minimization
- Water influence
- Centre and flexibility of the catalytic pocket
- Different software, scoring functions and searching algorithms

Final protocol

- PDB: SHG1
- Gold S.20
- GoldScore
- Glu742
- r=15 Å
- No H2O
- No flexible residues

Protocol Validation

- Lowest RMSDs between docked and crystallographic structures
- Best correlation between experimental and in silico data

SBVS

Synthetic and Natural Product-focused databases

- 23 databases -

Pre-selection, remove:
- MW>800
- Isolated atoms
- Polymers
- Small inorganic molecules

Protonation (pH=7.4) | Energy minimization (Amber12)

Molecular docking

Scoring (score >60)

Visual inspection


Characteristics Prevision of drug-like properties

- Docking results
- Drug-like properties
- Commercial reasons
- 111 suitable molecules for testing

Conclusions and Future work

- An in silico protocol for virtual screening of HK2 inhibitors was generated.
- 2981 potential HK2 inhibitors were selected from docking results
- SBVS results were filtered based on drug-like properties and 111 molecules were selected as suitable for testing.
- 64 selected molecules are being used to validate the SBVS with biochemical assays.

References:

**INTRODUCTION**

**Boron**

- Beneficial for life in trace amounts
- Toxic in high concentrations
- Drinking water: Usually below 0.5 ppm

World Health Org. guidelines [1]: < 2.4 ppm

**BORON DETECTION**

Detection based on hexahydroxytriphenylene [2,3]

We proposed 2,3,6,7,10,11-hexahydroxytriphenylene as an optical sensor for boron, using spectrofluorimetry or UV-visible spectrophotometry detection [2,3]

Complexation of our sensor with boron at pH = 9 leads to an increase in emission intensity.

**Limits of detection**

<table>
<thead>
<tr>
<th></th>
<th>Fluorimetry</th>
<th>Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boric acid</td>
<td>10 ppb B</td>
<td>5 ppm B</td>
</tr>
<tr>
<td>Phenylboronic acid</td>
<td>6 ppb B</td>
<td>0.3 ppm B</td>
</tr>
</tbody>
</table>

**Polymeric Hydroxytriphenylene Derivatives [4]**

Polymeric fluorescent boron sensor

- Excellent water solubility
- High boron sensitivity
- Easy to handle
- Can be easily recovered after use

**Boron Scavenging**

**Smart Polymeric Nanoparticles [5]**

- Diol groups
- Boron

Stages of the scavenging process

- After synthesis
- Scavenging

Fluorescence decreases with increasing diol (NP) concentration as less boron remains in water. Of the three NP types tested, the smallest ones bearing GAEM groups were the most efficient in boron scavenging.

**Boron-chelating membranes based in hybrid mesoporous silica NP [6]**

- NP's able to remove up to 93% of the initial boron concentration
- Hybrid membranes reduce boron to 70% of initial value in a single filtration step
Mechanochemically built bio-inspired metalorganic frameworks as a tool to improve drugs’ efficiency

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INTRODUCTION

The interest on metalorganic frameworks (MOFs) towards pharmacological applications has been increasing, especially for controlled drug delivery and release. Our group has been designing novel bio-inspired MOFs (BioMOFs) exploring the possibility of using active pharmaceutical ingredients (APIs) as ligands. This approach presents several benefits over the traditional methodology of encapsulating APIs in the pores of MOFs built with safe organic ligands: i) porosity is no longer required as the release of the API or bioactive molecules is achieved by degradation of the compound; ii) no multistep synthesis is required as the molecules are part of the matrix; iii) synergistic effects between the active molecule and the metal may be explored; iv) the co-delivery of drugs may be possible if a porous network is built with one and the incorporation of a second one is feasible.1,2 Here we present some of the most successful examples:

Seventeen new BioMOFs of gabapentin, a neuroleptic drug, with Y(III), Mn(II) and several lanthanides were prepared. These have shown potential luminescent properties that can be further explored for theranostic applications.3 BioMOFs with azelaic acid have also been explored. The well-known antibacterial and antimicrobial activities of this API have been enhanced opening new routes for its dermal application.

The development of novel coordination frameworks with nalidixic acid, a quinolone antibiotic, using safe metals has proven to affect the solubility of the API. Furthermore, the BioMOFs show increased antimicrobial activity while exhibiting adequate cytotoxicity.4-5

In these studies we resorted to mechanosynthesis as the main synthetic pathway. This environment-friendly technique drastically reduces the amount of solvents and time, proving to be very effective in different areas, including MOFs’ synthesis.6,7

To conclude, we have been proving that BioMOFs are promising candidates for the development of more effective therapies.

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synthesis

API

Gabapentin

Azelaic acid

Nalidixic acid

+ Safe metal

BioMOF

Biological/Pharmaceutical application

Gabapentin

La (III)

Ce (III)

Nd (III)

Mn (II)

La (III)

Y (III)

Ce (III)

Er (III)

Nd (III)

Mn (II)

• 17 new metal coordination networks

• Fully characterized


Introduction

Bar adsorptive microextraction (BAµE) technique was introduced in 2010 as an alternative cost-effective enrichment process for trace analysis of polar to nonpolar compounds in aqueous media. This solid-based microextraction approach, presents several advantages, including the possibility of selecting the most convenient sorbent coating (e.g. activated carbons (ACs), polymers (Ps), etc.), according to the target compounds involved [1-2].

More recently, hollow fiber microextraction (HFµE) was proposed as an alternative liquid-based microextraction approach [3]. Nevertheless, both BAµE and HFµE were never applied for the analysis of the organic compounds in gas phase.

Figure 1: HS-BAµE and HS-HFµE analysis of the aroma profile in wines samples.

In this work, BAµE and HFµE prior to gas chromatography-mass spectrometry were applied for the first time in headspace (HS) analysis to characterize the aroma profile of wine samples. Several assays were performed, including the study of different types of wines using several sorbent phases at various extraction temperatures and equilibrium times. For comparison purposes, stir bar sorptive extraction (SBSE) was also tested.

Experimental Procedure

1. Extraction procedure
   HS-SBSE, HS-BAµE (Sorbent selectivity, Equilibrium time and Ionic strength) and HS-HFµE ( solvent selectivity, Equilibrium time and Ionic strength)
2. Back-extraction step (Solvent type, Sonification time)

Microextraction

- HS analysis
- Porto, Madeira and red wine samples
- 3h and 1000 rpm

Microextraction

- Microliquid desorption
- 100 and 200 μL of solvent
- 30 minutes under sonication

Instrumental analysis

Gas chromatograph: 6890 Agilent Technologies System (U.S.A)
Column: Zebron ZB-5 (30 m × 0.25mm × 0.25μm) (Phenomenex)
Software: MSD ChemStation (version C.00.00); Injection Mode: Splitless (1 μL); Injector Temperature: 260 °C (held 1 min); Oven: 40 °C (held 1 min) and then at 10 °C min⁻¹ to 300 °C (hold for 10 min); Mobile Phase: He, at constant pressure mode

Conclusions

- BAµE coated with ACs and HFµE soaked with convenient solvents, showed for the first time, good performance for the HS analysis.
- HS-HFµE(iso-C8) and HS-BAµE(CN 1) showed better response when compared with well-established microextraction techniques (e.g. HS-SBSE).
- The applied techniques showed remarkable performance for the analysis of the aroma profiles from red, Porto and Madeira wines.
Bioinspired polymers for the development of optical immunosensors

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

Introduction

• The efficient linkage of functional proteins to biocompatible films is crucial when developing BIOSENSORS.

• Polydopamine (PDA) films are inspired on the mussel-foot proteins and have been used in many biomedical applications, due to their biocompatibility and adhesive properties, provided by the catechol groups [1,2].

• Electrochemical synthesis is an alternative route to chemical methods to prepare PDA with defined physico-chemical properties (e.g. thickness, wettability and available functional groups) for a reproducible attachment of proteins [3].

• Herewith, potentiodynamically grown PDA films on gold electrodes are used as platforms for the sensitive detection of antigen-antibody interactions. Immunoglobulin G (IgG) or protein A, for an improved orientation of the antibody, are directly adsorbed on PDA matrices. A post-modification of PDA/IgG or PDA/Protein A with ethanalamine (ETA) is proposed to inhibit the non-specific protein adsorption and increase the selectivity.

• This platform is versatile and can be tailored into any trial of interest, including the construction of sandwich-type architectures for the detection of small target molecules, such as toxins.

Electropolymerization and characterization of PDA films

Decrease in the current of the main redox processes (dopamine/ dopaminequinone, A6/B6) of polydopamine reveals the formation of a poorly conducting polymer [4].

Decrease of the number of electroactive sites upon ETA incubation

 Binding of ETA, possibly through NH2 groups to the available quinone moieties at PDA surface

PDA-modified film biosensor performance

Surface Plasmon Resonance (SPR)

Real-time SPR are carried out to evaluate the performance of the new bottom-up approach regarding the specific immunosensor biorecognition reactions (IgG-Anti/IgG)

Conclusions

• Biocompatible and uniform PDA films can be formed by potentiodynamic control.

• Successful immobilization of ETA on PDA-modified films allows to inhibit the non-specific biomolecule interactions, not affecting the bioaffinity reaction – High potential to be employed in optical IMMUNOSSENSORS.

References:


Funding:

Centro de Química Estructural is funded by Fundação para a Ciência e Tecnologia (FCT) – project UID/QUI/00100/2019. This work was supported by FCT through the projects IF/0008/2013/CP1159/CT0003 (POPH, UE-FSE), PTDC/CTM-ANA/0994/2014 and UID/MULTI/00612/2013.

EOF CE

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EOF CE
Catalytic applications of Cu(II) complexes towards microwave-assisted peroxidative oxidation of toluene and 1-phenylethanol

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Abstract: Two Cu(II) complexes in two different tautomeric forms (keto and enol) derived from the arylhydrazone Schiff base 2-hydroxy(2-hydroxybenzylidene)benzhydrazide (H2L) have been synthesized (Scheme 1) and characterized by elemental analysis, IR spectroscopy, ESI-MS and single crystal X-ray crystallography. Compound 1 with the enol form of the ligand exists as the 1D polymer but compound 2 with the keto form of the ligand exists as the monomer. Both 1 and 2 act as good catalysts towards the microwave-assisted peroxidative oxidation of toluene and 1-phenylethanol with tert-butyl hydroperoxide. 2 exhibits the highest activity in both catalytic reactions, leading selectively to a maximum product yield of 39 and 92%, respectively [1].

Syntheses

X-ray structures

Catalysis

Microwave-assisted peroxidative oxidation of toluene and 1-phenylethanol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive (mol%) vs. substrate</th>
<th>Yield (%)</th>
<th>Selectivity (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Benzoaldehydes</td>
<td>Benzylic alcohol</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td></td>
<td>4.3</td>
<td>1.4</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td></td>
<td>1.9</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>TEMPO (0.6)</td>
<td></td>
<td>1.4</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>HNO3 (0.2)</td>
<td></td>
<td>12.5</td>
<td>0.2</td>
</tr>
<tr>
<td>5</td>
<td>HNO3 (0.7)</td>
<td></td>
<td>7.4</td>
<td>0.4</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td></td>
<td>38.1</td>
<td>0.6</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td></td>
<td>29.3</td>
<td>0.5</td>
</tr>
<tr>
<td>8</td>
<td>TEMPO (0.6)</td>
<td></td>
<td>1.6</td>
<td>0.6</td>
</tr>
<tr>
<td>9</td>
<td>HNO3 (0.2)</td>
<td></td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>10</td>
<td>HNO3 (0.7)</td>
<td></td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>11,12</td>
<td>-</td>
<td></td>
<td>2.4</td>
<td>2.1</td>
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<tr>
<td>13,14</td>
<td>-</td>
<td></td>
<td>3.7</td>
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<tr>
<td>15</td>
<td>Cu(NO3)2</td>
<td></td>
<td>2.8</td>
<td>0.8</td>
</tr>
<tr>
<td>16</td>
<td>H2L</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Reaction conditions unless stated otherwise: toluene (1.67 M), catalyst precursor 1 or 2 (0.3 × 10^-3 M), TBHP (70%aq., 3.3 M), NCMe (3.3 m), 50 °C, 1 h, MW (3W). *Moles of products (benzaldehyde + benzylic alcohol)/100 mol of toluene, determined by GC. *Solvent-free. *Reaction performed using conventional heating. *1 h, 6 h, 12 h, 24 h. A possible mechanism of the catalytic reaction may involve the metal-assisted generation of t-BuOO* and t-BuO* radicals [2], upon oxidation or reduction of t-BuOOH by a Cu or Cu centre, respectively. The t-BuOO* radical can undergo dismutation to the t-BuO* radical and O2, and the t-BuO* radical can abstract an H atom from toluene (RH) to form the benzyl radical R which upon reaction with O2 forms the benzyl peroxy radical ROO2. Dismutation of the latter radical leads to ROH (benzyl alcohol) and benzaldehyde (plus O2). Moreover, H-abstraction from toluene (RH) by ROO2 forms ROOH (plus R*) which upon reduction by a Cu centre, forms the benzylxyl RO• radical (plus hydroxide) that leads to benzyl alcohol (plus R*) by H-abstraction from toluene [2].

Effect of temperature on the catalytic oxidation of toluene in the presence of 2.


Dependence of total benzaldehyde + benzylic alcohol product yield on the catalyst concentration (0.67-10 mM), catalyzed by 2. Reaction conditions: [toluene] = 1.67 M; [TBHP] = 3.3 M, in NCMe at 50°C during 1 h under MW-irradiation (5 W).
Bioinspired Copper(II) Aminoalcohol Complexes and Coordination Polymers: Self-assembly Synthesis, Structural Features and Catalysis

Tiago A. Fernandes, Marina V. Kirillova, Carla I. M. Santos, Vânia André, Alexander M. Kirillov

Introduction

As a continuation of our research on the synthesis and catalytic application of bioinspired multicopper(II) cores, the main aim of the current work consisted in the self-assembly generation of new water-soluble copper(II) compounds bearing aminoalcohols as principal N₂O₄ ligands. The solubility of coordination polymers (CPs) in aqueous medium can be achieved by introducing into the structure at least one organic building block that is soluble in water. Aminoalcohols are particularly attractive examples of such ligands owing to their coordination flexibility, low toxicity, high stability and solubility, and low cost.

Results

N-benzylationalanine (Hbala), trispropylanamine (H₃tipa), N,N-dimethylenvlalanine (Hdma), N-methylthielenalanine (H₂mdea) or N-ethylthielenalanine (H₂edea) were applied as N₂O₄-building blocks for the self-assembly generation of seven novel copper(II) complexes: [Cu(Hbala)(NO)₂] (1), [Cu(H₃tipa)(μ₂-mpm)He₄O] (2), ([Cu(H₂mdea)(H₂mdea)H₂mdea]NO)₄ (3), ([Cu(H₂mdea)(H₂mdea)H₂mdea]NO)₄ (4), ([Cu(Hbala)(Hbala)Hbala]NO)₄ (5), ([Cu(H₂mdea)(H₂mdea)H₂mdea]NO)₄ (6), and ([Cu(H₂mdea)(H₂mdea)H₂mdea]NO)₄ (7). All products were isolated in good yields and fully characterized by IR spectroscopy, ESI-MS(z), elemental analysis, and single-crystal X-ray diffraction.

Catalysis

Catalytic activity of the obtained compounds was also investigated in the mild homogeneous oxidation (Table 1, Figure 2) or hydrocarboxylation of cycloalkanes (Table 2) to give the corresponding cyclic alcohols and ketones or carboxylic acids.

Although water typically strongly inhibits alkaline oxidations due to the reduction of H₂O₂ concentration and lowering of the alkaline solubility, in some catalytic systems we observed a significant growth of an initial reaction rate in the cyclohexane oxidation on increasing the amount of H₂O₂ in the reaction mixture. H₂O₂ showed a remarkable promoting behavior in some related Cu-containing catalytic systems as well as acted as unusual hydroxylating reagent and solvent component in mild copper-catalyzed alkaline hydrocarboxylations. Such promoting role of water is still uncommon but may open a possibility of applying diluted in situ generated aqueous solutions of H₂O₂ as a green oxidant in alkaline oxidation processes.
Water-borne smart polymer nanoparticles for high-performance applications

Tiago D. Martins, Carlos Baleizão, José Paulo S. Farinha

GOALS

➢ Here, we aimed the synthesis of functionalized polymer nanoparticles that can covalently bond for high-performance self-healing materials.
➢ A combination of dynamic covalent chemistry with BMA allow us to obtain a formulation where the low $T_c$ of BMA increase the mobility of the macromolecules at low temperatures and facilitating the reversible reaction.
➢ The combination of aldehyde and amino functionalized monomers into core-shell nanoparticle structure allow a reversible covalent bond between different nanoparticles.

✓ Growth of the core-shell nanoparticles followed by dynamic light scattering (DLS).

Final product was analyzed by diffuse reflectance infra-red Fourier transform (DRIFT).

Polymerization followed by $^1$H-NMR.

References:

Outlook

➢ Functionalized core-shell nanoparticles were successfully synthesized and characterized.
➢ DLS measurements show the formation of a core and the growth of its shell.
➢ NMR spectra show the monomer consumption due to the efficient polymerization reaction.
➢ FTIR-DRIFT shows the formation of a new band due to imine bond formation, when the two nanoparticles are mixed.
Microplastics in the marine environment:
Raise awareness and challenges

Vanessa Morgado,1,2 Carla Palma,2 Ricardo B. Silva1

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Even the firsts scientific reports are dated from the 70s years, the plastic pollution in marine environment stood out as a serious problem only after the discovery of “The Great Pacific Garbage Patch” – the largest of five offshore plastic accumulation zones in the oceans – 90s years. Currently, the plastic debris can account over than 60 % of marine litter. Microplastics – plastic pieces less than 5 millimeters long – have been studied from the last decade to present, due to their accelerated increase and widespread in the environment. These SMALL contaminants are released into the environment as manufactured particles with a microscopic size (i.e. less than 5 mm) or as a result of the fragmentation and degradation of large plastic products (e.g. macro plastic debris). As such, these small pieces are classified as primary and secondary, respectively. Actually, microplastics can reach already concentrations of 100 000 particles per m2 in water or sediments (Wright, 2013; Conkle, 2018).
Exploring crystal engineering to revive old drugs

Vânia André, Fátima Minas da Piedade, João Luís Ferreira da Silva, Inês Martins, Sofia Domingos, Mariama Djaló, Martin Zabransky, Merve Arpacıoğlu, M. Teresa Duarte

INTRODUCTION

Crystal engineering (CE) has been widely used over the last years in the discovery of new crystal forms of active pharmaceutical ingredients (API). One of CE most important applications is the rational design and arrangement of molecular packing, which affects and controls the API properties, such as stability, solubility and bioavailability. The new crystal forms enclose not only polymorphs, hydrates and solvates but also co-crystals and molecular salts and even though solution techniques were traditionally used in their synthesis, mechanochemistry has been assuming an important role in the screening and preparation of these new crystal forms. As important as the synthesis of these new compounds is the injection of their structure-properties relationships. Solubility is a major factor that is known to strongly affect API’s performance and therefore its correlation with structural and thermal data is of utmost importance.

In the last decade a large part of our group’s research has been oriented for the synthesis and characterization of polymorphs, co-crystals and salts of APIs using mechanochemistry as primary synthetic technique. We targeted different APIs, such as gabapentin,\textsuperscript{1,2} gabapentin-lactam,\textsuperscript{3} 4-aminoosalicylic acid,\textsuperscript{4,5} dapsone,\textsuperscript{6} sulfadimethoxine,\textsuperscript{1} sparfloxacin, pipemidic acid and azelaic acid.\textsuperscript{7} The new crystal forms obtained are overall stable and, in most cases, their effect in solubility has been studied revealing promising results.

MECHANOCHEMISTRY

Consists on grinding together the reactants to promote a reaction

- Straightforward and clean
- Desired products are obtained in high purity and high quantitative yield
- It is environmentally friendly, combining high reaction efficiency and minimal input of energy and solvent
- It is rapidly becoming a method of choice in different areas of chemical and materials synthesis

CRYSTAL ENGINEERING

CE is the design of molecular solids with specific physico-chemical properties through the understanding and manipulation of intermolecular interactions, such as hydrogen bonds, halogen bonds and π-π interactions.

APIs = multiple functional groups =
Multiple pathways to give rise to new forms exploring CE principles

SUMMARY OF THE MOST RELEVANT RESULTS

**4-Aminosalicylic acid**
- 9 multicomponent crystal forms
- 3 concomitant polymorphic salts

**Azelaic acid**
- 5 multicomponent crystal forms
- Preliminary solubility studies

**Gabapentin**
- 2 new polymorphic forms and 1 ester derivative
- 2 multicomponent crystal forms

**Gabapentin-lactam**
- 5 multicomponent crystal forms
- Preliminary solubility studies

**Sulfadimethoxine**
- 8 multicomponent crystal forms
- Solubility studies

**Ibuprofen**
- 2 multicomponent crystal forms
- Chiral resolution studies

**Flurbiprofen**
- 10 multicomponent crystal forms
- Chiral resolution studies

**Dapsone**
- 2 co-crystals
- 1 solvate

**Proline**
- 13 multicomponent crystal forms
- Chiral resolution studies

**Perindopril**
- First crystal structure determined
- New hydrated form
- Dissolution studies

**Perindopril Erbumine**
- New perindopril erbumine hydrate and the commercial form have similar dissolution profiles

![Crystal packing of gabapentin-lactam 4-hydroxybenzoic acid co-crystal](image)

Mathematical models developed for the solubility as function of pH

![Crystal packing of sulfadimethoxine (left) and sulfadimethoxine:piperazine salt (right)](image)

Chirality is maintained in the new perindopril hydrate

![New perindopril erbumine hydrate and the commercial form have similar dissolution profiles](image)

References:
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Hydrogen peroxide as a key player in bystander effects

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BACKGROUND

During radiotherapy for cancer treatment protocols, cells that were not directly exposed to ionizing radiation (IR) show similar phenotypes, as for example DNA damage, to the ones directly irradiated, a phenomenon denominated bystander effect (BE). Investigating the molecular mechanisms underlying the BE has impact in several clinical applications, such as undermining the resistance to radiotherapy and adapting sensitization to BE in order to improve treatment efficacy, and is the focus of our research 1–2.

WORKING HYPOTHESIS

Hydrogen peroxide (H2O2) has the potential to be a key molecule responsible for this cell-cell communication, on the account of being one of the chemical species generated by H2O radiolysis when cells are exposed IR and easily diffuses through biological membranes. Also, H2O2 has emerged as a key regulatory molecule involved in a variety of distinct biological processes. Nowadays, the essential regulating role played in vivo by H2O2 is unquestionable and has important implications in health and disease 3.

AIMS

The specific aim of this work is to identify dose-response relationships that correlate H2O2 with the onset of BE in exposed cells to IR. In a first step we established a setup in which tumor (HeLa cells) and non-tumor cells (hTERT-RPE1) were exposed to different regimens of H2O2 doses (continuous and single dose by bolus addition), that were able to produce DNA damage - double-strand breaks (DSB), quantified by changes in γH2AX foci numbers, mimicking cell exposition to IR.

RESULTS

CONCLUSIONS: H2O2 is able to produce DNA damage - double-strand breaks (DSB) which was quantified by changes in γH2AX foci numbers/Intensity/area. H2O2 effects are dependent on the distinct regimens of exposing cells to H2O2 doses; both strategies of exposure to H2O2 seems to affect pFAK pattern of staining. We have established two sets up to compare the obtained results to those that will be obtained in cells exposed to radiation that allow testing whether H2O2 is a key signaling molecule responsible for BE.
Natural fibers modification with metal chalcogenides nanoparticles with photocatalytic properties for pollutants degradation

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Introduction

Throughout the years the modification of fibers caught the scientists’ special attention, in particular due to the possibility of using nanoparticles (NPs) to improve their characteristics and impart new properties.[1] Examples include antimicrobial/antibacterial, self-cleaning and photocatalytic properties being the later relevant for pollutants degradation processes.[2,3]

In this work, Bi$_2$S$_3$ and ZnS NPs were used to modify cotton, the natural fiber. The photocatalytic performance was then evaluated towards the degradation of pollutants using a dye molecule.

Experimental details

- NPs present a non-crystalline structure or/and have a very small size.
- It is not possible to confirm that NPs are attached to cotton by XRD.

Structural and morphological characterization

- DRX
- TEM and SEM
- EDS

Optical characterization

- DRS shows the successful modification of the fibers with NPs.
- Bi$_2$S$_3$ band edge in the visible range and ZnS in the UV range.
- Presence of small amount of ZnS in the mixture $\Rightarrow$ $\varepsilon$ shift to higher values than pure Bi$_2$S$_3$.
- Blue shift for the Bi$_2$S$_3$ and Bi$_2$S$_3$-ZnS NPs synthesised in the presence of fibers $\Rightarrow$ smaller size NPs produced.

Photocatalytic degradation

- Adsorption ability:
  - Bi$_2$S$_3$ $\rightarrow$ Bi$_2$S$_3$-ZnS $\rightarrow$ ZnS
  - Cotton$-$ZnS $\rightarrow$ Cotton$-$Bi$_2$S$_3$ $\rightarrow$ Cotton$-$Bi$_2$S$_3$-ZnS

Conclusions

The successful modification of the fibers was confirmed by DRS and SEM analysis. It could not be confirmed by XDR, due the small size of crystallites and/or the non-crystalline structure. The mixture of both NPs presents a higher superficial area than the pristine NPs, although the XRD analysis did not allow the ZnS identification, it was confirmed by EDS analysis. The complete degradation of a dye from the leather industry was attained using Bi$_2$S$_3$-ZnS NPs under visible light irradiation for 5 hours. Encouraging results were also obtained for NPs-modified cotton fibers, with ca. 60% degradation achieved with the Cotton-ZnS composite.

References


Funding:
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06 Chemistry for the Environment - Chem4Env