



2nd George Olah Conference

*XVIII Conference of the George Olah
Doctoral School*

28 September 2020



George Olah Conference

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Program

EVENT VENUE: TEAMS: GEROGE OLAH CONFERENCE 2020, CODE: pfdv9su

[Link to the event](#)

8²⁵ **Opening**

ORAL PRESENTATIONS

Chairman: **Prof. Dr. László Poppe**

8³⁰-9⁰⁰ **Prof. Dr. Tamás István Horváth**, *invited lecturer* – Sustainable and Green Molecular Engineering

9⁰⁰-9³⁰ **Dr. Balázs Kirschweng**, *George Olah Prize winner in 2019* – Natural antioxidants: a new way to stabilize polyethylene

Chairman: **Prof. Dr. György Keglevich**

9³⁰-9⁵⁵ **Dr. Zsombor Nagy**, *invited lecturer from Department of Organic Chemistry and Technology* – Development of innovative continuous technologies for the pharma industry

9⁵⁵-10¹⁰ **Lara Alexandre Fogaça** – Ammine silver complexes – synthesis, characterization and properties relationship

10¹⁰-10²⁵ **Bence Varga** – Resolution and application of *P*-stereogenic secondary phosphine oxides and *H*-phosphinates

10²⁵-10⁴⁰ **Fernanda Paiva Franguelli** – Studies on some amminecobalt(III) salts – structural features and its effect on preparation and properties of various cobalt-oxide based catalyst precursors

10⁴⁰-10⁵⁰ **Break**

Chairman: **Prof. Dr. Beáta Vértessy**

10⁵⁰-11¹⁵ **Dr. Csaba Fehér**, *invited lecturer from Department of Applied Biotechnology and Food Science* – Biorefining of lignocellulosic residues

11¹⁵-11⁴⁰ **Dr. Péter Polyák**, *invited lecturer from Department of Physical Chemistry and Materials Science* – Preparation of monodisperse poly(3-hydroxybutyrate) particles by chromatographic separation

11⁴⁰-11⁵⁵ **Shereen Farah Ahmed Farah** – Aging of concentrated aqueous graphene oxide suspension

11⁵⁵-12¹⁰ **Aysel Mammadova** – Degradable polyaspartamide derivatives and hydrogels

12¹⁰-13⁰⁰ **Lunch Break**

Chairman: **Prof. Dr. György Pokol**

13⁰⁰-13²⁵ **Dr. Zsolt Kelemen**, *invited lecturer from Department of Inorganic and Analytical Chemistry* – Towards a new generation of carborane-fluorophore conjugates

13²⁵-13⁴⁰ **Eszter Supala** – Multiplexed redox gating measurements with a microelectrospotter. Towards electrochemical readout of molecularly imprinted polymer microarrays

13⁴⁰-13⁵⁵ **Derek Ovc-Okene** – Development of Polymer type Li-ion electrolytes for solid state Li-ionbatteries

13⁵⁵-14⁰⁵ **Break**

Chairman: **Dr. Edit Székely**

14⁰⁵-14³⁰ **Dr. Dániel Fózer**, *invited lecturer from Department of Chemical and Environmental Process Engineering* – Bioenergy with Carbon Emission Capture and Utilization: a Power-to-Gas approach

14³⁰-14⁴⁵ **Balázs Decsi** – Development of a continuous flow microfluidic Liver-on-a-Chip system

14⁴⁵-15⁰⁰ **Dorián László Galata** – Prediction of in vitro dissolution profile of controlled release tablets with artificial neural networks

15⁰⁰-15²⁰ **Break**

15²⁰-16⁰⁵ **Poster session 1 (9 posters)**

Chairman: **Prof. Dr. Kirsztina László**

16⁰⁵-16¹⁵ **Break**

16¹⁵-17⁰⁰ **Poster session 2 (9 posters)**

Chairman: **Prof. Dr. György Marosi**

17⁰⁰-17¹⁰ **Break**

17¹⁰-17⁵⁵	Poster session 3 (9 posters)
	Chairman: <i>to be announced</i>
17⁵⁵	Closing

Poster session 1

P01	Lu Cui
Rheology of PLA/regenerated cellulose nanocomposites prepared by the pickering emulsion process: network formation and modeling	
P02	Amer Aljamal
Improving thermal and flame-retardant properties of sorbitol-based bioepoxy by phosphorus-based flame retardants	
P03	Júlia Domján
Real-time monitoring of amino acids in chinese hamster ovary cell culture using Raman spectroscopy	
P04	Le Ba Thong
Investigation of thermal conductivity and viscosity of nanofluids containing halloysite	
P05	József Csóka
Speeding up density fitting Hartree–Fock calculations with multipole approximations	
P06	Mariana Menoncin
Characteristics and analysis of water chemistry of a cave in Budapest, Hungary	
P07	Samantha Kathiuska Samaniego Andrade
i-Carrageenan - urea based carbon aerogel. Synthesis and characterization	
P08	Marietta Klaudia Juhászné Szentmiklóssy
Variability and cluster analysis of arabinoxylan properties in crossed wheat lines	
P09	Bálint Lóránt
Novel method for the determination of biochemical oxygen demand with microbial fuel cells	

Poster session 2

P10	Ahmed Mohamed Rozza
MD and QM/MM study of a bacterial H-NO _x protein as a model of human SGC activation by nitric-oxide	
P11	Gergely Becskereki
A novel method of molecular imprinting applied to the template cholesterol	
P12	Brigitta Nagy
Modeling of integrated, continuous pharmaceutical manufacturing processes	
P13	Levente Kollár
Virtual screening and biochemical testing of borocycles as immunoproteasome inhibitors	
P14	Máté Mihalovits
Testing the goodness of fit of regression models estimated with extremely small samples in pharmaceutical stability studies	
P15	Edina Jaksics
Chemical and technological properties of rye varieties and fractions obtained from industrial milling trials	
P16	Alexandra Farkas
Investigation of the varietal effect on the compositional, technological and the baking quality of oat flours	
P17	Zsolt Benedek
Interplay between theory and experiment: applications of microkinetic modeling in molecular catalyst design and in cancer research	
P18	Dániel Vadas
Flame retardancy of flax fabric reinforced polylactic acid composites	

Poster session 3

P19	Sándor Nagy
Synthesis and application of heterogeneous recyclable cinchona-based organocatalysts	
P20	András György Németh
Application of elemental sulfur in multicomponent reactions	
P21	Nguyen Thanh Thuy Tien
Synthesis and characterization of new intumescent flame-retardant additives in polypropylene	
P22	Vincent Otieno Odhiambo
Synthesis of TiO ₂ /WO ₃ composite nanofibers by a water-based electrospinning process and their application in photocatalysis	
P23	Kornélia Tacsí
Design of continuous crystallization techniques for direct procession of a flow reaction mixture	
P24	Dorottya Fruzsina Bánhegyi
Preparation of optically active antipyrine derivatives by Mannich reaction	
P25	Edina Szabó
Effect of the preparation method on the dissolution of amorphous solid dispersions	
P26	Jose Alejandro Martiz Chalen
In-flight synthesis of nanosized ZrC particles from various precursors in RF thermal plasma	
P27	Péter Kisszékelyi
C ₃ -symmetrical molecular size-enlarged organocatalysts for membrane-supported recovery	

Abstracts

PhD students' oral presentations

AMMINE SILVER COMPLEXES – SYNTHESIS, CHARACTERIZATION AND PROPERTIES RELATIONSHIPS

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Transition metal complexes having reducing ligands and oxidizing anions very interesting materials due to its mild and selective oxidation properties in organic application^[1] and also, as precursors in preparation of various nanosized metal oxides^[2-4]. Only some permanganate complexes with ammonia ligands were tested in preparation of nanosized oxide catalyst materials^[5-7], therefore in this work three complexes, namely diamminesilver(I) permanganate, perchlorate and sulphate were prepared and characterized. Diamminesilver(I) permanganate and perchlorate were prepared in the reaction of NaXO₄ (X=Cl or Mn) compounds with cold ammoniacal solution of silver nitrate and after decomposed into nanosize products in solid phase. Diamminesilver(I) sulphate was obtained by cooling an ammonia solution of silver sulphate. The synthesized complexes and decomposition products obtained through different heat-treatments were characterized using IR, far-IR, Raman and XRD analysis. The complexes formed were characterized with vibrational spectroscopy and XRD methods, then their solid phase decomposition products were compared and analyzed under inert atmosphere and in the presence of air. The existence of a High-temperature tetragonal polymorph of diamminesilver(I) sulphate have been detected by PXRD and DSC. Also, the decomposition products of the permanganate complex were characterized and tested in photocatalytic reactions of dyes like Congo red and methyl orange.

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RESOLUTION AND APPLICATION OF *P*-STEREOGENIC SECONDARY PHOSPHINE OXIDES AND *H*-PHOSPHINATES

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Secondary phosphine oxides and *H*-phosphinates are of special importance in the field of organophosphorus compounds. They might be regarded as intermediates with a stable *P*-stereogenic center which can be substituted in a stereospecific manner to give optically active tertiary phosphine oxides or boranes.^[1,2] Furthermore, these P(O)H compounds can react with *S* or *Se* to afford the corresponding acids, which can be used as chiral NMR shift reagents or organocatalysts.^[3]

As a first step in our research, the resolution methods previously developed for tertiary phosphine oxides were extended to secondary phosphine oxides and *H*-phosphinates.^[4,5] In case of the secondary phosphine oxides (**1**), a detailed optimization study was conducted on a diaryl phosphine oxide model compound using TADDOL-derivatives as the resolving agents, and the resolution method was extended to other diaryl and aryl-alkyl secondary phosphine oxides (**1**). Furthermore, the stereospecific substitution of the model compound was also carried out resulting a series of optically active tertiary phosphine oxides [(*R*)-**2**]. In case of the adamantyl *H*-phosphinates (**3**), first the structure of the resolving agent, and then the main parameters influencing the efficiency of resolution procedures were optimized. The resolution method was extended to other alkyl *H*-phosphinates (**3**). In case of the adamantyl phenyl-*H*-phosphinate (**3**), a chromatography-free decomposition of the diastereomeric complex and the preparation of the corresponding thioic acid (**4**) were also carried out. Finally, an attempt was made to use the resulting adamantyl phenylphosphonothioic acid (**4**) as a chiral NMR shift reagent, to determine the *ee* of chiral amines.

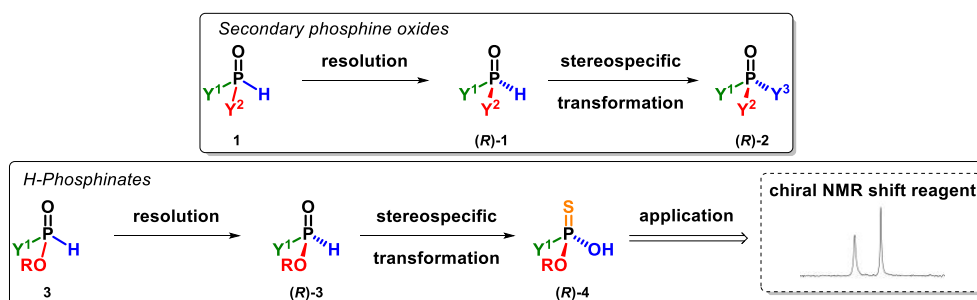


Figure 1. Resolution and application of secondary phosphine oxides and *H*-phosphinates.

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STUDIES ON SOME AMMINECOBALT(III) SALTS – STRUCTURAL FEATURES AND ITS EFFECT ON PREPARATION AND PROPERTIES OF VARIOUS COBALT-OXIDE BASED CATALYST PRECURSORS

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According to previous studies, the solid-phase quasi-intramolecular redox reactions might take place between complex cations having redox active ligands or anions. This enables the preparation of different type of compounds as precursors for the formation of various Co-oxide catalysts^[1]. The present work focuses on the preparation and characterization of [carbonatotetraamminecobalt(III)] sulfate trihydrate, $[\text{Co}(\text{NH}_3)_4\text{CO}_3]_2\text{SO}_4 \cdot 3\text{H}_2\text{O}$ – which is known for a long time and which has been used before as a water soluble ionic sulfate compound precursor for the preparation of other type Co-complexes^[2]. Some other amminecobalt(III) permanganate complexes as $[\text{Co}(\text{NH}_3)_6]\text{MnO}_4$, $[\text{Co}(\text{NH}_3)_6]\text{Cl}_2\text{MnO}_4$, and a novel compound $[\text{Co}(\text{NH}_3)_5\text{Cl}](\text{MnO}_4)_2$ have been also studied by us. The spectroscopic (IR, Raman) and crystallographic (SXR and PXRD) measurements were considered to determine the structure of each complex and also to clarify some missing information about them. Thermal studies (TG-MS and DSC) were performed under oxidizing and inert atmospheres to assign the decomposition products of each complex, where some redox reactions took part resulting in nano-sized cobalt or cobalt-manganese spinel oxides in different stoichiometric ratio. The SEM and BET analysis provided data about the morphology and specific surface area of these decomposition products which helped to understand the mechanism behind the photocatalytic degradation of some organic dyes, i.e. methyloange, methylene blue and congo red.

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AGING OF CONCENTRATED AQUEOUS GRAPHENE OXIDE SUSPENSION

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Graphene oxide (GO) which has found numerous applications also in material engineering [1] is commercialized in various forms, e.g., as highly concentrated (1 w/w%) suspension. This suspension tends to gelate and aggregate. These processes influence the microstructure (both morphology and chemistry) of the GO suspension during their shelf-life. Herein we report the results of rheology and Raman spectroscopy on GO suspensions of different age.

Aqueous GO suspensions of 1 w/w% were obtained by chemical exfoliation of natural graphite using the improved Hummers' method [2]. The GO samples was characterized by various methods [3, 4]. The effect of aging was studied by rheology and Raman spectroscopy. The rheological behaviour of the 1 w/w% aqueous samples of different age was studied with parallel plate geometry. This behaviour was interpreted from four aspects: i) liquid characteristics, usually determined by viscosity; ii) solid characteristics, evaluated by yield stress or elastic modulus; iii) thixotropic characteristics; and iv) viscoelastic characteristics described by elastic and viscous modulus (Figure 1a). Raman spectra of the three GO samples were collected both on 1 w/w% aqueous suspensions and freeze-dried samples. The first-order (1100-1800 cm^{-1}) and the second-order (2300-3300 cm^{-1}) ranges of the spectra were deconvoluted (Figure 1b).

Interpretation of our results helps to understand how the interactions between GO sheets and their interaction with water change in time.

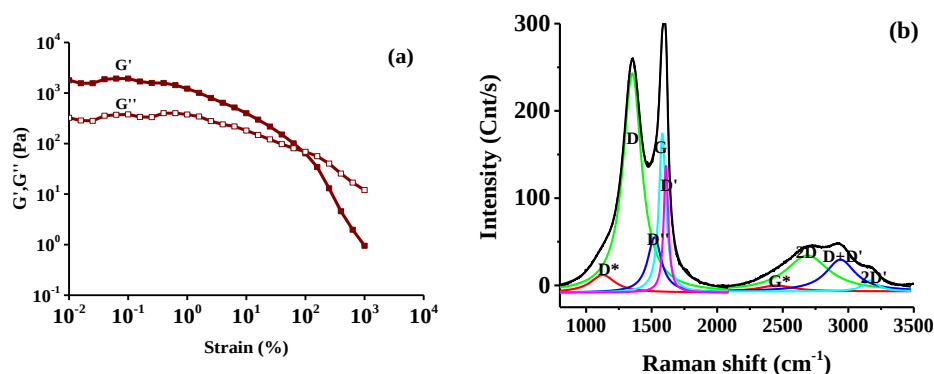


Figure 1
(a) Oscillatory shear measurements on GO suspension (1%w/w).
(b) Raman spectrum of freeze-dried GO of the same age.

Acknowledgments

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- [3] Farah S. et al. *2nd J. of Thermal Anal and Calor. Conference*, **2019** Budapest, Hungary, Poster presentation.
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DEGRADABLE POLYASPARTAMIDE DERIVATIVES AND HYDROGELS

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Thiolated polymers with cationic side groups are attracting huge attention in different biomedical fields, as they can bind negatively charged phosphodiester backbones of DNA and mucous membrane of [epithelial cells](#).^[1] To investigate the effect of side group on polymer stability and degradation we synthesized thiolated polyaspartamides with cationic *N,N*-dimethylethylenediamine (DME), 3-(dimethylamino)-propylamine (DMP) and neutral 2-hydroxyethyl (HE) side groups in various amounts to cysteamine repeating units. The results of experiments on linear polymers and their disulfide cross-linked counterparts show that, polymers with high DMP and HE content were more stable against hydrolytic degradation in physiological and endosomal pH values, while polymers with high DME content degraded at pH=7.7 within a day due to breakage of polymer main-chain structure without releasing side groups. Degradation of linear polymers due to main-chain breakage was confirmed by viscosity measurement as polymer with high DME content followed by molecular loss of polymer in comparison with original polymer. The results of rheological measurements on disulphide cross-linked hydrogels show that dynamic moduli of polymers with high DME content became frequency-dependent at lower frequencies (it was possible to see transition from gel to sol within few hours), which suggest weaker gel structure compared to polymer with high DMP and HE content.^[2]

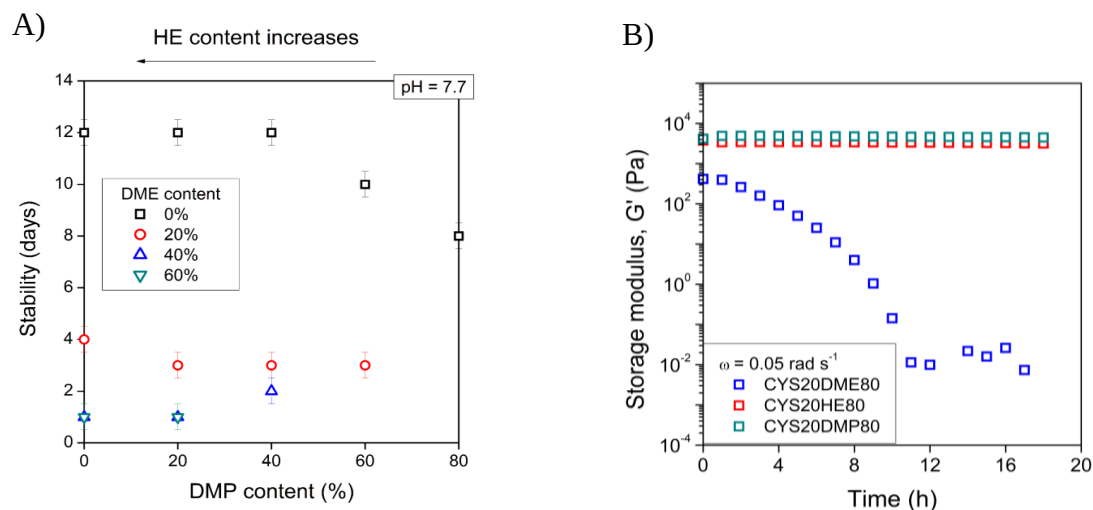


Figure 1. Stability of polymers at pH=7.7 after two days (A) and the change of storage modulus of hydrogels over time ($\omega = 0.5 \text{ rad/s}$) (B).

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MULTIPLEXED REDOX GATING MEASUREMENTS WITH A MICROELECTROSPOTTER. TOWARDS ELECTROCHEMICAL READOUT OF MOLECULARLY IMPRINTED POLYMER MICROARRAYS

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Molecularly imprinted polymers (MIPs) emerged as alternatives of antibodies for selective protein recognition with clear advantages in terms of robustness and tailorable chemical synthesis. During the synthesis of MIPs, functional monomers prearrange around the template proteins and this structure is then fixed by the polymerization. The removal of the template leaves behind complementarily shaped and functionalized binding sites, which can be used to selectively detect it. To overcome the main challenges in protein-imprinting, i.e. the slow diffusivity of the macromolecules in the polymer matrix and structural damage, surface imprinted nanofilms with thicknesses comparable with the diameter of the macromolecular templates (< 10 nm) can be electrosynthesized in aqueous media onto a solid support. ^[1]

Earlier we showed that MIP nanofilm microarrays can be electrosynthesized with the microelectrospotter for the surface plasmon resonance imaging (SPRi) coupled, high-throughput investigation of protein MIPs. ^[2] We realized however, that the microelectrospotting method can offer the multiplexed redox readout of these microarrays as well. As a proof of concept study, IgE-imprinted polyscopoletin nanofilm microarrays were electrosynthesized with the microelectrospotter on gold SPRi chips. The concentration dependent binding of the target protein on the polymer spots was then followed by the suppressed electron-transfer of the ferrocenecarboxylic acid redox marker. As confirmation of the results, rebinding was followed with SPRi as well. The preliminary results suggest that microelectrospotting can provide a simple, cost-effective alternative to SPRi for the high-throughput readout of protein microarrays with results that are less influenced by out-of-cavity non-specific binding. ^[3]

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DEVELOPMENT OF POLYMER TYPE LI-ION ELECTROLYTES FOR SOLID STATE LI-ION BATTERIES

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The development of modern technology depends greatly on improvements in electrochemical devices such as energy storage batteries. Polymer electrolytes have received a great deal of attention due to their potential application in such electrochemical devices because of its various advantages such as good mechanical properties, ease of the film fabrication, and ability to form proper electrode-electrolyte contacts. [1-4] In this research, the aim was the examination of the performance of a unique polymer family, that have not been investigated from this aspect yet, poly(3,6-dioxa-1,8-octanedithiol) (PDODT) homopolymer and three copolymers of PDODT with PEG-diacrylate (PEGDA) or PEGdiglycidyl ether as solid-state solvent free polymer Li-ion electrolytes.

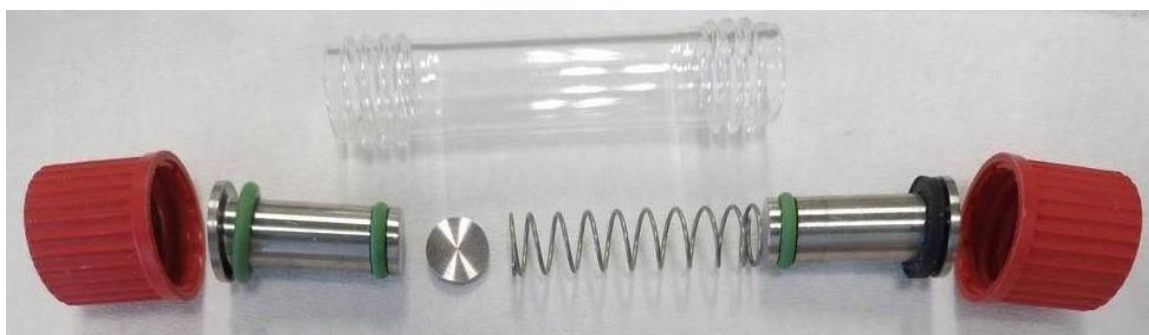


Figure 1. Layout of the cell used in measurement.

To investigate our polymer samples, we needed to characterize them structurally, this was carried out by nuclear magnetic resonance spectroscopy and the differential scanning calorimetry. Electrochemical characterization, in the form of electrochemical impedance spectroscopy and linear sweep voltammetry, was also carried out, to determine the most important property of our polymer Li⁺ electrolytes, its Li⁺ conductivity and electrochemical stability.

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DEVELOPMENT OF A CONTINUOUS FLOW MICROFLUIDICAL LIVER-ON-A-CHIP SYSTEM

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In the early stages of drug discovery research, metabolism studies have an important role. The main goal of these tests are to characterize the metabolites of the drug candidate molecules. The main organ of the drug metabolism is the liver, thus the experiments are carried out traditionally using in vitro cell- or liver microsome-based methods. However, this approach presents many challenges from an analytical point of view and ethical issues can be raised. Biomimetic oxidation can be an alternative solution for metabolic tests. Synthetic metalloporphyrins are feasible catalysts to mimic the liver-based metabolism of xenobiotics in presence of an oxygen donor. Their application is based on the structural similarity to the active site of the cytochrome P450 isoenzyme family.

“Organ-on-a-chip” reactors, being a subtype of Lab-on-a-chip family, mimicing the (coordinated) operation of the living organism’s one (or more) organ(s). Enzymes or biomimetic catalysts can be immobilized to solid supporters, which can be trapped inside a microfluidical chip. These systems offer a unique, efficient, fast and robust way to model the metabolism of the body. The microfluidical system can be easily coupled with HPLC-MS method to gain analitical information rapidly.

In my work I developed a magnetic nanoparticle bound metalloporphyrin as a reactive catalysts for microfluidical biomimetic system.^[1] The surface properties of the magnetic carrier were optimized and characterized by ζ -potential and DLS measurement. The tailored chatalitic system was loaded in a microfluidical chip reactor using permanent magnets. The continious flow reaction was optimized along the concentration of the substrate and the flow rate. Amlodipine was used as modell substrate in our experiments. Metabolites of amlodipine can be identified in 15 minutes using our microfluidical system.

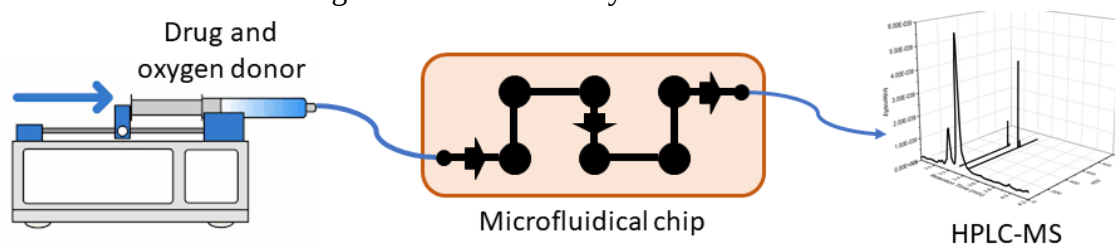


Figure 1. The scheme of microfluidical biomimetic oxidation system.

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PREDICTION OF IN VITRO DISSOLUTION PROFILE OF CONTROLLED RELEASE TABLETS WITH ARTIFICIAL NEURAL NETWORKS

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In the last decade, continuous manufacturing technologies made their first appearance in pharmaceutical manufacturing. In order to ensure the quality of the product, the application of real-time analytical sensors is desirable. Most quality inspection methods used in current batch manufacturing processes are slow and can only measure a small minority of the produced tablets. Consequently, there is a growing demand for spectroscopic techniques which can be applied real-time to measure various properties of pharmaceutical products.

In vitro dissolution testing is a crucial quality inspection method of pharmaceutical tablets. It is designed to simulate the behavior of the tablet in the gastrointestinal system of the patient. However, it is a slow process, requiring at least several hours to perform it and its sampling ability is also very small, usually 6-12 tablets are measured out of 100.000. Thus, a continuous tablet manufacturing process would greatly benefit from a technology which yields the same result without performing this cumbersome process. In this work [1], near-infrared (NIR) and Raman spectra of tablets was recorded, the information derived from these was combined with the compression force data yielded by the tablet press. An artificial neural network was used to predict the dissolution profile of the tablets (*Figure 1*).

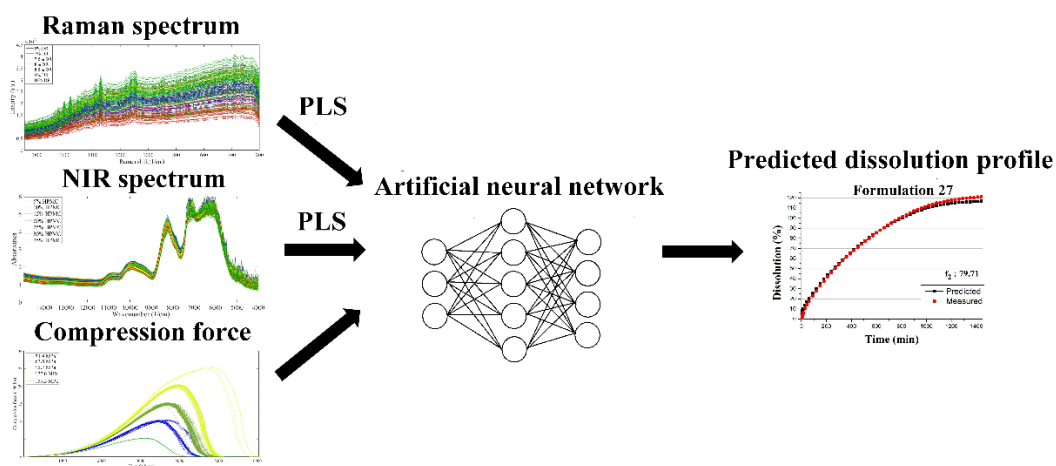


Figure 1. Visualization of the dissolution profile prediction method.

The performance of the model was evaluated by comparing the measured and predicted dissolution profile of 28 validation tablets using the f_2 similarity parameter defined in pharmacopoeias. All profiles were predicted with a similarity parameter higher than 50, thus the accuracy of the predictions was found to be satisfying.

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Abstracts

PhD student's poster presentations

RHEOLOGY OF PLA/REGENERATED CELLULOSE NANOCOMPOSITES PREPARED BY THE PICKERING EMULSION PROCESS: NETWORK FORMATION AND MODELING

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PLA/regenerated cellulose (RC) nanocomposites containing 0.5, 1.0, 1.5, 2.0, 3.0 and 5.0 wt% cellulose were prepared by the Pickering emulsion process [1]. The rheological properties of the composites were characterized by the determination of melt flow rate and by oscillatory rheometry carried out in the plate-plate configuration. Viscosity was modelled with the modified Carreau-Yasuda [2] and the modified Cross models [3] and a new model was proposed as well. The results showed that regenerated cellulose is a suitable reinforcement for PLA and the Pickering emulsion process produces homogeneous materials. The small size and relatively large aspect ratio of the cellulose nanofiller leads to the formation of a network structure already at small cellulose content. Viscosity increases rapidly with increasing cellulose concentration and a yield stress appears already at 0.5 wt% RC content. Modeling helps the quantitative analysis of the experimental results and offers additional information about the structure and properties of the composites studied. All models used in this work have advantages and drawbacks. All three predict yield stress well, but only the new model gives reasonable values for the power law exponent. Other parameters and their composition dependence are difficult to interpret. Fitting parameters must be evaluated carefully and critically for all models.

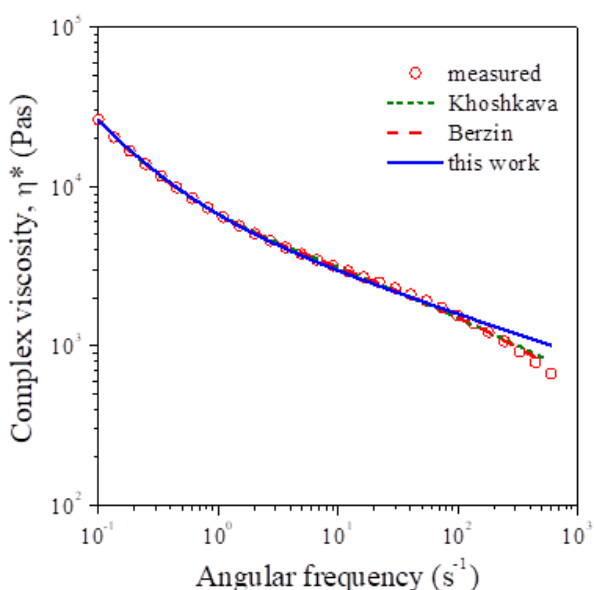


Figure Comparison of complex viscosities predicted by various models to experimentally determined values. Symbols: (○) measured, --- Khoshkava [2], - - - Berzin [3], — this work.

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IMPROVING THERMAL AND FLAME RETARDANT PROPERTIES OF SORBITOL BASED BIOEPOXY BY PHOSPHORUS-BASED FLAME RETARDANTS

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Epoxy-based composites have the broadest range of applications among all thermosetting polymers due to the versatility of structurally different epoxy resins, hardeners, and additives [1]. Flame retardants (FR) are important additives due to the inherent flammability of polymers, which restricts their application in fields where a high flame retardancy is required [2]. The aim of this study was to study the effect of different flame retardant on the properties of an aliphatic polyfunctional epoxy resin (Sorbitol Polyglycidyl Ether), by comparing different additive type flame retardants at the same levels of phosphorus content.

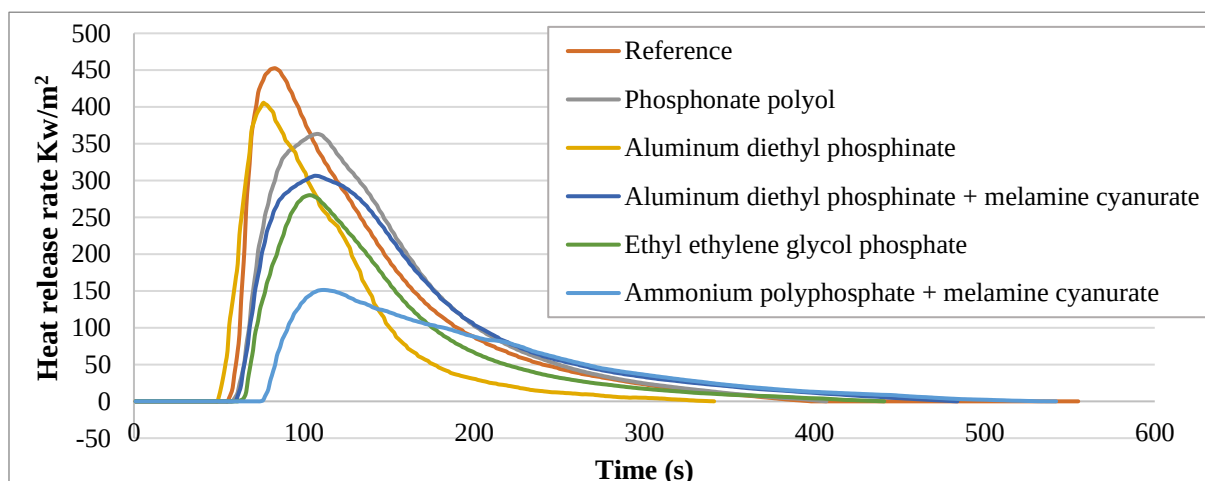


Figure 1. Heat release rate of the different FR formulations at 3% P-content

Mass loss calorimetry results confirmed that at 3% phosphorus (P) content, the char became continuous and dense, such structure can provide protection to the underlying polymer below by hindering the oxygen and heat exchange. In case of Phosphonate polyol and the combination of aluminium diethyl phosphinate and melamine cyanurate flame retardants, by the addition of 3 %P, the limiting oxygen index (LOI) values were good. However, they lowered glass transition temperature (T_g) very significantly. Whereas, Ethyl ethylene glycol phosphate formulations have relatively good T_g due to its oligomeric structure. It showed the self extinguishing V-0 UL-94 rate at 3%P content due to the charring effect of phosphate ester, but LOI values were relatively low. Only Aluminium diethyl phosphinate and the combination of Ammonium polyphosphate and melamine cyanurate formulations showed self-extinguishing V-0 UL-94 rate and high LOI values at 3%P content.

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REAL-TIME MONITORING OF AMINO ACIDS IN CHINESE HAMSTER OVARY CELL CULTURE USING RAMAN SPECTROSCOPY

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The measurement of critical process parameters during mammalian cell cultures has a central role in term of effective bioprocess control. As the cell cultivations occur in complex and dynamically changing bioreactor medium, the demand for rapid, robust and reliable in-line analytical techniques is growing intensively. Over the last decade, Raman spectroscopy has been shown to have the advantage to determine the most important cultivation parameters (such as glucose, lactate, glutamine, glutamate, ammonia or viable cell density) with good accuracy in real-time.^[1]

In this study, the focus was placed on amino acids, what are essential components in cell culture medium as they building blocks of proteins and playing key roles in several metabolic pathways.^[2] Currently, the amino acids are determined by taking sample from the bioreactor culture and applying off-line analytical methods such as liquid chromatography, GC-MS, NMR or capillary electrophoresis.^[3] The biggest problem with these techniques, that they require comprehensive sample preparation and are time consuming, making the real-time process monitoring and control impossible. Therefore, with the aim to avoid offline sampling and to better understand the metabolic changes of amino acids during mammalian cell cultivation, Raman-based calibration models for several amino acid components (e.g arginine, asparagine, aspartic acid, leucine or phenylalanine) were built using parial least squares regression. The calibration dataset included 65 data points obtained from four bioreactor cultivations. The reference data points for amino acid concentration were generated by using Sykam Automatic Amino Acid Analyzer. The calibration models were accurate and could predict the concentration of 11 amino acids with good performance (RMSEC: 200-800 μ M, RMSECV: 180-600 μ M). The developed models were validated by applying them to predict the amino acid concentration during an independent bioreactor run. By using our self-developed process monitoring system, the changes of amino acid concentrations were monitored in real-time through the duration of the bioreactor cultivation. Based on the results, the Raman models were able to determine the concentrations with a prediction error value of 250-1200 μ M.

In conclusion, this study demonstrates that Raman spectroscopy coupled with chemometrics is a suitable technique for real-time measurement of amino acids in mammalian cell culture process. In the future, the developed monitoring system can be applied for effective process control (e.g nutrients replenishment based on an indicator amino acid) in order to improve cells productivity and product quality.

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INVESTIGATION OF THERMAL CONDUCTIVITY AND VISCOSITY OF NANOFLUIDS CONTAINING HALLOYSITE

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In literature, the nanofluids based on halloysite and water with changing pH were investigated in only one research. ^[1] In this study, the halloysite nanofluids were prepared by using surfactants and changing pH for comparison. The halloysite nanotube (HNT) nanofluids were studied for several volume fractions (0.5, 1.0, and 1.5 vol%) and temperatures (20, 30, 40, 50, and 60 °C). The properties of HNT were studied with a scanning electron microscope (SEM), energy dispersive X-ray analysis, Fourier-transform infrared spectroscopy, X-ray powder diffraction, Raman spectroscopy and thermogravimetry/differential thermal analysis. The stability of the nanofluids was proven by zeta potentials measurements and visual observation. ^[2] With surfactants, the HNT nanofluids have the highest thermal conductivity increment of 18.30 % for 1.5 vol% concentration in comparison with the base fluid. The thermal conductivity enhancement of nanofluids containing surfactant is slightly higher than nanofluids with pH=12. The prepared nanofluids were Newtonian. The viscosity enhancements of the nanofluid were 11 % and 12.8 % at 30 °C for 0.5 % volume concentration with surfactants and pH=12, respectively. The novel equations of viscosity and thermal conductivity for these nanofluid were proposed. The thermophysical properties showed the halloysite nanofluids were potential for being used as heat transfer fluid.

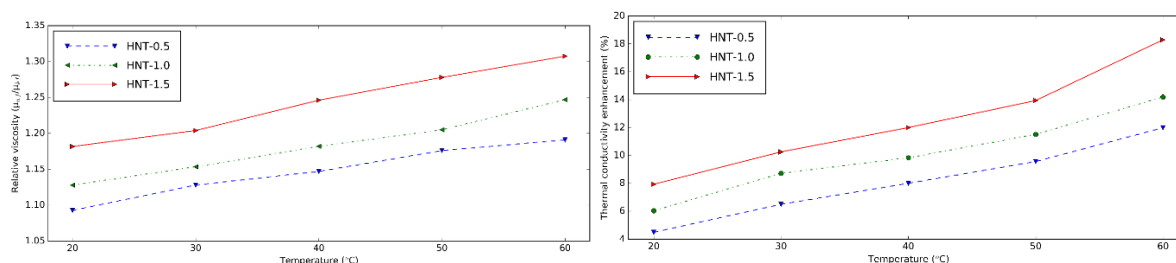


Figure 1. Relative viscosity and thermal conductivity enhancement of halloysite nanofluids with surfactants

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SPEEDING UP DENSITY FITTING HARTREE–FOCK CALCULATIONS WITH MULTIPOLE APPROXIMATIONS

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The Hartree–Fock method is one of the most important approaches in quantum chemistry. Usually it is used for generating initial molecular orbitals for correlation calculations and not as a standalone method. Due to the recent development of reduced-scaling correlation approaches^[1] the Hartree–Fock method has become the most time consuming step in the calculations. The bottleneck of the procedure is the formation of the exchange matrix. The computational time needed for this step scales as the fourth power of the system size which limits the applicability of the method to small and medium sized molecules. Many algorithms have been developed to increase the efficiency of Hartree–Fock calculations, for example density fitting (or resolution of identity)^[2], local density fitting^[3] and the multipole approximation^[4].

In density fitting the product of the atomic orbitals are expanded on a set of atom centered basis functions called the fitting or auxiliary basis functions. The resulting algorithm is much faster than conventional ones however it still scales as the fourth power of the system size. To overcome this difficulty local density fitting methods have been introduced. By using localized molecular orbitals one can develop asymptotically linear scaling algorithms. Despite of the favorable scaling properties of these methods the exchange matrix construction remains the bottleneck of a Hartree–Fock or hybrid density functional calculation.

In our work^[5] we further improved the density fitting algorithm with multipole expansion. The three-center electron repulsion integral tensor which appears in both local and non-local density fitting algorithms is approximated using the multipole expansion. As a result the tensor indices can be separated from each other which can be used to reduce the scaling of the algorithm. Our results suggest that computation times for a conventional density fitting calculation can be reduced roughly by a factor of 1.5 while the speedups are somewhat more moderate if local density fitting approximations are also deployed. We also investigated the magnitude of the error introduced by the multipole expansion. It turned out to be negligible compared to the error of the density fitting.

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CHARACTERISTICS AND ANALYSIS OF WATER CHEMISTRY OF A CAVE IN BUDAPEST, HUNGARY

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Budapest is divided by the Danube river. Buda hill, in the right side, is characterized by its hypogenic karst system with the presence of thermal waters, named Buda Thermal Karst (BTK)^[1,2]. At Rózsa hill are five known caves larger than 1 km. Molnár János Cave (MJC) is the only underwater cave located behind the discharge zone and the only active karst system in the region^[3]. At MJC there is a large amount of water that can be considered as a possible source of drinking water. The aim of this study is to evaluate the physical-chemical parameters of the cave water to understand natural and possible anthropogenic interference in water quality. Therefore, measurements of temperature, hydrogen carbonate (HCO_3^-), conductivity, pH, sulphate (SO_4^{2-}), nitrate (NO_3^-), calcium (Ca^{2+}), chloride (Cl^-) and magnesium (Mg^{2+}), sodium (Na^+) and potassium (K^+) ions, were performed for drip water, water from the cave conduits and upstream water. Cluster, boxplot and seasonal analysis were applied to understand the different sampling points' water characteristics. The hydrogeological relationship was taking in consideration in the analysis, because most of the chemical parameters may be associated with the lithological formation of the cave, but some of them can be related to external, anthropogenic action.

Keywords: water chemistry; karst system; cave hydrology.

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i-CARRAGEENAN – UREA BASED CARBON AEROGEL. SYNTHESIS AND CHARACTERIZATION

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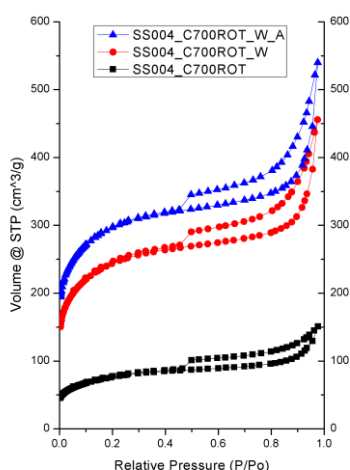
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The aim of this work is the synthesis and characterization of a marine biomass based carbon aerogel for its application in electrocatalysis^[1]. Carrageenan is a natural polysaccharide obtained from edible red seaweeds which is widely used in food, medicine, pharmaceutical, and cosmetic industries due to its gelling, thickening, and stabilizing properties. The i-carrageenan has between 28-30% of sulfate also carrying 4-6% potassium, 2-4% calcium, and 1-2% sodium which improve its ability to form stable gels. In the presence of urea in aqueous medium, the carrageenan solution follows a thermoreversible gelation throughout a coil to helix conformational transition providing a polymer matrix with simultaneous S and N dopants. After freeze drying, the dry polymer obtained was converted to carbon in inert (N₂) atmosphere at 700°C. The carbon material was then washed using HCl to remove the metal sulfides partly filling the pores. The final stage comprehends the annealing of the washed carbon material at 1000°C in inert (Ar) atmosphere. This annealing step is aimed to promote the redistribution of the N and S atoms in the carbon network which is expected to enhance the electrocatalytic activity of the final material. SEM images were taken to visualize the morphological changes.



Low temperature nitrogen adsorption was used to follow the development of the morphology of the carbon materials (Figure 1). The crystalline inorganic salts and their removal was followed by powder X ray diffraction (XRD). The surface composition of the carbon samples were analysed by X-ray photoelectron spectroscopy (XPS). Finally, the annealed carbon material was used as a catalyst in an oxygen reduction reaction (ORR) to determine its electrocatalytic activity in acidic and basic electrolytes.

Fig. 1. Low temperature N₂ adsorption/desorption isotherms of the carbonized (SS004_C700ROT), acid washed (SS004_C700ROT_W), and annealed (SS004_C700ROT_W_A) aerogels.

References

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VARIABILITY AND CLUSTER ANALYSIS OF ARABINOXYLAN PROPERTIES IN CROSSED WHEAT LINES

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Non-starch polysaccharides (NSP) in cereals, after starch and gluten proteins, determine the technological and nutritional properties of flour, dough and end product. From NSPs, the arabinoxylans (AXs) are the most important components studied in wheat nowadays. The novelty of our study is the investigation of the variability and clustering ability of the wheat lines based on different quantitative and qualitative traits of arabinoxylans. The quantitative properties, the AX content of wheat flours were measured by GC [1]. The qualitative property referring to the structure of the molecule was the molecular weight distribution measured by SE-HPLC [2]. According to the results the variability of AX properties in the breeding lines varied between wider ranges than the values measured for the parental varieties. The correlation between the quantitative parameters, and a trend between quantitative and qualitative parameters were described. During the cluster analysis, the parents were well separated into different groups. The parameters that played an important role in the clustering were the ratio of the probability of occurrence of molecular size ranges along with the quantitative traits of AX. The selected samples can be used for further targeted breeding while the methodology was used in this work can be suitable for selecting lines for special food or industrial applications.

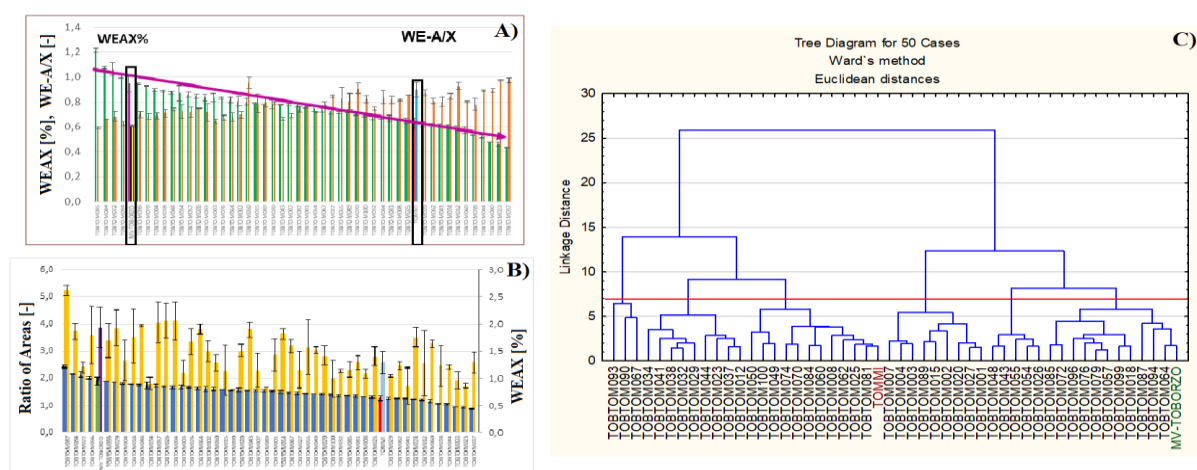


Figure 1. A) Relationship between WEAX content (green) and their WE-A/X ratio (red). B) WEAX content (blue) and the ratio of high and low MW WEAX (R) (yellow). C) Hierarchical cluster analysis based on the arabinoxylan properties (the intersection of the red line shows the members of the six clusters from left to right).

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NOVEL METHOD FOR THE DETERMINATION OF BIOCHEMICAL OXYGEN DEMAND WITH MICROBIAL FUEL CELLS

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Microbial fuel cells (MFCs) are special bioreactors that can convert the chemical energy stored in biodegradable organics directly into bioelectricity by exoelectrogenic bacteria. With MFC-based biosensors, the biodegradable organics content can be measured or the presence of toxic pollutants can be detected in wastewaters and in natural water bodies^[1,2].

For the characterization of wastewaters, biochemical oxygen demand (BOD, mg O₂ l⁻¹) is one of the most important parameters. In order to simplify the standard respirometry-based BOD₅ measurement, a novel methodology and low-cost single-chamber air cathode MFCs were developed. Initial tests with various artificial samples (acetate, peptone, corn starch and milk) demonstrated that besides soluble readily biodegradable substrates, the elaborated method is also appropriate for the BOD measurement of samples containing suspended and/or colloidal substrates.

Experiments with real domestic and brewery wastewater were carried out as well. The relative error of BOD values determined by MFCs related to the BOD₅ concentrations measured with standard respirometry method was less than 10 %. Also, the obtained voltage vs. time curves showed typical characteristic (Fig. 1.): a higher voltage peak in the beginning of the measurement (supposedly related to the biodegradation of readily biodegradable soluble substrates) and a “shoulder” with lower voltage values (presumably belonging to the hydrolysis and consequent biodegradation of suspended slowly biodegradable substrates) were observed. Thus, qualitative analysis of organics content might be possible by the determination of soluble readily biodegradable and suspended slowly biodegradable substrate ratio.

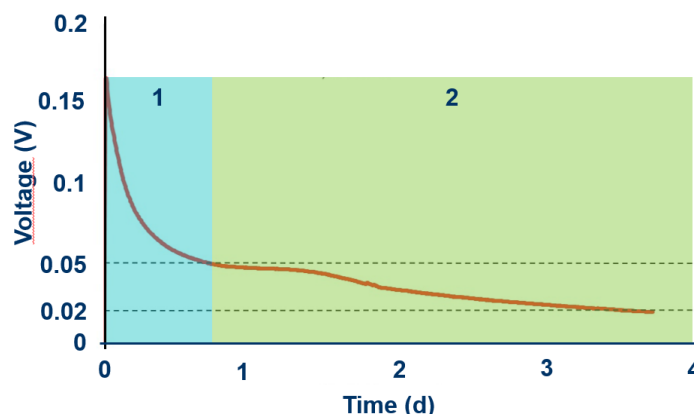


Figure 1. Typical characteristic of voltage curves: a higher voltage peak (1) from the biodegradation of soluble substrates followed by a shoulder (2) of lower voltage values from the biodegradation of suspended organics

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MD AND QM/MM STUDY OF A BACTERIAL H-NOX PROTEIN AS A MODEL OF HUMAN SGC ACTIVATION BY NITRIC-OXIDE

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NO-sensor soluble guanylyl cyclase (sGC) is a heme protein playing a vital role in the maintenance of cerebral blood flow, vascular homeostasis and platelet function through the NO/cGMP signaling pathway. Impairment of the sGC-based signaling cascade has been linked to cardiovascular, neurological disorders and inflammatory diseases. NO binds to the ferrous heme moiety called the “H-NOX domain” of sGC and activates the production of cGMP hundred-fold. However, the detailed binding mechanism remain unclear despite extensive experimental works.^[1]

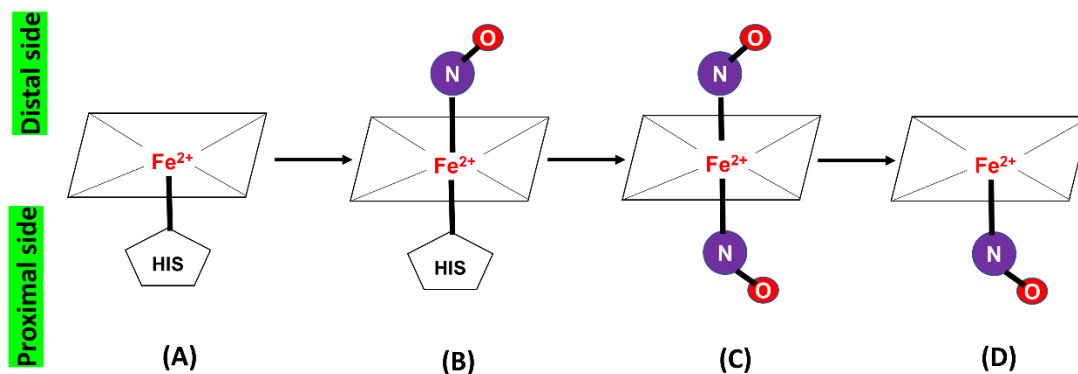


Figure 1. Proposed mechanism of sGC maximal activation.

We used the x-ray structures of the H-NOX protein from *Shewanella oneidensis* as a homologous system of human sGC in order to elucidate the mechanism of NO binding and protein activation. Experiments suggest that NO binds both to the distal and proximal sides of the heme group and it is accompanied by the cleavage of the iron-histidine bond (Figure 1), a crucial element of sGC activation. We used MD simulations to address the diffusion of NO into the distal and proximal pockets as well as to study the dynamic properties of the various states. Furthermore, using a porphyrin model of the heme group the performance of DFT functionals in describing the energetics of NO-binding events was critically evaluated with the help of CCSD(T) and DLPNO-CCSD(T) methods. Finally, we investigated the potential pathways contributing to the conversion of the various states using QM/MM calculations. Our results suggest that the Fe-histidine linkage can easily break after the NO-Fe bond was formed on the distal side, and a second NO molecule arrived in the proximal pocket. Cleavage of the Fe-histidine bond is followed by the rotation of the histidine group out of the proximal pocket triggering a conformational change, which is most likely relevant for the activation of sGC.

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A NOVEL METHOD OF MOLECULAR IMPRINTING APPLIED TO THE TEMPLATE CHOLESTEROL

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Molecular imprinting is a widely used technique to obtain selective adsorbents. The most commonly used method for making molecularly imprinted polymers (MIP) is the non-covalent method. Generally, the template interacts with the monomers in the prepolymerization mixture, creating secondary forces (van der Waals, ionic, hydrogen bonding) between the template and monomer. The mixture also contains porogen solvent to create larger surface and more porous polymers. After polymerization a highly crosslinked polymer is formed, with sites or cavities which are selective to the template and similar molecules.

A novel method has been successfully tested for non-covalent imprinting [1]. The polymers were created in a simpler way than usual MIPs, skipping the step of the formation of prepolymerization complexes. The template is cholesterol, and no functional monomer is used. The prepolymerization mixture contains only an acrylic diester crosslinker and the porogen solvent. In this mixture ionic interactions are unlikely, and the porogen isopropanol prevents even hydrogen bonding between the template and the monomer. Despite of these apparently inadequate conditions, significant imprinting factor and improved selectivity were measured for cholesterol against some other steroids. The obtained imprinting factor and selectivity improvement are remarkable even when compared to other non-covalent imprinting systems based on functional monomers.

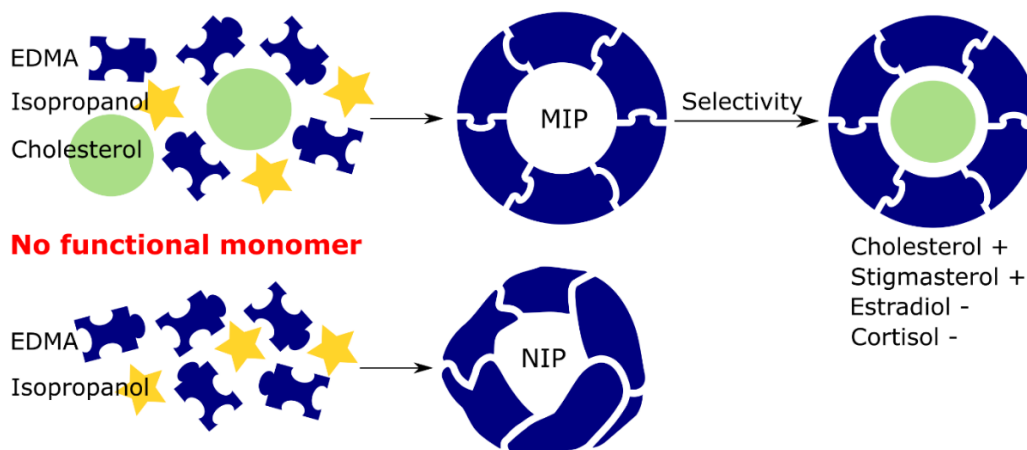


Figure 1. Simple procedure of MIP and NIP production

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MODELING OF INTEGRATED, CONTINUOUS PHARMACEUTICAL MANUFACTURING PROCESSES

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Continuous pharmaceutical manufacturing is rapidly gaining interest as a promising way to improve efficiency, reduce operating costs, and ensure easier scale-up and shorter time-to-market^[1]. However, the conversion from batch to continuous manufacturing also entails the necessity of changing the current quality assurance approaches to accommodate real-time decision making and to address the risk of error propagation through the integrated continuous process line. To tackle this challenge, the importance of process and product modeling and model-based system approaches is rapidly increasing^[2].

In this work, a flowsheet model was developed for modeling an integrated, continuous manufacturing line for acetylsalicylic acid (ASA) production, including the two-step flow synthesis of the ASA, followed by a continuous crystallization and filtration. Furthermore, a surrogate model was developed for the *in vitro* dissolution testing of the final ASA capsules based on the crystal sized distribution (CSD) of the ASA powder to facilitate the quality assurance of the product. All units of the flowsheet model were developed and validated based on real experimental data, that is the simulation can serve as a digital twin of a real pharmaceutical production line.

Optimization and sensitivity analysis studies were conducted on the validated flowsheet model to gain deeper process understanding. The results showed that by optimizing the integrated manufacturing as a unit, a threefold increase in the final ASA yield can be achieved as opposed to the case when all unit operations are optimized separately. Furthermore, at the same time, the excess of the reactants could be significantly reduced. The sensitivity analysis revealed those operational parameters that are the most crucial to be controlled to avoid out-of-specification products, as well as the dynamics of the error propagation could be studied.

The study clearly demonstrated the advantages of the model-based analysis of continuous, integrated continuous manufacturing, such as finding the optimal point of operation, which results in a more economic and environmental-friendly process and contributing to the risk analysis. Consequently, the presented approach could play a significant role in further integration of continuous processes.

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VIRTUAL SCREENING AND BIOCHEMICAL TESTING OF BOROCYCLES AS IMMUNOPROTEASOME INHIBITORS

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The proteasome is a multiprotein complex which has multicatalytic properties. It can be divided into two parts: the 19S regulatory particle (19S RP) and the 20S catalytic core particle (20S CP). The immunoproteasome (iCP) is an isoform of the 20S CP. Selective inhibition of iCP offers new opportunities in the treatment of inflammation, autoimmune diseases, hematologic malignancies and central nervous system diseases and senility. ^[1]

Recently we have turned our attention to identify inhibitors for the chymotrypsin-like ($\beta 5i$) subunit of the iCP. Boronic acids are known and potent covalent inhibitors of the CP and iCP ^[2,3] and one representative CP inhibitor, Bortezomib is already in clinical use. Inspired by the success of boronic acids against CP we have turned our attention to cyclic boronic acids. As a first attempt, 404 commercially available 5- and 6-membered borocycles were collected for virtual screening. The top scored docking poses were visually inspected to select compounds for experimental testing. Six compounds with 5-membered ring and another six compounds with 6-membered ring were subjected to biochemical tests. All compounds exhibit detectable inhibitory activity at 100 μ M concentration, the remaining activity is around 50%, suggesting IC₅₀ values in the 100 μ M range. Figure 1. shows the general formula of the examined borocycles, and two hit examples, which have the best inhibitory activity. To the best of our knowledge, no cyclic boronates were investigated as iCP inhibitors until the present work.

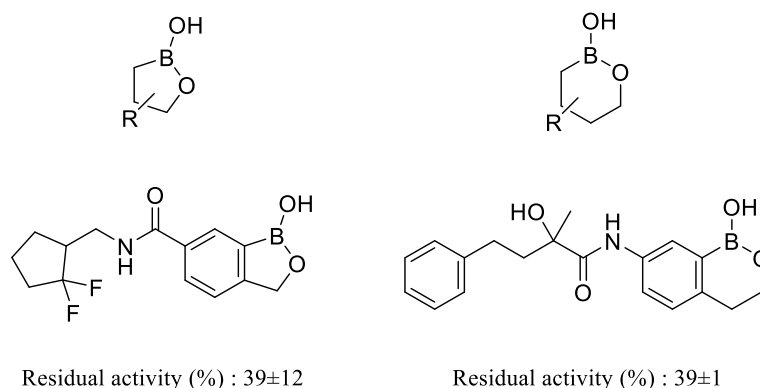


Figure 1. General formula for the borocycles with 5- and 6-membered rings, two hit examples with inhibitory activity at 100 μ M concentration.

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TESTING THE GOODNESS OF FIT OF REGRESSION MODELS ESTIMATED WITH EXTREMELY SMALL SAMPLES IN PHARMACEUTICAL STABILITY STUDIES

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Pharmaceutical stability studies are conducted with the purpose of estimating the shelf life, i.e. the time period during which the drug maintains its identity and stability. In stability studies certain attributes of the drug products are monitored over time. Regression curve is fitted on the data obtained during the study and the shelf life is determined by using the fitted curve. The evaluation method of determination of shelf life is given in ICH Q1E guide.[1] The guide considers the evaluation process in the case when the true relationship between the measured attribute and time is linear. However, the guide does not help the practitioner to decide if the linear model is appropriate for their dataset. This is a major problem, as falsely fitted model can distort the estimated shelf life in a great extent making the whole quality assurance system unreliable. The difficulty in model verification (i.e. detection of model misspecification) is that very few observations are available in a given stability study. The conventional methods applied for model verification might not be appropriate or effective. We address this problem, by employing information obtained from historical stability studies and use it in our developed methods. The methods can be applied for any process where the regression estimation is performed on independent small samples. Beside stability studies, frequently performed construction of single calibration curves for an analytical measurement is another case where the methods can be useful. It is showed that the methods are statistically appropriate and some of them have high effectiveness in detection of model misspecification.

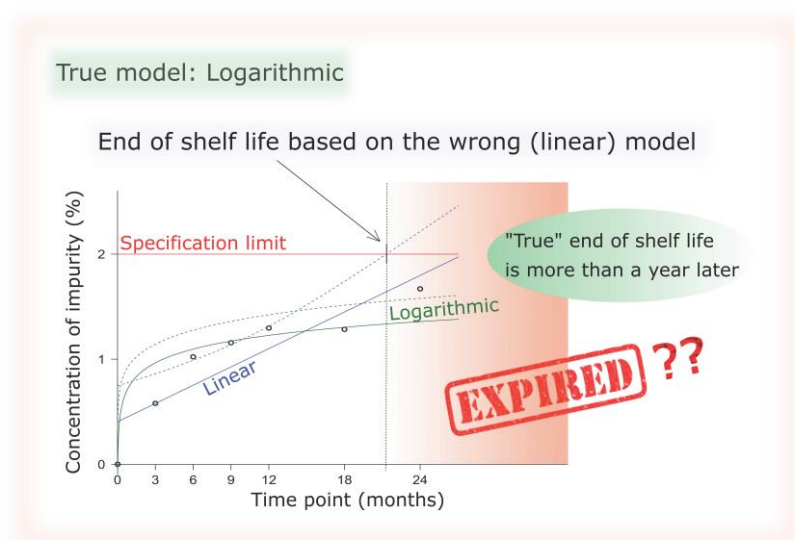


Figure 1. Motivation of the work: Estimation of shelf life is more than a year earlier when the wrong model is fitted

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CHEMICAL AND TECHNOLOGICAL PROPERTIES OF RYE VARIETIES AND FRACTIONS OBTAINED FROM INDUSTRIAL MILLING TRIALS

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The utilisation of rye shows a continuous increase in the food industry. Its favorable nutrient composition, especially dietary fiber content and composition, has beneficial effects on the nutritional and health promoting properties of food products. Baking industry is the main processing sector for rye, where, in addition to the chemical composition, the technological properties of the rye flours (e.g. the rheological properties of dough) fundamentally determine the complex quality of bakery products. The aim of our work was to determine the macronutrient composition and technological properties of different rye varieties and their flour fractions, produced in experimental design based industrial-scale milling trials. Standard and/or widely used approved analytical (moisture, ash, crude protein, crude fat, dietary fiber) and rheological (Falling number, RVA, Zeleny index, Mixolab) methods were used for fulfilling our research goals.

In terms of chemical composition, no significant differences were found between the wholemeal flours of the studied rye cultivars. The samples had a crude protein content of 11-13% and a crude fat content of 1.7-2.2%, similarly to wheat, however, their dietary fiber content (14.4-15.1%) exceeded the literature value of wholemeal wheat flour. The rye varieties showed significant differences in the rheological properties of dough, especially in the viscous behavior, which has been less studied so far. Regarding the industrial milling fractions, significant differences were measured in protein, ash and especially in dietary fiber content and composition. Based on these results, some rye milling fractions with acceptable yield, valuable nutritional properties and technological character were selected for further variety-dependent investigations.

Using the methodology described above, the complete “map” of the investigated milling technology and its milling products was created. Currently, the effects of variety on the chemical and technological quality of milling fractions were investigated. This solution is novel in our field and allows the production of milling products rich in health-promoting ingredients with special, designed composition and properties. In addition, there is an opportunity to study the relationships between the investigated properties and chemical composition, as well as macromolecular characteristics.

This research and breeding activity was financially supported by “GalgaGabona” Projects (2017-1.3.1-VKE-2017-00004). The work is also connected to the goals of the BME-Biotechnology FIKP grant of EMMI (BME FIKP-BIO).

INVESTIGATION OF THE VARIETAL EFFECT ON THE COMPOSITIONAL, TECHNOLOGICAL AND THE BAKING QUALITY OF OAT FLOURS

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A broader utilization of oat in human diet is taken an interest because of its favorable nutritional value: beside the complex source of carbohydrates, special dietary fiber components like β -glucane, high unsaturated fatty acids, oat is also rich in health promoting and biologically active components.^[1] Furthermore oat can be included in a gluten-free diet assuming that contamination with wheat is eliminated by monitoring the whole production chain with strict food safety oversight. To achieve this, we need to get a better understanding of oat flours.^[2] The aim of our research is to investigate the varietal effect of some common and some special oat varieties on the compositional, rheological and baking quality properties, and together with this develop the overall qualification system of oat.

The nutritional parameters of the selected oat varieties and the commercial oat flours were examined by standard methods. The rheological properties were measured by instruments routinely used in wheat qualification with slightly modifications in the methodology (Mixolab, farinograph, rapid viscoanalyzer). The baking quality was investigated with a modified standard baking method to get a better insight of the pasting properties of oat flours. To understand the molecular changes, flours and breads were examined by scanning electron microscope.

As our results show, there are differences among the oat varieties in the chemical composition. A special variety contains nearly equal quantity of soluble and insoluble fibre, which can be really favorable. We can detect differences in the rheological properties, too. According to the baking test, it can be said that the loaves have stable crumbs and acceptable organoleptic qualities, but the loaves made from heat treated oatmeals turned out much more acceptable than the others. This shows that the heat treatment can affect not only the stability and durability of flours, but their rheological and technological behavior, too. Our further plan is to take wider examinations. In conclusion, we can state that the qualification methods used for wheat can be used in the characterization of oat flour, but with slightly modifications. With a proper material selection, baking product with higher nutritional value and preferable technological properties can be made. Our work is connecting to the goals of the BME – Biotechnology FIKP grant of EMMI and the “GalgaGabona” project (2017-1.3.1-VKE-2017-00004).

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INTERPLAY BETWEEN THEORY AND EXPERIMENT: APPLICATIONS OF MICROKINETIC MODELING IN MOLECULAR CATALYST DESIGN AND IN CANCER RESEARCH

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The two branches of chemistry, theory and experiment, are interdependent: theoretical calculations are required for the evaluation of experimental results (e. g. for the exploration of mechanisms), while experimental data are indispensable for theoretical works (e. g. for method validation). Still, the cooperation between the areas is often cumbersome as the results of computations - typically reaction and activation energies - are difficult to interpret for experimentalists who observe macroscopic properties such as yield, reaction time and the time course of concentrations.

Our research group utilizes microkinetic modeling as a bridge between computational and experimental data. In this approach, the computed activation Gibbs free energies ($\Delta G^{\ddagger 0}$) of elementary reaction steps are converted to rate constants (k) using the Eyring equation:

$$k = \frac{k_B T}{h} e^{\frac{-\Delta G^{\ddagger 0}}{RT}}$$

Then, the system of reaction rate equations is solved numerically to obtain the the time course of concentration of all intermediates, which is exactly what one can measure experimentally (Figure 1). By comparing the simulated evolution of concentrations to available experimental data, the rate constants can be fine-tuned to eliminate the error of computation. In this way, an accurate theoretical model of the studied reaction mixture can be gained, which can be used to optimize reaction conditions or explore quantitative structure-reactivity relationships without the need of a large number of experiments.

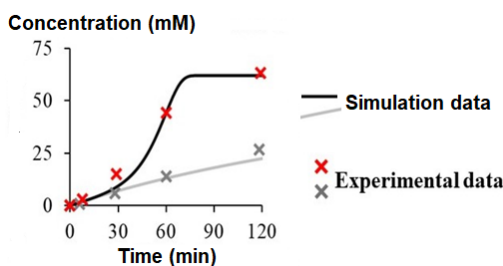


Figure 1. Validation of a microkinetic model: comparison of simulated (solid lines) and experimentally measured (crosses) time course of concentration of two selected intermediates.

In this presentation, two practical applications of microkinetic modeling is discussed: the rational (mechanism-based) design of biomimetic ammonia synthesis catalysts [1-3] and the evaluation of carcinogenic potential of estrogen hormones.

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FLAME RETARDANCY OF FLAX FABRIC REINFORCED POLYLACTIC ACID COMPOSITES

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Flame retardancy and mechanical performance of multi-layered biocomposites, consisting of polylactic acid (PLA) matrix films and plain-woven flax fabrics as reinforcement, were investigated. Full factorial design (3^2) was applied to evaluate the effects of the distribution of P and N containing compounds between the matrix and the fibrous carrier. Composition property correlations of the composite constituents (i.e. flax fabrics treated in aqueous solutions of diammonium phosphate (DAP) and urea with differing ratio and concentrations and matrix films with 0 to 20 wt% ammonium polyphosphate based intumescent flame retardant content) were determined by thermogravimetric analyses and open flame tests. Positive interaction between the composite constituents was revealed for green composites consisting of various combinations of treated fabrics and intumescent PLA systems. The biocomposites flame retarded with a combined approach, i.e. with a balanced distribution of P containing additives between the phases, were found to gain improved mechanical performance and fire retardancy. It was confirmed by tensile testing and electron microscopy as well as by UL-94, limiting oxygen index and cone calorimeter tests (Fig. 1). As a conclusion, interpretation is given for the optimum found.

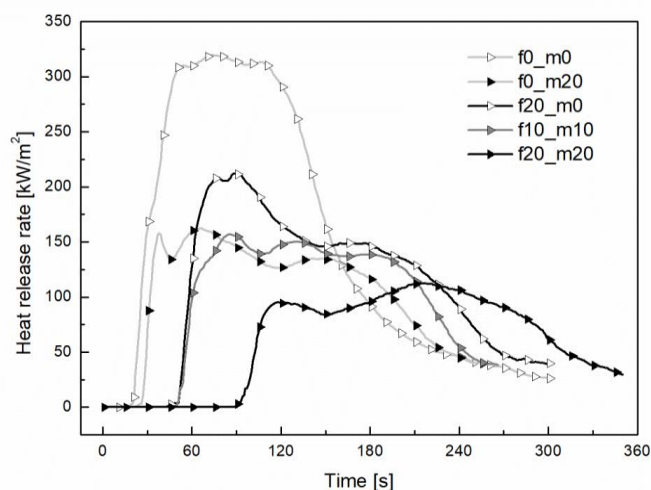


Figure 1. Heat release rate curves of the flame retarded biocomposites (fX marks the DAP/U concentration of the flax fabric treating solution and mX marks the IFR content of the matrix films).

SYNTHESIS AND APPLICATION OF HETEROGENEOUS RECYCLABLE CINCHONA-BASED ORGANOCATALYSTS

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Owing to their successful application in asymmetric reactions, cinchona-based organocatalysts are widespread in the field of organocatalysis. Since the recovery of homogeneous catalysts is essential for their economical application, their recycling is crucial. Heterogenization or immobilization on a support promises a solution for reusing them. Herein this work presents two new heterogeneous recycling methods for reusing these organocatalysts: immobilization of cinchona-based organocatalyst on a polymer carrier (Figure 1A), and their heterogenization by preparing non-soluble nickel complex^[1,2] (Figure 1B).

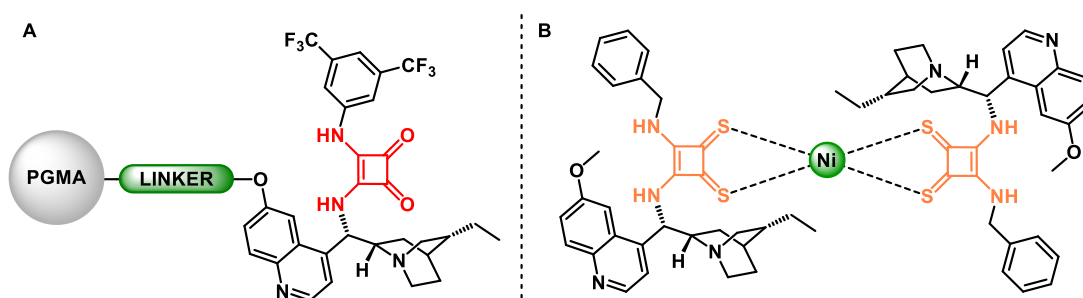


Figure 1. Heterogeneous cinchona-based organocatalysts.

As a polymer support, poly(glycidyl methacrylate) (PGMA) microspheres were prepared by radical dispersion polymerization. By taking advantages of reactive epoxy-groups, cinchona squaramide was immobilized on PGMA via linker containing primer amino groups.^[2] In the reaction of Ni(OAc)₂ and the corresponding thiosquaramide, a complex was prepared, which is insoluble in the most organic solvents.

The catalysts were tested in *Michael* addition reaction of *trans*- β -nitrostyrene and pentane-2,4-dione. Up to 96% enantioselectivity and 99% yield was obtained. Following the first round, they were recycled four times by centrifugation. The enantioselectivity did not change, but a slight decrease in yields was observed.

This research was funded by the New National Excellence Program of the Ministry of Human Capacities, grant number ÚNKP-19-3-I-BME-325, ÚNKP-19-4-BME-415, and the Janos Bolyai Research Scholarship of the Hungarian Academy of Science. It was also supported by the National Research, Development and Innovation Office (former OTKA, grant number K128473).

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APPLICATION OF ELEMENTAL SULFUR IN MULTICOMPONENT REACTIONS

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Multicomponent reactions (MCRs) are significant and efficient methods in modern synthetic chemistry due to their ability to produce complex structures, even in one technological step, or to provide environmentally friendly, atom economic and safe alternative to existing synthetic procedures.^[1–3] In addition, using the naturally occurring, non-toxic and easy-to-handle elemental sulfur in organic synthesis promotes the substitution of hazardous, toxic reagents and maximizes the atomic efficiency of chemical reactions^[4–6].

Herein we present our research from the recent 2 years on the field of multicomponent reactions with elemental sulfur (Figure 1). Our work covers the development of efficient methods for the catalyst-free synthesis of isothiocyanates from isocyanides and elemental sulfur and their application in multicomponent reactions to synthesize thiocarbamates,^[7] thioureas,^[8] 2-aminothiazoles and thiazole-2-imines. Moreover, the introduction of the aqueous solution of polysulfide anions enabled the use of elemental sulfur under continuous flow conditions^[9] and the clean, chromatography-free synthesis of thioureas.^[8] In continuation of our efforts in developing new multicomponent reactions, the novel synthesis of thiols and thioethers starting from electron deficient olefins and elemental sulfur is presented.

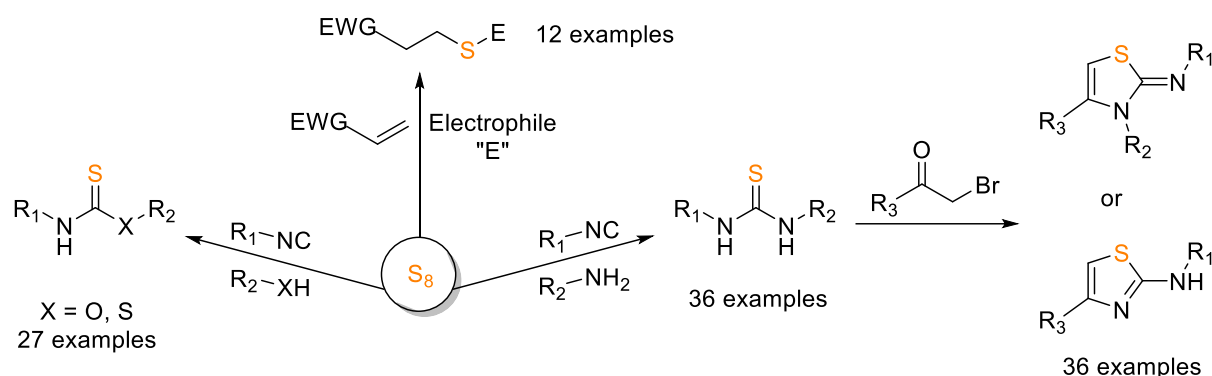


Figure 1. Multicomponent reactions based on elemental sulfur.

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SYNTHESIS AND CHARACTERIZATION OF NEW INTUMESCENT FLAME RETARDANT ADDITIVES IN POLYPROPYLENE

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Abstract

The aim of the research was to improve the flame retardant properties of polypropylene (PP) with a new, bio epoxy resin microencapsulated ammonium-polyphosphate (APP) with different APP:epoxy resin ratio. The synthesized flame retardants were added to the PP at different loadings (5wt% - 35wt%) to test their efficacy on the flame retardancy of the polymer. As PP has no ability to form a charred layer on its own, the flame retarded system needs the addition of carbonizing agent in a relatively great amount. Bio epoxy resin encapsulated APP contains all the properties which characterize an effective intumescent flame retardant system: it acts as the acid source, blowing agent and charring agent, and therefore the flame retardant properties of polypropylene were significantly improved.

Keywords: flame retardant, microencapsulation, polypropylene, ammonium-polyphosphate

SYNTHESIS OF TiO₂/WO₃ COMPOSITE NANOFIBERS BY A WATER-BASED ELECTROSPINNING PROCESS AND THEIR APPLICATION IN PHOTOCATALYSIS

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Coupling TiO₂ with other semiconductor oxides like WO₃ is one of the methods of enhancing the efficiency of its photocatalytic activity. It increases the light-absorbing range of TiO₂ to higher wavelength and decreases the recombination speed of the charge carriers^[1,2,3]. The challenge of synthesizing composite TiO₂/WO₃ nanofibers using a single technique has been that while most TiO₂ precursors hydrolyze in water, WO₃ precursors are water-soluble. In this study TiO₂/WO₃ nanofiber were prepared in a one-step process by electrospinning using water soluble precursors. Further, to that the as-spun fibers were annealed in oxidizing and inert atmospheres to investigate the effect of annealing conditions on the fiber composition and characteristics. Titanium (IV) bis(ammonium lactato)dihydroxide (TiBALDH) and ammonium metatungstate (AMT) were used as water-soluble Ti and W precursors, respectively. Polyvinylpyrrolidone (PVP) and varying ratios of TiBALDH and AMT were dissolved in a mixture of H₂O, EtOH and CH₃COOH. The as-spun fibers were then heated in air and argon at 1 °C min⁻¹ until 600 °C to form TiO₂/WO₃ composite nanofibers. Fiber characterization was done using TG/DTA, SEM–EDX, FTIR, XRD, UV-Vis diffuse reflectance spectroscopy and Raman. Fibers annealed in air had smallest diameter compared to the fibers annealed in argon. The 100% TiBALDH nanofibers annealed in air had a diameter range of 130–170 nm, while those annealed in argon had a diameter range of 320–3420 nm. The results showed an increase in the fiber diameter with an increasing amount of WO₃. Pure TiO₂ had a band gap of 3.06 eV, the band gaps of the composite fibers decreased as the amount of WO₃ increased. The photocatalytic property of the fibers was also checked for methyl orange bleaching in visible and UV light. In visible light, the photocatalytic activity increased with an increase in the ratio of AMT, while 50% TiBALDH composite fibers showed the highest activity among the as-prepared fibers in UV light

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DESIGN OF CONTINUOUS CRYSTALLIZATION TECHNIQUES FOR DIRECT PROCESSION OF A FLOW REACTION MIXTURE

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Crystallization — as the most widespread separation, purification, and morphology-determining method — is a critical technology, that could be made safer and more economical by using continuous crystallization alternatives. Several flow syntheses are presented in the literature, however, just some of the produced reaction mixtures are processed with continuous crystallization techniques.^[1,2] Accordingly, we aimed to develop continuous crystallization methods for direct isolation and purification of acetylsalicylic acid (ASA) from its multicomponent reaction mixture.^[3] It was accomplished in three different continuous crystallization equipment (Fig. 1): (i) a single-stage mixed suspension mixed product removal (MSMPR) crystallizer equipped with an overflow tubing and an inner buffer element,^[4] (ii) a plug flow crystallizer (PFC) with a coaxial mixer, and (iii) a triple impinging jet (IJ) mixer supplemented by MSMPR crystallizer with an overflow. The effect of process parameters such as the operation temperature, the length of residence time (flow rate), the antisolvent to ASA solution ratio on product quality, and quantity was studied at more levels. We also aimed to compare the listed continuous crystallizers by characterizing their product in terms of crystal size, crystal size distribution (CSD), and purity. We found that in MSMPR crystallizer large isometric but polydisperse crystals with appropriate purity (>99.5%) and yield (58-79%) could be obtained due to the longer residence time. In PFC small, uniform, needle-shaped crystals ranged in 12-20 μm was produced with a slightly higher impurity content ($\sim 0.7\%$). Using the triple impinging jet mixer smaller crystalline product, with narrow CSD were collected with higher yield (64-83%) comparing to the yield of an MSMPR crystallizer without the IJ element. Our study could serve as a guide to choose among continuous technologies for producing a crystalline product with desired morphology, purity, and yield.

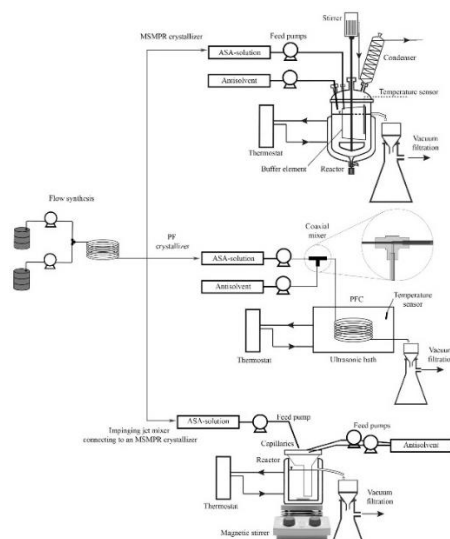


Figure 1. Schematic image of the developed continuous crystallization techniques.

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PREPARATION OF OPTICALLY ACTIVE ANTIPYRINE DERIVATIVES BY MANNICH REACTION A NOVEL METHOD

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Increasing number of active ingredients produced by the pharmaceutical industry are asymmetric molecules, which are mostly obtained in racemic form during syntheses. However, in many cases, only one enantiomer of the racemic compound possesses the desired therapeutic effect, so this effective enantiomer must be prepared. The best known and most economical method used in the pharmaceutical industry is enantiomeric separation through diastereomeric salt formation (resolution). Now I would like to present the possibilities for the preparation of pure enantiomers of the base obtained in the Mannich reaction. Mannich bases prepared from antipyrine and its derivatives have come to the fore mainly due to their antipyretic and analgesic effects^[1], but their antiviral, antibacterial, antifungal, and herbicidal effects have also been observed^[2]. Complexes of these Mannich bases with certain metals (Pt (II), Co (II), Cu (II)^[3]) have also shown antitumor activity in in vitro studies.^[4-7] In a joint project with a research group of the Romanian Academy of Sciences in Timisoara, our goal was to create additional pharmacologically active, chiral Mannich products, preferably from reactants that possess physiological effects. The preparation of these Mannich bases were performed in three ways.

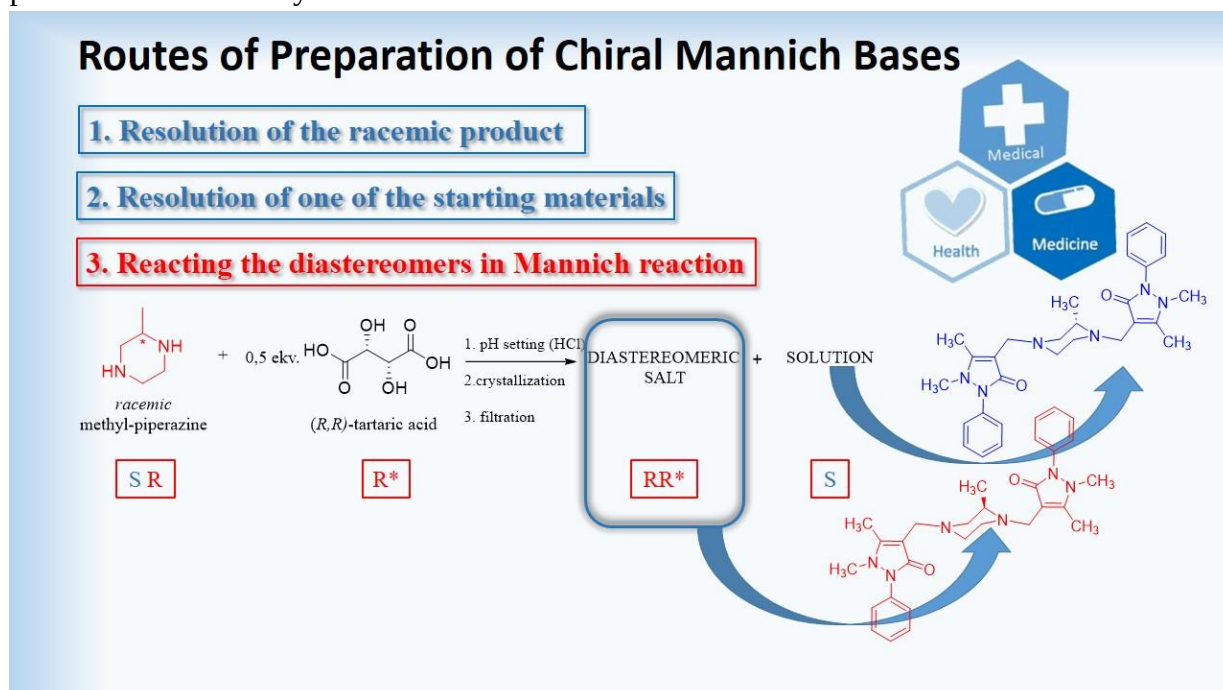


Figure 1. Three possible ways to produce chiral Mannich products

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EFFECT OF THE PREPARATION METHOD ON THE DISSOLUTION OF AMORPHOUS SOLID DISPERSIONS

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Preparation of polymer-based amorphous solid dispersions is a widely used strategy to improve the dissolution of poorly water-soluble drugs [1]. However, the selection of the preparation method can be challenging. [2] To explore the possible pitfalls, this research aimed to compare two solvent-based methods, namely the electrospinning and the spray drying.

During the experiments, spironolactone was used as a model drug while poly(vinylpyrrolidone-co-vinylacetate) was applied as a polymer matrix. The drug-loaded electrospun and spray-dried materials were prepared by using the same equipment. Both products proved to be amorphous according to the differential scanning calorimetry and the X-ray powder diffraction results. However, the dissolution of the spray-dried sample showed similarity with the micronized crystalline drug while the electrospun sample reached close to 100% dissolution. The polarized microscope images and Raman microscopic mapping of the samples showed that small crystalline traces were in the spray-dried particles, which can contribute to the deteriorated dissolution. The precipitated particles were visible during the dissolution. In addition, Raman spectroscopic measurements confirmed the appearance of the crystalline active pharmaceutical ingredient. The potential reasons for the presence of crystalline traces were investigated as well.

The results highlighted that the evaporation rate of residual solvents and the influence of the electrostatic field during the sample preparation have a great effect on the formation of crystalline traces and thus on the dissolution of the electrospun and spray-dried products. Consequently, it is worth putting a lot of emphasis on the selection of a suitable preparation method to avoid poor dissolution.

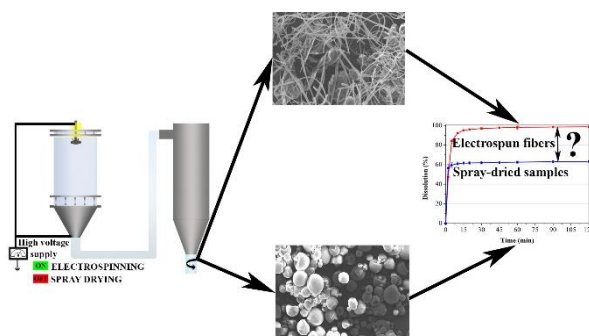


Figure 1. Preparation of amorphous solid dispersion by electrospinning and spray drying

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IN-FLIGHT SYNTHESIS OF NANOSIZED ZrC PARTICLES FROM VARIOUS PRECURSORS IN RF THERMAL PLASMA

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Synthesis of zirconium carbide (ZrC) powder was investigated applying a non-conventional atmospheric radiofrequency (RF) thermal plasma process. In one case, zirconium dioxide (ZrO₂) was reacted with solid carbon or with methane (CH₄) gas with varying molar ratio. On the other, zirconium-propoxide (NZP), containing both constituents, was thermally decomposed in the argon plasma.

Temperature-dependence thermodynamic analysis was performed in the 500-5500 K temperature range to estimate the formation of products in equilibrium for each system. A broad temperature range exists for the stability of solid ZrC for each explored reaction. In accordance with this prediction, X-ray diffraction studies detected the ZrC as the major phase in all the prepared powders. The yield of particular runs ranged from 39% to 98%. Practically, full conversion was typical for the case of NZP precursor. However, only partial conversion could be detected in ZrO₂ reactions.

The average particle size of the powders falls between 10 nm and 100 nm depending on the type of the reaction systems (either calculated from the specific surface area or derived from broadening the XRD reflections). The transmission electron micrographs indicated mostly globular shape of the nanosize particles. Quantitative analysis of the surface of the powders by X-ray photoelectron spectroscopy (XPS) revealed the presence of oxygen and carbon. Evaluating the spectra of the powders prepared from NZP, and taking in the account its spherical shape, a ZrC core covered by a very thin (≈ 1.0 nm) ZrO₂ layer may be accounted for the measured oxygen and a thicker carbonaceous layer.

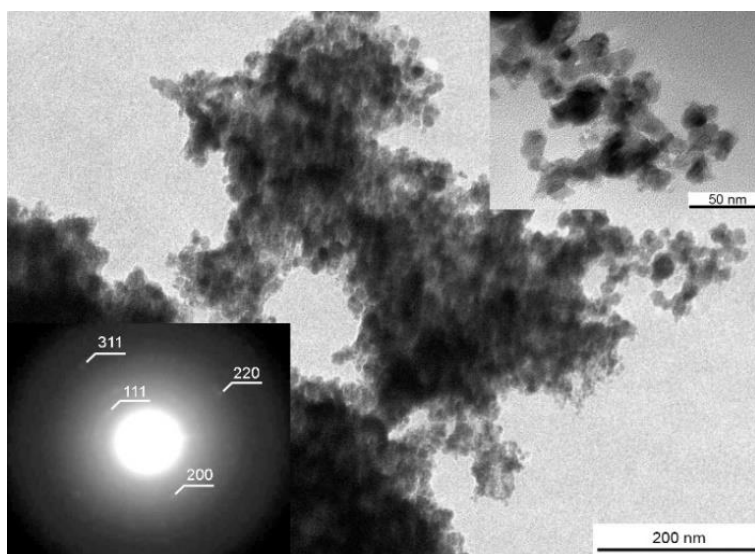


Figure 1. TEM micrograph and SAED pattern of the product obtained from NZP.

C₃-SYMMETRICAL MOLECULAR SIZE-ENLARGED ORGANOCATALYSTS FOR MEMBRANE-SUPPORTED RECOVERY

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Doubtless, catalysis has significantly affected the chemical industry as more than 90% of the chemical processes utilize some catalyst. Due to catalysis, a substantial amount of energy and resources are saved, while considerably less waste is generated. Organocatalysts are generally small, metal-free, organic molecules capable of accelerating chemical transformation. In spite of the advantages organocatalysis has, high catalyst loadings and long reaction time are generally experienced disadvantages. In the pursuit of improved organocatalytic methodologies, increased attention is paid to the recovery and reuse of organocatalysts. Membrane-based separations are proved to be sustainable with low energy needs. As the efficiency of separation depends mostly on (i) the molecular weight gap, and (ii) the absolute catalyst retention, thus, molecular weight enlargement (MWE) of small catalysts is usually required.^[1] In this work, MWE of cinchona- and TEMPO-based organocatalysts using the “hub-approach” is presented.^[2]

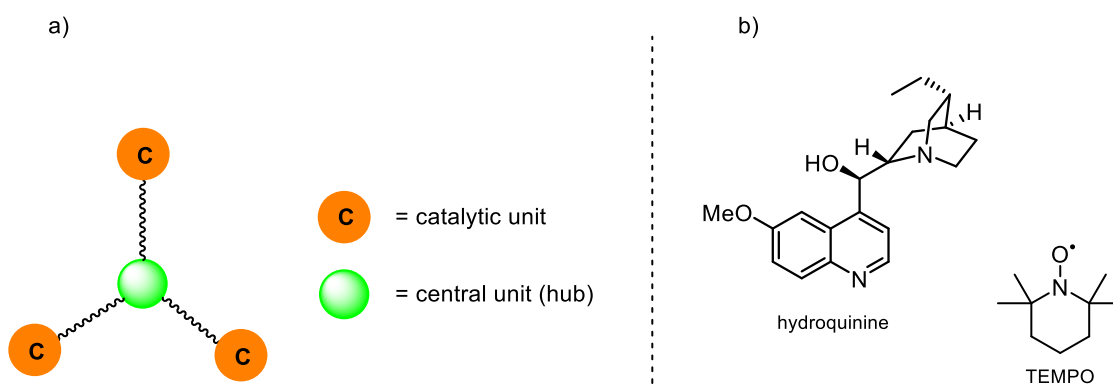


Figure 1. “Hub approach” for molecular weight-enlargement of organocatalysts (a), and the applied organocatalysts (b)

Several C₃-symmetrical cinchona- and TEMPO-based organocatalysts were prepared to facilitate their recovery by membrane filtration. The newly prepared cinchona derivatives were used in the hydroxyalkylation reaction of indole and in Michael addition reaction with low to high selectivities and yields. The size-enlarged TEMPO catalyst showed similar catalytic activity to the native TEMPO and was successfully applied in the electrochemical oxidation of biomass-based 5-hydroxymethylfurfural into 2,5-diformylfuran with excellent selectivity. Following the applications, the C₃-symmetrical catalysts were easily recovered using organic solvent nanofiltration.

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