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ABSTRACTS OF PHD THESES

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DEVELOPMENT OF ORGANIC PHASE BIOSENSORS FOR ANALYSING FOOD SAMPLES

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The objective of our research was to develop organic phase enzyme based biosensors applied in an FIA system. We developed methods for determining glucose, hydrogen peroxide and cholesterol. We investigated the conditions of enzyme activity, and optimized the chemical and biochemical parameters of the biosensor. The methods were applied to the analysis of different food samples, and simple sample pre-treatment was developed.

A flow-through measuring apparatus for the determination of glucose content was developed as a model system in organic media; properties of the biosensor were compared in organic and in aqueous solutions. On the basis of these results, I concluded that biosensors using enzymes with covalent immobilization can be used in an organic phase FIA system with the eluent containing the optimized quantity of buffer.

A simple stopped-flow system was developed in order to ensure that samples spend the time required to complete the enzymatic reaction in the enzyme cell; different immobilization methods were compared. For measuring hydrogen peroxide content, the enzyme immobilized together with PEG showed reliable and repeatable results, and in addition this enzyme cell could be used for the longest time.

An indirect way to determine moisture content in different food samples was also developed, and the results obtained by our method were compared to those of reference.

For determining free cholesterol, a cholesterol oxidase containing enzyme cell was developed. The effect of apolar solvent on the activity of the enzyme was studied.

For determining total cholesterol, a bienzyme cell containing cholesterol oxidase and cholesterol esterase was developed. The rate of conversion of cholesterol oleate was investigated.

The biosensor methods developed were used successfully to measure the chemical composition of different food samples, only partly soluble in water. Easy and rapid methods were developed for food sample pre-treatment.

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SYNTHESIS, THERMAL AND ENZYMATIC STABILITIES OF OLIGONUCLEOTIDE CHIMERAS

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Model trideoxynucleotides ($G_{PS}C_{PO}$AZT, $G_{PS}C_{PO}$T and $T_{PS}A_{PO}$AZT were prepared according to the H-phosphonate method in solution. Model compounds ($G_{PS}C_{PO}$FdU, $T_{PS}A_{PO}$FdU and $T_{PS}A_{PO}$T were synthesized on solid phase by using the phosphoramidite protocol. Their hydrolyses by snake venom phosphodiesterase (SVPDE) showed that all the six chimeric trimers were substrates of the enzyme. Selective cleavage of the phosphodiester bonds was observed in each case. The base modification (C^5-Me $\rightarrow$ F exchange) and especially the sugar modification (3'-OH $\rightarrow$ 3'-N_3 exchange) increased the enzymatic stability. In order to study the applicability of this model a 18-mer thiophosphate AON and its three chimeras, containing 1, 3 or 6 FdU units connected by phosphodiester bonds, were synthesised on solid phase using phosphoramidite protocol. Although the thiophosphate AON selectively and efficiently inhibited the biosynthesis of the MMP-9 isoenzyme of human collagenase IV, but it did not have any antiproliferative activity in HT 1080 human fibrosarcoma cell line. At the same time, the PS-PO chimeras were about by one order of magnitude more active than the reference FdU.

In order to study the biophysical and biochemical properties of PNA-DNA chimeras four PNA-DNA dimer synthons (oeg_t^{NH}T, oeg_t^{NH}dA, oeg_up^{NH}T, oeg_uh^{NH}T) were prepared in solution and according to the standard solid phase phosphoramidite DNA synthesis protocol they were incorporated into internal and terminal positions of different oligonucleotides. By incorporation of oeg_t^{NH}T and 5-alkynyl-uracil containing PNS derivatives T_{12}- and T_{20}-, by incorporation of oeg_t^{NH}dA dimer alternating $(TdA)_{10}$- analogues were prepared. Incorporation of dimer synthons led to drop of T_m values relative to those of reference T_{20}:dA_{20} or $(TdA)_{10}$ duplexes, but the degree of T_m drops strongly depended on the number and position of dimers incorporated. Interestingly, when two oeg_t^{NH}dA dimer blocks were positioned in the middle of the sequence of alternating $(TdA)_{10}$ it resulted in smaller T_m drop than similar incorporation of only one oeg_t^{NH}T unit into T_{20} caused. It can be explained by the different duplex structures since $(TdA)_{10}$ analogues are equilibrium mixtures of inter- and intramolecular duplexes. In the latter case the two middle dimers form a loop so they cannot involve in duplex formation. The methyl $\rightarrow$ propynyl exchange in the uracil PNA moiety resulted in noticeable duplex stabilization effect independently on the place of incorporation. For chimeras containing 5-hexynyl-uracil PNA units, the stabilizing effect of the triple bond and destabilizing effect of the long alkyl side-chain give little

positive ΔT_m values relative to the thymine containing counterparts. Incorporation of dimer blocks increased the stability against exonucleases in each case. The 5'-modified analogues were found to be much less resistant to the hydrolysis by 5'-exonuclease (BS PDE) than the 3'-modified derivatives to the 3'-exonuclease (SV PDE) digestion. It can be explained by the higher endonuclease activity of BS PDE. In cases of both enzymes the stability of chimeras increased with the longer 5-substituent of PNA base moiety since the bulky substituents may inhibit the substrate binding to the active site of enzyme. Neither exonucleases (SV PDE and BS PDE) nor an endonuclease (Nuclease P_1) could hydrolyse the unnatural phosphodiester bond between the secondary OH of thymidine and the terminal OH of N-(2-hydroxyethyl)glycine PNA moiety.

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SYNTHESIS OF CARBOHYDRATE-BASED CROWN ETHERS AND THEIR APPLICATION IN ENANTIOSELECTIVE REACTIONS

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Chiral macrocycles having D-glucose-, D-mannose-, D-mannitol units have been synthesized, these compounds consist of different heteroatoms (C, N, S, P) in the crown-ring. Some 18-crown-6 type compounds incorporating two desoxy-ribo-hexapyranoside have been obtained in seven steps. These crown ethers were used as chiral phase transfer catalysts in three enantioselective reactions: in a Michael addition, in a Darzens condensation and in an epoxidation of double bond, with high enantioselectivity (92-97 % ee). Connection between the structure of the catalysts and their influence have been established.

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THIACALIXARENES AND THE MITSUNOBU REACTION- A NEW PERSPECTIVE FOR THE SYNTHESIS OF CALIX[4]CROWN ETHERS

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1. Thiacalix[4]bis(crown-5 and 6)ethers were synthesized by the cyclization of thiacalix[4]arenes with tetra- and pentaethylene glycol derivatives in the presence of alkali carbonates and it was revealed that the reaction does not stop at monocrown level. The latters were preparated from 1,3-thiacalix[4]diethers by the same method. The complexing abilities of ligands were determined by alkali (Li^+, Na^+, K^+, Rb^+, Cs^+) picrate extraction method and it was found that these mono- and bis(crown-6) derivatives exhibited excellent cesium selectivities, suitable for analytical purposes as ion-selective potentiometric PVC membrane electrodes.

2. The selective 1,3-di-*O*-alkylation of *p-tert*-butylthiacalix[4]arene with a series of alcohols was demonstrated for the first time under the Mitsunobu protocol and the method was expanded to the synthesis of tetraethers.

3. The first regioselective cyclization of *p-tert*-butylcalix[4]arenes with oligoethylene glycols was accomplished under Mitsunobu protocol and a mechanistic pathway was suggested to describe the outcome of the reaction. The scope of cyclization was expanded to a series of aza- and thiaanalogues, and a number of novel 1,3-thiacalix[4]aza-and/or thiacrowns were synthesized.

4. On the basis of the products obtained in the reactions of calix[4]arene and thiacalix[4]arene with several long chained 1,n-diols I have printed out that the regioselectivity of cyclizations described in thesis points 3 and 4 depends on the intramolecular distances of the reactive groups in the open chained betaine intermediete formed after the first alkylation step. The different behaviour of calix[4]arene and its thia analogue can be attributed to the difference in the ring size of the macrocycles and to the acidity of the hydroxyl groups.

An unprecedented *O*, *S*-cyclization was observed in the Mitsunobu reaction of *p-tert*-butylthiacalix[4]arene and 1,2-diols affording the unique sulfonium phenoxide betaines **40**, **41** and their stuctures were elucidated by NMR and chemical methods.

5. I have synthesized for the first time *p-tert*-butylthiacalix[4]dimers by the Mitsunobu coupling of *p-tert*-butylthiacalix[4]arene and diethylene glycols. Depending on the glycol used dimers and/or the inherently chiral 1,2-thiacalix[4]crown-3 derivatives were formed.

The enantiomeric separation of the 1,2-thiacalix[4]mono(phenyl-azacrown-3) derivative was achieved by chiral HPLC and the CD spectra of the fractions confirmed their enantiomeric nature.

6. Efforts have been made to synthesize thiacalix[4]tubes i.e. dimers containing terminal crown rings which may be mimetics of the iontransport in cell

membranes. All attempts with the Mitsunobu coupling and with base-mediated cyclizations of dimers or monocrowns failed, instead half-crowned dimers or 1,3-*alt* biscrowns were formed. Therefore, the reactivity of the hydroxyl groups in dimers was studied in base-promoted exhaustic alkylations and it was found that in most cases only partially alkylated products were formed with different stereoselectivity.

7. A part of the macrocycles was further transformed to ionophores (with or without chromogenic function) and preliminary binding studies were carried out to estimate the ion-sensing properties by ^{1}HNMR, UV/VIS spectroscopic and potentiometric methods.

We found that ligands with cyclic O_2S_2N binding site recognize soft metal ions such as Ag^+, Hg^{2+}, Zn^{2+}, Cu^{2+}.

8. I have synthesized thiacalix[4]monocrown-6 based cesium ionophore which can be immobilized by chemisorption on the surface of a gold plate. The sensor fabricated from these ligands are expected to eliminate the problems of the classical membrane technics, providing at the same time variable possibilities for the analytical detection.

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PHARMACEUTICAL AND POLYMER TECHNOLOGICAL DEVELOPMENTS BASED ON COMPUTER CONTROL

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The automatic reactors are commonly used in the industry, because the safety of the production process and the consistent quality of the products can be most effectively guaranteed by automated systems. According to the literature, the capabilities of the highly automated batch and semi-batch reactors are not adequately exploited, because the development is mainly done by traditional laboratory techniques and equipment, even in the cases of new technologies. The more economical production is limited by the lack of controlled model equipment and specialized knowledge. The aims of this dissertation were the development and application of the computer-controlled reactor calorimeter for batch and semi-batch reactions, which was applied in both education and research. The operation level control concept, proposed in the literature of process control, was improved by forming a programme part at basic process level. At this level the general operation units, which represent different chemical basic processes can be developed and stored. This highly reduces the time and the cost of the creation of process control recipes. Recipe modules at basic process level were elaborated for aromatic alkylation, chloromethylation and diazotization reaction types. The process control algorithms of the new technologies can be adapted at industrial scale.

During the technological development, several advantages of the computer aided process control i.e. safety, environmental and efficiency improvements were presented. During the production of pharmaceutical intermediates, replacements of environmental contaminating and harmful solvents realized and the optimal conditions of the reactions were determined. More know-hows and patent-capable procedures for the production of additives in the area of polymer industry were developed. The thermal characteristics of synthesis and conditions for prevention of runaway were determined to increase the production safety of peroxide-type polymerization initiator. New type of reactive surfactant additives produced using Raman spectroscopic method to trace the reactions. In the synthesis of new phosphatid and boroxosiloxane type flame retardant additives the control was based on the heat release and the changes of torque of the stirrer. New environmental friendly method was developed for production of nanocomposite. More efficient and non-polluting technology was elaborated to produce 1-phenylazo-2-naphtol type pigments using simulation of the diazotization process.

Some of the synthesized polymer additives were successfully applied for the modification of interfacial layers in polymer composite systems improving mechanical properties, hydrolytic, heat and photostability and flame resistancy. Several process control algorithms and technology developed in the laboratory were applied successfully at industrial scale after scaling-up.

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STRUCTURE DETERMINATION OF THE MODEL MEMBRANES WITH SMALL ANGLE SCATTERING

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In my PhD thesis three topics were discussed: the evaluation of the small angle scattering measured at the Jusifa beamline (German Synchrotron, Hamburg), the interpretation and the simulation of the small angle scattering of liposome systems generally, and the description of the bilayer structure of the 1,2-dipalmitoylphosphatidylcholine (DPPC)/water liposome system in its three phases (gel, rippled-gel and liquid crystalline phases).

A model was developed in order to interpret the small angle scattering of liposome systems, in which the fluctuation of the layer arrangement was considered. The relation between the structural parameters of the centrosymmetric layer structure and the properties of the small angle scattering curve was also studied.

I have found that the positional resolution of the detector, and the precision of the evaluation was worse than the precision required by the interpretation methods. Therefore I have studied all parameters set in the small angle X-ray scattering measurements, especially at the Jusifa beamline. I have determined the torsion function of the detector. Using the corrections I have interpreted the scattering data obtained on the liposome system.

Finally, I have simulated the small angle X-ray scattering of the gel, rippled gel, and liquid crystal phases of the DPPC/water liposomes. I have determined the structural properties of the system. Most of the known structural characteristics of the phases were reproduced in the simulation, and new structural properties, such as the fluctuation of the layer thickness, the number of layers in the liposomes were determined.

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STRUCTURE ELUCIDATION OF MOLECULES WITH BIOLOGICAL IMPORTANCE BY VIBRATIONAL AND NMR SPECTROSCOPY

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Based on many years of spectroscopic research, this Thesis provides a selection of my papers, published in the last decade. The aim of the work was to give a general view about the potentials of vibrational and NMR spectroscopy, applied for structure determination of molecules with biological importance.

Tagging the surface of enzymes with known structure by organometallics proved unambiguously that the applied irontricarbonyl complexes are excellent biosensors, being able to monitor the changes nearby the surface. For the first time in the literature, I applied these organometallic tags in real biological systems, when I recorded the IR spectra of irontricarbonyl–labelled flavonoids, attached to the protein fractions of plant extract.

Structure elucidation of the starting materials of some organic syntheses – ergoline and cyclophane derivatives – has been performed. According to the requirements IR and NMR spectra were recorded, in some cases theoretical calculations were also performed to support the interpretation. The presented work provides a firm basis for answering the questions that may arise in further investigations of new derivatives.

Regioselective alkylations and nucleophilic addition reactions were studied applying vibrational spectroscopy and NMR methods. Based on NMR data, correlation has been found between the nucleophilic reaction pathway and the structure of the reacting salts. The nucleophilic attack is mainly influenced by the charge distribution along the molecule while the site of a possible ring opening is determined by the bond orders. The ^{13}C chemical shift was considered as a diagnostic parameter, being also influenced by the atomic charges near the carbon nuclei and the bond orders. Both, the atomic charges and the bond orders were calculated by quantum chemical methods. So far two out of the four products of the nucleophilic addition have been identified by NMR methods.

The NMR measurements carried out on the product of the alkylation of a studied linearly fused tricyclic heteroaromatic compound under anhydrous conditions revealed its structure as a mixture of N5 and O3 alkylated derivatives. Their NMR data were completely assigned. The alkylation in aqueous base resulted in an unexpected ring opening followed by the formation of two N-alkylated products, one of them having a zwitterionic structure.

VIBRATIONAL SPECTROSCOPIC STUDY OF NITROGEN HETEROCYCLES

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Nitrogen heterocycles can be found in several biologically active compounds. Their better identification and the discovering of their effects in living organisms need the high level knowledge of their structure and spectroscopic properties.

The investigation of the N-heterocycles builds a traditional project of the Department of Physical Chemistry of the Budapest University of Technology and Economics. I would have liked to continue and extend this tradition. At first, I investigated five membered N-heterocycles (pyrrole, pyrazole, imidazole, triazoles and tetrazole). Later I studied pyrazine and its methyl and chloro substituted derivatives, the substituent effect on the pyrazine structure and vibrational spectra. Similarly, I dealt with the isotopic effect of chlorine. On the request of the collegues from the Babeş-Bolyai University in Cluj (Romania) I studied 10-methyl-(10H)-phenothiazines and 10-methyl-(10H)-phenothiazine-5-oxides. These compounds are promising medicament materials. I investigated the vibrational spectroscopic behaviour of the phenothiazine skeleton and dealt with the aldehyde and the alcohol substitutient effect on the vibrational spectroscopic and structural properties of these skeletons.

The aim of the study of the investigation of the N-heterocyclic compounds was to build a comprehensive idea on the vibrational and structural properites of these compounds. For these purpose I worked both experimentally and theoretically.

In the frame of the experimental work I recorded both the infrared and the Raman spectra of the investigated N-heterocycles. A part of the compounds were deuterated. The theoretical work covered my quantum chemical calculations. I calculated the optimized geometrical parameters, the vibrational force fields and the fundamental vibrational frequencies of the investigated molecules. The HF/6-31G** method was used for the phenothiazine calculations, while the density functional theory with the Becke3P86 functional and the 6-311G** basis set for the five- and six-membered heterocycles. The results of the calculations were applied to the assignment of the vibrational fundamentals. The measured fundamental frequencies were used to refine the vibrational force constants.

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DEVELOPMENT OF NEW TYPE OF FLAME RETARDED POLYPROPYLENE SYSTEMS

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In the last decade the application area of those plastics and fibers expanded, which possess special, mainly new properties distinguishing them from the general products. In most of these application areas – automotive industry, electronical industry, building industry, protective clothing- the reduced flammability or entire flame retardance is a basic requirement.

Due to their favourable price, advantageous physical and chemical properties and simple, versatile processing the polyolefines are increasingly preferred among the different types of polymers. On the other hand these polymers are very combustible and increase the risk of their application in many fields. Accordingly one of the main area of polymer research is developing new and modified systems with improved fire retardant performance.

The thesis covers ammonium polyphosphate base fire retardant systems. For the efficient application of these additives there is a need to improve their hydrothermal stability. Surface treatment is one of the effective methods to overcome these difficulties. Surface coating of ammonium polyphosphate (APP) was performed using suitable surfactant (glycerol monostearate) and melamine. The formation of the protective layers was confirmed using surface analitical method (XPS). These surface treatments were effective in hindering the water adsorption of ammonium polyphosphate during storage.

Little amount of polyboroxo siloxane was found to be effective in delaying the esterification reaction of APP and polyol (that causes difficulties during processing because of the evolved water). Polyorganosiloxanes showed synergistic effect with ammonium polyphosphate/polyol system in fire-retardancy performance. The synthesized polyboroxo siloxanes act in a complex way: the additive promotes the accumulation of fire retardant components on the surface in case of fire, forms a barrier layer and increases the melt viscosity of polymer to avoid dripping. Due to the applied additives other properties (hydrolitic stability, elongation at break, impact resistance) were also improved. The presence of boric atom has an important role in the efficiency of polyboroxo siloxanes: it increases the residue of the polysiloxane during burning and forms a coherent glassy/ceramic layer on the polymer surface. Using XPS method it was proven that the transformation of polyboroxo siloxane to inorganic (ceramic) layer is not complete at the temperature of fire. This advantageous behaviour preserves the deformable, durable character of the protecting layer on the surface.

Combination of two mechanism for barrier layer formation, the use of nanoparticles (montmorillonite) and organic polymer precursors (polyboroxo siloxanes), is a new way for improving the performance of flame retarded polymers. Forming an

interfacial layer around nanoparticles and their combination with the intumescent fire retardant system had a beneficial effect on the fire performance. The system showed good fire resistance even at ignition in vertical position. We composed a schematic model to describe the behaviour of such system. According to this polyboroxo siloxane coated nanoparticles accumulate on the surface in the case of fire and act as a skeleton in the transformation of the precursor to the barrier layer. Polyboroxo siloxane, in turn, may act as glue keeping the particles together. The assumed mechanism was proved using WAXS, μ-TA, XPS and thermal analytical methods.

Phosphorilation of the polyol additive of the intumescent fire retradant system inhibited its esterification reaction with ammonium polyphosphate, which was established by conductivity measurements. Decreasing the part of phosphor pentoxide and using nanoparticles respectively improved the hydrolitical stability. Combination of phosphorylated polyol and nanoparticles effects the fire retardant performance significantly. The additives accumulate on the polymer surface and hinder the degradation of the polymer matrix in a very early stage of fire. Our concept was confirmed by TG and XPS methods.

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SYNTHESIS OF OXYGEN CONTAINING MACROCYCLIC COMPOUNDS

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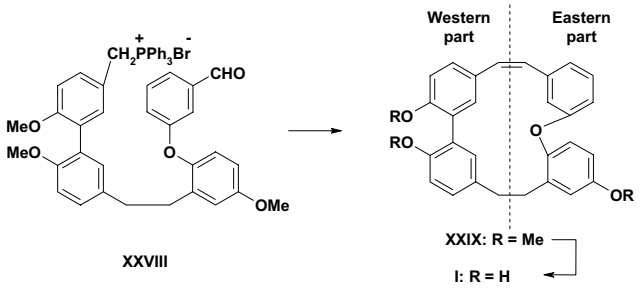
Synthesis of Isoplagiochin A

Asakawa and his co-workers isolated from *Plagiochila fruticosa* a new bis(bibenzyl)-type macrocycle, called isoplagiochin A (**I**) (*Scheme 1.*). The structure of the molecule showed several unusual features as compared to the previously isolated plagiochins.

Our synthesis started with the separate preparation of the Eastern and Western parts of the molecule. The key intermediates were coupled by the Wittig reaction, followed by a series of functional group transformations to obtain the open-chain intermediate **XXVIII** (*Scheme 1.*).



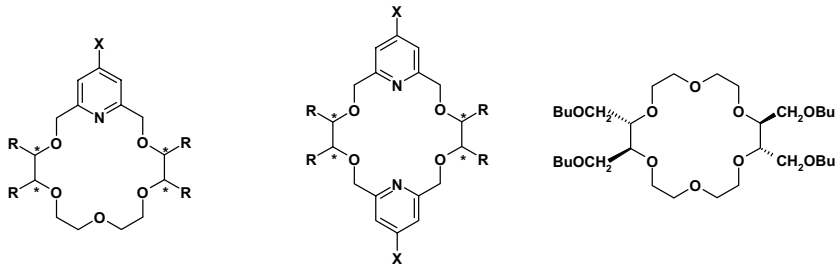
Scheme 1.

The formation of the macrocycle was performed by an intramolecular Wittig-reaction giving the trimethylether **XXIX**, which was demethylated with boron-tribromide providing the triphenol **I**.

Based on the above results the structure of isoplagiochin A was unambiguously verified and we also showed that some NMR data in the original publication were incorrect.[1]

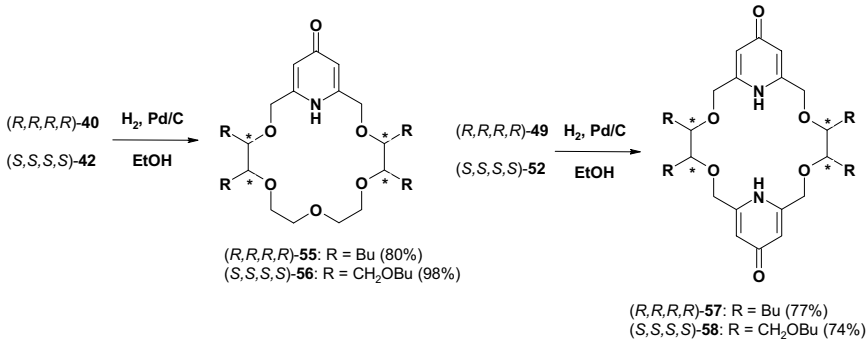
Synthesis of new optically active pyridino/pyridono and bis-pyridino-/bis pyridono-18-crown-6 type ligands containing four chiral centers

In my Ph.D. dissertation I report the synthesis of four new optically active pyridino-18-crown-6 type ligands containing four chiral centers [(*R*, *R*, *R*, *R*)-**39**-(*S*, *S*, *S*, *S*)-**42**] [2] using the ‚one-to-one' cyclization reaction of the 2,6-bis(tosyloxymethyl)-pyridines [3] and the optically active tetraethylene glycol derivatives in the presence of a strong base (*Scheme 2.*).



Scheme 2.

Using the same conditions I prepared four new optically active bis-pyridino-18-crown-6 type ligands containing four chiral centers [(*R*, *R*, *R*, *R*)-**49**-(*S*, *S*, *S*, *S*)-**52**] [4] using a ‚two-to-two' cyclization reaction (*Scheme 2.*). I also describe the synthesis of the new tetrabutoxymethyl-substituted-18-crown-6 ether (*S*, *S*, *S*, *S*)-**53** [4] which was performed by the usual 'one-to-one' method (*Scheme 2.*).



Scheme 3.

The pyridono- and bis-pyridono-18-crown-6 type ligands (*R*, *R*, *R*, *R*)-**55**–(*S*, *S*, *S*, *S*)-**58**[2,4] were prepared by catalytic debenzylation of the appropriate benzyloxy derivatives (*R*, *R*, *R*, *R*)-**40**, (*S*, *S*, *S*, *S*)-**42**, (*R*, *R*, *R*, *R*)-**49** and (*S*, *S*, *S*, *S*)-**52**, respectively (*Scheme 3.*).

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LAMELLAR LIQUID CRYSTALLINE SYSTEMS

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Nowadays the different lyotrop liquid crystalline systems show an ever increasing importance in cosmetics and household chemical industry. They can be successfully applied for controlled and transdermal drug delivery. Between the dead cells of the stratum corneum there is a liquid crystalline material that protects the lower layer of the skin against the impact of both polar and apolar materials. The only component that relatively freely but in a controlled way can move through this barrier is water. This liquid crystalline layer has a very complex composition and structure, and therefore is not easy to investigate. At the same time the state of this barrier is a very important factor in the health and beauty of the skin.

The ethoxylated fatty acids studied by me can serve as a simple chemical model of this biological system. Their concentrated aqueous solutions have a lamellar liquid crystalline structure at around 70 w/w % surfactant concentration. (This concentration falls very close to the lipid concentration of the stratum corneum.)

During my work I have studied these systems by different optical and rheological methods. My goal was to understand the above mentioned protecting mechanism of the human skin, and to suggest methods by which this effect can be influenced or reinforced. I have applied static and dynamic rheological measurements, polarised microscopy and small-angle X-ray scattering.

As the function of a biological system is highly determined by its structure, the main goal of the rheological measurements was to clarify the structure dependent mechanical properties of the protecting barrier. By the frequency dependent measurements the so-called rheological fingerprint of the system can be determined. The different mesophases can be distinguished according to this suite of physical properties. At the same time the mechanical model of the studied system can be determined by static measurements.

The optical methods served as a reinforcement of the hypothesis suggested for the microstructure according to the rheological findings. If a system consists of lamellae it must be optically active and therefore can be studied by polarized microscopy. At the same time the regularity and the characteristic lengths (domain sizes and repeat distance) of structure can be determined by small-angle X-ray scattering.

During my work I have suggested a new rheological model which is suitable for the description of the dynamic rheological properties of the above mentioned liquid crystalline systems containing surfactants and some additives. The most important new element of this model was the so-called orientation modulus that is the energy requirement of the domain orientation process under shear.

I have shown that very similar structural changes and domain orientation processes take place in the studied samples during rheological and optical mea-

surements. In case of the optical investigations the initiator of these changes is an interface effect, while during the rheological measurements the process is governed by the shear flow. Comparing the dependence of the time required for the complete pseudo isotropy and the dependence of the orientation modulus on the concentration and polarity we can see a very strong correlation. This means that although these two observations seem first completely different, their physical background is the same.

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BIOSCOURING OF COTTON FABRICS

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Biopreparation of the cellulosic fibres is an enzyme-aided process by which the noncellulosic impurities are removed mainly by pectinase rich enzymes. Enzymes act under mild conditions with low water consumption; while the conventional alkaline scouring carried out with hot caustic soda is unquestionably an energy, water and chemical-intensive process. Thus, bioscouring provides an environmentally-friendly alternative to the conventional alkaline process.

In this study three commercial enzymes were tested during bioscouring: a cellulase, a hemicellulase-pectinase and a xylanase. The latter is applied mainly in pulp and paper industry for biobleaching. The results prove that besides cellulases and pectinases, xylanase enzymes can also be used effectively in biopreparation of cotton fabric. Biopretreatment results in hydrophilic and homogeneously absorbent fabric with excellent colour evenness. The conventionally scoured fabric appears much cleaner and lighter than the bioscoured fabrics, therefore great colour differences can be measured between the conventionally scoured and the bioscoured fabrics. Hydrogen peroxide bleaching decreases the colour difference significantly. Reactive dyeing results in homogeneously dyed fabrics, the colour evenness is equal to that of the conventionally scoured and dyed fabric.

Addition of ethylenediaminetetraacetic acid (EDTA) to the treatment bath enhances significantly the efficiency of bioscouring. In order to explore the role of the chelating agent, 'EDTA-enzyme' and 'EDTA-substrate' interactions have been investigated in detail. Results prove that EDTA does not have any inhibitory or stimulating effect on the main enzyme activities. Furthermore, EDTA modifies the substrate structure by removing the calcium ions from the cross-bridges that link the macromolecules in pectin to one another or pectin to other polysaccharides. Biopreparation of linen fabrics has confirmed that EDTA modifies the substrate structure by removing the calcium ions from the cross-bridges of pectin.

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SYNTHESIS OF AMPA RECEPTOR MODULATORS AND THEIR PRECURSORS

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We elaborated a procedure for the synthesis of 6-chloro and 6,7-dichloro substituted phtalazine derivatives, structurally related to the noncompetitive AMPA antagonist phthalazine SYM-2207.

Contrary to the former procedures (e. g. synthesis of SYM-2207) using isocyanate for the introduction of the *N*-monosubstituted carbamoyl moiety, our method allows the synthesis of *N*,*N*-disubstituted carbamoyl phtalazines as well.

We investigated the lithiation reaction of chlorinated acetophenone ketals. We established that in derivatives exhibiting *meta* chlorine substituent – under the reaction conditions applied – the lithiation occurred between the chlorine and the 1,3-dioxolane-2-yl substituents. 2-(4-Chlorophenyl)-2-methyl-1,3-dioxolane was lithiated *ortho* to the ketal group. In some cases, the lithiation reaction was extended to propiophenone ketals.

We synthesised *o*-acylbenzoic acid and *o*-acylbenzenesulfonyl chloride derivatives *via* lithiation of acetophenone ketals followed by carboxylation and chlorosulfonylation. These compounds are precursors of potential drugs acting as positive AMPA modulators.

We investigated the lithiation reaction of substituted benzophenone ketals having one or two chlorine substituents in one of the aromatic rings and various *ortho* directing groups in the other one. In these metalation reactions two substituted benzene rings compete for the lithium.

We synthesized *o*-benzoylbenzoic acid and *o*-benzoylbenzenesulfonyl chloride derivatives – *via* lithiation of benzophenones ketals followed by carboxylation and chlorosulfonylation – in good yields, which are the precursors of potential drugs acting on the central nervous system. We established that the new derivatives were lithiated *ortho* to the ketal group in the chloroaryl ring.

We established that the '*meta* acidifying' effect of the chloro substituent combined with the ability of the 1,3-dioxolane-2-yl group to coordinate lithium – under the applied conditions – obviously outperforms the co-operative directing effect of 1,3-interrelated methoxy and 1,3-dioxolane-2-yl groups.

The presence of a chlorine substituent in *meta* position (*para* to the 1,3-dioxolane-2-yl substituents) with respect to the metalation site determines the regiochemistry of the lithiation of ketals by the long-range (*meta*) electron-withdrawing (acidifying) effect of the chlorine substituent.

We demonstrated that the chloro substituent exerts a stronger acidifying effect on its *meta* site than the fluoro substituent does.

Our results prove that the variously substituted benzophenone ketals – because of the presence of two substituted benzene rings in the same molecule – are

especially interesting compounds to study the directing ability of the various *ortho* directing groups in metalation reaction.

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PARTICULATE FILLED POLYMERS, INTERACTION, STRUCTURE AND MICROMECHANICAL DEFORMATIONS

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The goals of my work include the reliable and accurate characterization and modification of the surface of fillers, the determination of the relation between the strength of interaction and the properties of the interface and finally to study interaction – structure – property relationships and to find quantitative correlation between them. We proved unambiguously that the determination of the surface characteristics of particulate fillers is difficult because of the adsorption of water by the high energy surface. As a consequence, the determined quantities are not material constants. We showed that the amount of monocarboxylic acids needed for the monolayer coverage of a filler depends on the chemical structure of the surfactant. Linear chains are assumed to be orientated vertically to the surface, and increasing chain length, branches as well as unsaturations lead to a less regular arrangement of the molecules, to a looser structure. We pointed out in the first time that the surface tension of the filler covered by aliphatic monocarboxylic acids is the same for all compounds at the same surface coverage. We proved that only the consideration of acid-base interactions gives an acceptable estimate of interfacial adhesion in particulate filled polymers. We were the first to establish quantitative correlation between the thickness of the polymer layer with decreased mobility and the strength of interfacial adhesion. We also showed that the treatment of $CaCO_3$ with a surfactant decreases the strength of interaction, and changes both the thickness and the properties of the interphase. We demonstrated that structure-property correlations are extremely complicated in particulate filled polymers having a crystalline matrix. The results indicated that not the nucleating effect, but the anisometric particle geometry of talc results in its strong reinforcing effect. Processing technology determines the structure of the matrix and the orientation of anisotropic particles; both influence properties significantly. Numerous factors, including the particle size distribution of the filler, influence the extent of aggregation and composite properties may depend also on the internal structure and strength of the aggregates. We showed that debonding might be the dominating micromechanical deformation process in particulate filled polymers, but in thermoplastic matrices considerable shear yielding of the polymer also takes place. The relative magnitude of the two processes strongly influences the number and size of the voids formed. Because of this competition only a fraction of the particles initiate the formation of voids.

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DEVELOPMENT AND APPLICATION OF NEW MASS SPECTROMETRIC

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The importance of early diagnosis of illnesses and their prompt treatment have long been recognized in human health care. Modern analytical methodologies continue to play an important role in the field of clinical diagnostics; furthermore new developments in mass spectrometry revolutionized biochemical and clinical research. The aim of my doctoral thesis is a) the development and application of new mass spectrometry based methods which can be used in clinical research and serve as basis for further developments; b) the introduction and spreading of mass spectrometry based diagnostic methods into the Hungarian clinical practice.

We introduced in Hungary the modern, increasingly used electrospray tandem mass spectrometric screening method for detection of inherited metabolic disorders. We identified several metabolic disorders including amino acidurias and beta oxidation disorders.

A novel approach for amino acid analysis in blood was developed, which doesn't require chemical derivatization. This eliminates the problems arising from site reactions during butylation in classical procedures and offers more flexibility for incorporating new types of compounds into the same measurement, hereby expanding the number of screenable diseases. A novel HPLC-MS technique was developed for the determination of very long fatty acids (C16-C26) in blood. The method doesn't require any chemical derivatization and is suitable for high-throughput investigations. It may be used as an alternative to the very timeconsuming GC-MS (gas chromatography mass spectrometry) methods for the screening of peroxisomal disorders.

We have developed an FT-ICR (Fourier Transform Ion Cyclotron Resonance Mass Spectrometry) technique for the monoisotopic resolution analysis of human alpha-1-acid glycoprotein in its intact (not digested) form. The results suggest that ultrahigh resolution mass spectrometry may play a key role when profiling post-translational modifications of proteins.

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ANALYTICAL CHARACTERIZATION AND APPLICATION OF MOLECULARLY IMPRINTED POLYMERS

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During my doctoral work I set myself the task to characterize molecularly imprinted polymers (MIP) and to develop analytical methods based on molecular recognition.

At first I have developed a solid phase extraction method for the determination of terbutylazine from surface water samples with terbutylazine imprinted polymer sorbent. During the optimization considering the need of using large volume samples and the negative effect of water on retention in case of MIPs I preconcentrated the water samples on a C 18 disk. I proved the efficiency of the coupled C 18 disk-MISPE method by measuring Danube water samples.

I have compared the capacity factors of the template and similar compounds on phenytoin MIP and NIP filled chromatographic columns. Comparing the retentions and the imprinting factors (IF=k'$_{MIP}$/k'$_{NIP}$) I concluded that the diphenyl group of phenytoin does not interact significantly with the surface in acetonitrile, but its role is to prevent the formation of obstacles in the way of access during the polymerization process.

Studying the shape of phenytoin elution peaks at different temperatures and concentrations and comparing them to the adsorption isotherm data I drew the conclusion that the reason of the tailing observed with MIPs is mostly the nonlinear isotherm.

In case of using molecularly imprinted polymer sorbents one needs to be able to estimate the effects of interfering substances. I have measured the isotherm points of two compounds; phenytoin (template) and atrazine (slightly bound). For the simultaneous adsorption measurements I have modified the batch adsorption method. Using this modified method one can estimate the adsorption isotherm of two simultaneously adsorbing species from fewer measurement points. Contrary to my expectations the results show that the phenytoin and atrazine enhance the adsorption of each other.

Finally after studying the MIP adsorption isotherms and the procedure of molecular imprinted sorbent assay I proved that the calibration curve of a MIP based ligand binding assay can be calculated from the adsorption isotherm and the amount of used reagents. Based on these results one can optimize his assay (according to any function) with calculations after measuring the isotherm without the need of using any kind of model for the isotherm.

KINETIC OPTIMIZATION OF THE ACTIVATED SLUDGE DENITRIFICATION PROCESS

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Kinetic optimization of activated sludge bioreactor configuration becomes extremely important in reactor system design, when the wastewater to be treated contains insufficient amount of biodegradable carbon source compared to the denitrifiable nitrogen. It has been verified that the impact of oxygen entering through liquid surface is not negligible in such cases, and must be taken into consideration in order to allow efficient and cost-effective nitrogen removal.

An experimental procedure based on the application of a Zero Head-space Reactor was developed for investigating the biological processes under oxygen-free conditions as well as for estimating the impact of dissolved oxygen on denitrification. It has been shown that the impact of oxygen entering the anoxic reactor through the liquid surface depends strongly on the actual denitrification rate. It was experimentally verified that while having an almost unchanged oxygen transfer rate through the liquid surface, the different dissolved oxygen levels caused by different consumption rates are responsible for the dynamic impact resulting in different measures of kinetic inhibition on denitrification processes. A mathematical model was developed in order to simulate the performance of open anoxic bioreactors. The model incorporated aerobic and anoxic microbial growth as well as death and lysis of heterotrophic bacteria, hydrolysis of particulate organics and O_2 mass transfer through the liquid surface. The overall anoxic growth was formulated using nitrate-, nitrite- and nitrous-oxide as terminal electron acceptors. The different inhibitory impact of different oxygen levels on denitrification, caused by different consumption at an unchanged oxygen transfer rate through liquid surface, was also verified by simulation studies. The effect of oxygen penetration on biological nitrogen removal was shown in simulation studies using different values of particular process key parameters, i.e. influent readily biodegradable substrate- and biomass-concentration, as well as oxygen mass-transfer coefficient and temperature. It has been pointed out that the bioreactor configuration becomes irrelevant at increasing influent readily biodegradable substrate concentration at given denitrifiable nitrogen content. However, coverage of anoxic basins surface provides a cost-effective optimization when having external substrate in shortage. Simulation studies have pointed out that the inhibitory impact of dissolved oxygen increases significantly when temperature decreases, thus application of anoxic reactor coverage is useful especially at low temperatures and can also overcome the problem of heat-lost, ensuring nitrogen removal at higher temperatures. Our studies showed that when external substrate was marginal, staging of anoxic reactors provided significant benefits on denitrification efficiency. This can provide a cost-effective optimization method for treatment of plants realizing inadequate nitrogen removal

or for the reduction of total required anoxic volume in newly established activated sludge installations. It has been shown that bioreactor staging represents the most effective optimization technique when increased levels of biomass concentration in either open or covered anoxic vessels are applied. In case of 4 gl^{-1} initial biomass concentration, simulation studies revealed that the reactor coverage resulted only a slight improvement on removal efficiency, even if readily biodegradable substrate concentration was either marginal or very low. The impact of reactor configuration on denitrification efficiency was also verified by comparative pilot-scale experiments, including systems with both staged and unstaged anoxic reactors. The obtained results revealed a good correlation between consumption rates and resulting dissolved oxygen concentrations in different unaerated vessels. On the basis of the obtained results, optimization strategies have been elaborated for kinetic control of activated sludge denitrification.

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SYNTHESIS OF *N*-AZOLYL ISOQUINOLINIUM SALTS

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In course of CNS research programme of EGIS Pharmaceuticals Ltd. we studied the reaction of 2'-acylphenylacetones or benzo[*c*]pyrylium salts with α-aminoazoles. In the reactions *N*-azolyl isoquinolinium salts were obtained. Their structure was proved with the help of their NOE experiments and X-ray crystallography.

The tautomeric structure of *N*-azolyl isoquinolinium salts in solid state and solution was studied with X-ray spectra and UV and ^{13}C-NMR measurements using also different *N*-benzyl derivatives prepared for this purpose.

The reactions of 2'-acylphenylacetones or the corresponding benzo[*c*]pyrylium salts with 5-amino-1,2-dihydro-1,2,4-triazol-3-thione led to *N*-(5'-thiolo-1'*H*-1,2,4-triazol-3'-yl)isoquinolinium salts. The structure of products obtained was proved with the help of their UV-, ^{1}H- and ^{13}C-NMR spectra as well as by preparative way.

The reaction of *N*-(5'-thiolo-1'*H*-1,2,4-triazol-3'-yl)isoquinolinium salts with dibromomethane led to dialkylated products. Providing the above reaction with 1,2-dibromoethane, 1,3-dibromopropane and 1,4-dibromobutane *N*-(5',6'-dihydrothiazolo[3,2-*b*][1,2,4]triazol-2-yl)isoquinolinium bromides, *N*-(6',7'-dihydro-5'*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-2-yl)isoquinolinium bromides and *N*-(5',6',7',8'-tetrahydro-[1,2,4]triazolo[5,1-*b*][1,3]thiazepin-2-yl)isoquinolinium bromides were obtained, respectively, representing novel ring systems. Their structure was proved by ^{13}C-NMR spectroscopy as well as by synthetical method.

A general method was elaborated to the synthesis of isomeric amino-thiazolo-[1,2,4]triazole, amino-[1,2,4]triazolo[1,3]thiazine and amino-[1,2,4]triazolo[1,3]-thiazepine derivatives, respectively. The 2-amino-5,6,7,8-tetrahydro-[1,2,4]triazolo-[5,1-*b*][1,3]thiazepine and the 3-amino-5,6,7,8-tetrahydro-[1,2,4]triazolo[3,4-b][1,3]-thiazepine represent two novel ring systems.

Contrary to the literature the reductions of *N*-azolyl isoquinolinium salts with sodium borohydride in methanol led to 1,2-dihydroisoquinolines. Their formation was explained by the electron withdrawing effect of the heteroring in position 2 of the isoquinolinium moiety, corroborated by the synthesis and reduction of different *N*-azinyl-, *N*-aryl and *N*-methylisoquinolinium salts.

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GENERAL AND INDUSTRIALLY FEASIBLE SYNTHESIS OF BENZYLPIPERIDINE AND BENZYLPYRROLIDINE DERIVATIVES

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A convenient and scaleable new method has been developed for preparation of benzylpiperidines by addition of substituted phenylmagnesium bromide to pyridine carboxaldehyde followed by the catalytic reduction of the intermediate arylpyridylmethanols. Essential difference in the result of the catalytic hydrogenation of aryl-2-, 3- and 4-pyridylmetanols was found. We concluded that the quality of the products (benylpiperidines or arylpyridiylmethanols) depended on the relative rates of dehydroxylation and pyridine-ring saturation, furthermore the arylpiperidylmethanols were not intermediates of benyzlpiperidines under the conditions investigated. To separate the two reduction steps, so achieve consecutive reactions and to optimise the reaction conditions, we have studied the catalytic hydrogenation of a benzylpyridine derivative. The effect of the solvents, the temperature, the quality of the catalytic metals and the amount of the catalyst on the conversion and the rate of hydrogenation were investigated. On the basis of the results we determined the optimum conditions for stepwise dehydroxylation and pyridine-ring saturation using the same Pd/C catalyst. The separation and the stepwise intermediate purification of the two reaction may cause waste of material, therefore we also developed a one-pot version of the process (temperature-programmed catalytic hydrogenation). Our new method was applied for the preparation of the pure d_4 isotopomer of 4-(4-fluorobenzyl)piperidine (**31e**), which was necessary for pharmacological research.

For elimination of the basicity of the nitrogen in the benyzlpiperidine ring, benzylpiperidine-2,6-dions were synthetised via cyclization of benzylglutaric anhydride with different amines.

To establish the relation between the biological effect and the chemical structure, we have developed a new synthesis of enantiomerically pure 3-benyzlpyrrolidines, based on the asymmetric hydrogenation of arylidenesuccinic acid.

The general methods for preparation benzylpiperidines and benyzlpyrrolidines made the synthesis of a number of potential NR2B selective NMDA receptor antagonists possible. As a result of our work, the clinical investigation of one derivative is in progress.

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USE OF CAPILLARY ELECTROPHORESIS FOR MONITORING WHEAT MATURATION AND IDENTIFICATION OF VARIETIES ON THE BASIS OF PROTEIN CONTENT

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The aim of the dissertation is the examination of the applicability of capillary electrophoresis in wheat protein analysis.

During capillary electrophoretic method development and optimization, a new capillary cleaning protocol in capillary zone electrophoresis was developed.

This was the first study done by capillary electrophoresis, investigating the complete maturation process of wheat varieties with different harvest time (Bánkúti 1201, Martonvásári 23 and Martonvásári 15), following the changes in the fine structure of the proteins of the different Osborne fractions (albumins, gliadins and glutenins). Albumins were present at the beginning of the studied time period; gliadins and glutenins appeared later. Albumin proteins accumulated similarly during maturation in the case of all three cultivars. Gliadins appeared before glutenins, but both gliadin and glutenin synthesis took place in 1,5-2 weeks. Gliadins appeared sharply, glutenin concentration increased slowly. Different glutenin accumulation dynamics were observed for the three cultivars. Gliadin and glutenin patterns were representative for the cultivars; some similarity were detected between the two Martonvásári varieties.

Capillary electrophoresis was also used for wheat variety identification. To develop a catalogue of capillary electropherograms of Hungarian wheat cultivars, this was the first study examining the gliadin fractions of six different wheat varieties. Results were evaluated using statistical methods, Polar Qualification System (PQS), and also visually. Visual evaluation appeared adequate for the six cultivars. With Polar Qualification System the majority of the varieties were distinguishable. Principal component- and cluster-analysis together with the calculation of the homology between the electropherograms resulted in the discrimination of the different cultivars with good safety.

BM180 protein – with a potential autoantigen role in Coeliac disease – were studied by capillary electrophoresis. The SDS-capillary gel electrophoretic system was suitable for the following of the purification process of this basement membrane protein. BM180 proved to be very sensitive, and easily underwent decomposition. In a capillary zone electrophoretic system proteins of the BM180 sample showed electrophoretic properties similar to low mobility gliadins.

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THEORETICAL STUDIES ON THE CHEMICAL ACTIVATION OF CARBON DIOXIDE

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My Ph. D. thesis is based on the work carried out in the Chemical Research Center of the Hungarian Academy of Sciences under the supervision of Dr. Imre Pápai. I studied the reactions of transition metal centers with carbon dioxide, as well as the structure of metal complexes having significance in CO_2 activation. The electronic structure of the investigated systems was described mainly by means of Density Functional Theory (DFT). The results were verified in some cases by higher-level ab initio methods. While modelling reactions in solutions, solvent effect was also taken into account.

I gave a detailed description of the mechanism of the reaction Sc + CO_2 → ScO + CO on the potential energy surfaces belonging to the electronic configurations ^{2}A' and ^{2}A". With the calculations I successfully interpreted the matrix isolation experiments concerning this reaction, I provided reasonable estimates for the activation energies of the gas phase reaction. [1]

I studied the presumed active $[RhH_2Cl(P^iPr_3)]_2$ form of the complex $[RhCl(P^iPr_3)(C_2H_4)]_2$ enhancing the catalytic '2+2' coupling reaction of allenes and carbon dioxide. I determined the structure of the newly prepared $[PdH(dppe)_2]^+$ complex using the QM/MM method. With my calculations, the existence of the experimentally observed unsaturated complex formed by the Pd-P bond breaking of pentacoordinated palladium-hydride could be supported, and also a low-barrier transition state corresponding to the break of the metal–phosphorous bond could be identified. [2, 3, 4]

I determined the structure of the $[M(C_2H_4)_2(PR_3)_n]$ (M = Mo, W; R = H, CH_3, n = 3, 4) complexes, and investigated the metal–ligand interaction. I studied in details the elementary steps of the mechanism of the reaction

$$2\ Mo(C_2H_4)_2(PMe_3)_4 + 2\ CO_2 \rightarrow [MoH(CH_2CHCOO)(PMe_3)_2]_2 + 2\ PMe_3.$$

The hypothetical mechanism of the reaction based on experimental data could be supported by theoretical calculations, as well. [5, 6]

I identified the elementary steps of the reaction

$$[Ni(cdt)] + L_2 + CO_2 + C_2H_4 \rightarrow [Ni(L_2)(CH_2CH_2COO)] + cdt$$

(L_2 = bpy, dcpe, mbpy, nbpy). I showed that in this case the co-ordination of the carbon dioxide to the metallic center is not a precondition of the reaction, and the reaction cannot proceed further because of the great stability of the metallacycle formed. [7]

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ACCUMULATION AND QSAR STUDY OF PHOTOSENSITIZERS

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Photodynamic therapy (PDT) is preferentially used for tumor cell killing applying porphine-based photosensitizers and related molecules. It is based on the action of a selectively accumulated photosensitizer molecule and light in the presence of oxygen in a given tissue. The bottleneck of PDT application in the clinics is the impurity of the used sensitizers, as well as their low efficiency. So, development of new porphine-based sensitizers is one of the main goals of synthetic chemistry.

The aim of this study is to help the development of new effective photosensitizers by testing and analysing the activity of porphine-based compounds as sensitizing molecules under the same laboratory conditions.

As a first step, we decided to adapt and develop an analytical method for sensitizer measurement and to select the appropriate quantitative structure-activity relationship method for assesment of activity data. Therefore, the main part of this work is the adaption and improvement of a system not commercially available, which is suitable for determination of photosensitizer accumulation in cells and animal tissues based on *in situ* fluorescent measurements using fiber optics. The method makes it possible to determine the tissue concentrations of a large number of porphine-based sensitizers using a technique much simpler and shorter than chemical extraction, with a minimal use of experimental animals.

In addition to the experimental work, we have selected the most appropriate model building methods for prediction of photodynamic activity, selective accumulation and anti-HIV-1 activity of the compounds based on literature data. We have compared several chemometric methods for selection of linear and non-linear descriptors, as well as for model building based on their predictive ability using a small number of congeneric and non-congeneric sensitizer molecules. Good predictive models were built for all studied activities. Based on the analyzed data, it has been established that MLR and PLS are not, while ANN is a suitable method for conducting quantitative structure-activity relationship studies of smaller and larger groups of homologous and non-homologous tetrapyrrole molecules in case of biological activities depending on structural parameters in linear and non-linear ways.

BIOETHANOL PRODUCTION: PRE-TREATMENT AND ENZYMATIC HYDROLYSIS OF CORN STOVER

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1. Introduction and Aim of the Dissertation

The dramatic increase in energy demand and parallel the more and more serious problems caused by green house effect have turned the world's interest to the alternative energy sources. The climatic and geographical conditions of Hungary offer good possibilities for more intensive use of biomass. One economical way to production biofuel or fuel additives is the utilization of agricultural or forest residues and by-products. Corn stover is the most abundant agricultural residue in Hungary, which is produced in 10-11 million tons annually. Less then 10% of this amount has been used as an animal feeding or bedding and the rest is simply turned in the ground. However, because of its high carbohydrate content it is a potential candidate for raw material of bioethanol production. Corn stover and herbaceous straws in general consist of three main components: 30-40% cellulose, 25-35% hemicellulose, 15-20% lignin. Cellulose is associated with hemicellulose and other structural polysaccharides, surrounded by a lignin sheath. Lignin, which is a complex three-dimensional polyaromatic matrix, is partly covalently associated with hemicellulose, thus preventing the structure from the action of hydrolytic enzymes. The highly ordered, crystalline structure of cellulose itself poses another obstacle to hydrolysis. To enhance the enzymatic susceptibility of the cellulose, application of a specific pre-treatment process is essential. The goal of the pretreatment is to disrupt the lignocellulosic matrix in order to make the substrate more accessible to the enzymes and also for the further fermentation step. The scheme of the ethanol production from lignocellulosic material has three main steps: (1) pre-treatment, (2) enzymatic hydrolysis of cellulose to glucose, (3) glucose fermentation to ethanol. The effects of the different pretreatment methods were investigated on the enzymatic hydrolysis and fermentation.

2. New Results of the Dissertation

Chemical Pre-treatments

The effects of chemical pre-treatment both on the composition of corn stover and on the enzymatic hydrolysis were investigated, and the following conclusions could be stated: (1) During acidic pre-treatment major portion (>80%) of the hemicellulose fraction was solubilized, however the degradation of the lignin fraction was only around 25%. The achieved highest enzymatic conversion of the acidic pre-treated corn stover was only 46%, thus the

enzymatic digestibility of the pre-treated material increased only slightly. (2) Alkaline pre-treatment increased the enzymatic hydrolysis of corn stover four times compared to untreated corn stover. The conversion increased from 18% to 72.4 and 79.4% using 5 and 10% NaOH, respectively. The original lignin content decreased by 90% and the solubilization of the hemicellulose fraction was also high (>85%). In spite of the achieved high conversions, the pre-treatment with concentrated base is not proposed for pre-treatment of lignocellulosic material due to environmental and economical condiclerations. (3) Dilute acid combined with dilute base resulted in a conversion close to the theoretical (96%). Although the convertibility of pre-treated cellulose is very important in characterisation of the pre-treatment, but a good fractionation method is also able to retain the cellulose in the pre-treated solid fraction. During this two-step chemical pre-treatment nearly half of the original cellulose and around 75% of the original hemicellulose was solubilized. The purification and/or utilisation of the solubilized sugars from the acidic and the alkaline solution and also from the washing-water is a difficult technical problem and causes a shock in process economy. Separation and the washing after both steps of this pre-treatment are necessary to remove the chemicals from the fibers, because they have a negative effect on the enzymes.

Physico-chemical Pre-treatment

To make the pre-treatment more environmental friendly and find an economically feasible method, steam pre-treatment and wet oxidation processes were tested for treating of corn stover and the following conclusions could be drawn from the results: (1) Steam pre-treatment and wet oxidation showed several common features. Both processes increased the enzymatic conversion significantly; the highest conversion was 83.1% following wet oxidation and 83.6% after steam pre-treatment. (2) In comparison with the hemicellulose recovery of this two processes, results were also similar around 60%, however cellulose recovery was 15% lower following steam pre-treatment. The wet oxidation was also much better in retaining cellulose in the solid fraction; approximately 90% of the original cellulose content remained in the solid, fiber fraction after wet oxidation, but only 78-80% after steam pre-treatment. (3) To obtain high ethanol yield, efficient enzymatic hydrolysis is necessary, however the good fermentability of the pre-treated material is also essential. The fermentability both of wet oxidized and steam pre-treated corn stover gave similar results. The achieved ethanol yield was above 80% and no inhibitory effect could be observed. (4) The highest ethanol yield of 85% of the theoretical was achieved using acidic wet oxidised corn stover with an ethanol concentration of 52.3 g/L, which exceeds the technical and economical minimum limit of the industrial-scale alcohol distillation.

Corn stover is a potential substrate for the ethanol production in Hungary, because of its huge amount and its high sugar content. The polysaccharides in this herbaceous material are highly convertible to monomeric sugars following pre-treatment at high temperature, such as wet oxidation or steam explosion. These pre-treatment processes used a minimal amount of chemicals (sulphuric acid or sodium-carbonate), whilst the achieved enzymatic cellulose conversions were generally four times higher compared to the untreated corn stover. Thanks to the sub-inhibitory levels of the potential fermentation inhibitors following pre-treatments, the hydrolysis-released glucose was convertible to ethanol using baker's yeast.

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SYNTHESIS OF 3-ALKYLOXINDOLES

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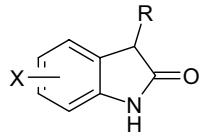

The planned synthetic route to potentially 5-HT$_7$ selective compounds containing an oxindole skeleton necessitated the elaboration of a new, practical synthesis of 3-alkyl- and 3-(ω-hydroxyalkyl)oxindoles. Although the synthesis of 3-alkyloxindoles has been studied in the literature in detail, no high-yielding one-step procedure has been published up to now. We set ourselves the task of developing an efficient method for the synthesis of this family of compounds.

As an improvement of Wenkert's pioneer work, we have developed the synthesis of 3-alkyloxindoles by the alkylation of oxindole with primary and secondary alcohols in the 3-position, in the presence of Raney nickel. In contrast to the reaction of Wenkert, our methodology gave high yields of the title products in reproducible reactions, using less than one mass equivalent of nickel. The synthetic usefulness of the Raney nickel-induced alkylation reaction is also demonstrated by the extension of the method to the preparation of 3-(ω-hydroxyalkyl)oxindoles in good yields. Treatment of oxindole with diols resulted in the formation of these hydroxyalkyl compounds, which are convertible into a range of new derivatives.

Since oxindole can be prepared by the catalytic reduction of the easily available isatin, we have investigated whether the whole reaction sequence might be carried out in one pot. We have found that using this methodology, isatin can be transformed in hydrogen atmosphere to 3-alkyloxindoles, indeed. The one-pot procedure has been extended to certain isatins substituted on the aromatic ring. We have also succeeded in carrying out the reaction of isatins with diols, resulting in the formation of the 3-(ω-hydroxyalkyl) derivatives.

In the course of this work we found an interesting 7-methylation reaction. When carrying out the reaction of isatin with isobutyl alcohol in the presence of Raney nickel, at temperatures higher than those needed for 3-alkylation, 3-isobutyl-7-methyloxindole was obtained instead of the expected 3-isobutyloxindole. We have further investigated this reaction and concluded that 3-alkyl- and 3,3-dialkyloxindoles can also be methylated at the 7-position. It was found that instead of alcohols, diglyme and paraformaldehyde can also be used as a methylating agent. A possible Fries-type mechanism has also been suggested for this 7-methylation reaction.

Based on the ^{13}C NMR chemical shifts of oxindoles synthesized at our laboratory, along with an overall search in the literature for published ^{13}C NMR data, we set up a model for the calculation of substituent effects of these compounds. By means of the calculated values, the ^{13}C NMR shifts of the oxindole skeleton containing various substituents can be accurately predicted.