SYMPOSIUM M

Molecularly Imprinted Materials

April 3 – 5, 2002

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SESSION M1: SYNTHESIS AND CHARACTERIZATION
Chair: Mingdi Yan
Wednesday Morning, April 3, 2002
Concordia (Argent)

8:00 AM OPENING REMARKS
PAST, PRESENT AND FUTURE OF MOLECULAR IMPRINTING. Kenneth J. Shea.

8:45 AM *M1.1
MOLECULAR IMPRINTING - A WAY TO EFFECTIVE MIMICS OF NATURAL ANTIBODIES AND ENZYMES. Günter Wulff, Heinrich-Heine University, Institute of Organic and Macromolecular Chemistry, Düsseldorf, GERMANY.

In order to mimick the active site of antibodies and enzymes a molecular imprinting procedure in polymers has been introduced quite some years ago. The principle of molecular imprinting is based on the crosslinking polymerization in the presence of binding site monomers around a molecule that acts as a template. After removal of the template, an imprint of specific shape and with functional groups capable of chemical interactions remains in the polymer.1) Such polymers can be used for selective chromatographic resolutions, as specific detection layers in chemosensors, as artificial antibodies in radioimmuno assays, or as catalysts working in a mode similar to enzymes.
In this lecture new developments in this technique will be discussed. New binding site monomers for non-covalent interaction are described. They show high association constants for binding to the template so that stoichiometric non-covalent interactions are possible during imprinting. This type of imprinted polymers is especially suitable for the preparation of catalytically active imprinted polymers. Using different transition state analogues of alkaline ester hydrolysis and suitable catalytic functional monomers catalysts with strong esterolytic activity for the hydrolysis of esters, carbonates, and carbamates can be obtained.
In case of stoichiometric non-covalent interaction the polymerization obtaining catalytically active polymers can also be performed by standard suspension and miniemulsion polymerization techniques. Thus regular beads of 10-400 mm and minigels of 100-300 nm particle diameter with narrow particle diameter distribution can be obtained. A further step down to nanoparticles involves the intramolecular crosslinking of macromolecules by which highly crosslinked, soluble polymers with molecular weights below 200 000 and particle diameter of 5-10 nm can be obtained. Thus these compounds approach enzyme dimensions.
1) For a review see: G. Wulff, Angew. Chem. Int. Ed. Engl. 1995, 34, 1812.

10:00 AM M1.2
DEVELOPMENT OF IMPROVED CROSSLINKING MONOMERS FOR MOLECULARLY IMPRINTED MATERIALS. David A. Spivak, Martha Sibrian-Vazquez, Louisiana State University, Department of Chemistry, Baton Rouge, LA.

Currently, cross-linking monomers used for molecularly imprinted polymers (MIPs) have primarily been EGDMA or DVB, which are commercially available. One benefit of using these monomers is that they are inexpensive and readily available in large quantities. This is important for applications that would require large amounts of material such as industrial catalytic reactors or separations on the industrial scale. However, many future applications of imprinted polymers are envisioned in the fields of microfabricated sensors and microseparations that will only require small amounts of material. Therefore, economic price considerations of the imprinting materials is less of a concern. Instead, materials with the best performance possible are the target for microfabricated and nanofabricated devices. Most of the research in molecularly imprinted materials has focused on choice of substrate or functional monomer of the pre-polymer complex. However, approximately 80-90% of the imprinted polymers are composed of the crosslinking monomer, with the remaining 10-20% comprised of functional monomer. The large percentage of crosslinking monomer materials in imprinted polymers affords the possibility of a commensurate improvement in polymer properties. Redirecting focus on the design of crosslinking monomers for molecular imprinting, we have developed new classes of crosslinked polymers to optimize the performance of molecularly imprinted polymers. New difunctional methacrylamide/vinylketone and methacrylamide/methacrylate hybrid crosslinking monomers have been investigated and compared with EGDMA containing formulations. The strategy for the design of new crosslinking monomers has been the development of crosslinking monomers derived from amino acids, that simultaneously serve as the functional monomer. Results for the carboxylate functionalized crosslinking monomers derived from L-aspartic acid and L-serine will be reported.

10:30 AM M1.3
NOVEL MONOMERS FOR NON-COVALENT MOLECULAR IMPRINTING : VORSPRUNG DURCH KREATIVITAET. Andrew J. Hall, Panagiotis Manesiotis and Börje Sellergren Institut fuer Anorganische Chemie und Analytische Chemie, Johannes Gutenberg Universitaet, Mainz, GERMANY.

Molecular imprinting is a technique whereby specific recognition sites can be formed in polymer matrices via the inclusion of a template molecule during the polymerisation process. With few exceptions(1), the "non-covalent" technique remains rooted in the use of commodity monomers, e.g. methacrylic acid, to serve as the recognition elements. The individual interactions of such monomers with a chosen template are generally weak, thus leading to the use of a large excess of functional monomer to favour template-monomer complexation. Consequently, the polymers are characterised by a heterogeneous distribution of binding sites and exhibit significant non-specific binding of the template/analyte. In an effort to overcome such problems, we have embarked upon a programme of design and synthesis of novel polymerisable recognition elements, drawing inspiration from the field of small molecule host-guest chemistry. The use of monomers capable of strong interactions with a given template should lead to a number of benefits, e.g. a reduction in non-specific binding due to stoichiometric monomer-template complexes, and may have implications for the preparation of MIPs in more practicable formats. As targets for our novel host monomers, template molecules bearing a wide array of functionality have been chosen, all of which have relevance in the biological, medical or environmental fields (see examples below). We now wish to report on the design and synthesis of these novel monomers, their binding capabilities (as determined by solution 1H NMR titrations), their incorporation into molecularly imprinted polymers and the recognition properties of the resulting polymers. Additionally, the ability of polymers imprinted against (1) to recognise larger molecules containing the glutamic acid sub-structure, e.g. folic acid, will be discussed(2).
References:
(1) (a) Wulff et al., Adv. Mat. 1998, 10, 957, (b) Tanabe et al., J. Chem. Soc., Chem. Commun., 1995, 23032 (c) Lbke et al., Macromolecules, 2000, 33, 5098, (d) Shea et al., J. Org. Chem., 1999, 64, 4627.
(2) For an example of a substructure approach to folic acid recognition, see Quaglia et al., J. Am. Chem. Soc., 2001, 122, 2146.

11:00 AM M1.4
CHARACTERIZATION OF MOLECULARLY IMPRINTED POLYMERS USING HETEROGENEOUS BINDING MODELS. Ken D. Shimizu, University of South Carolina, Department of Chemistry and Biochemistry, Columbia, SC.

MIPs are heterogeneous materials containing binding sites with a broad range of affinity constants. We have recently quantitatively measured the breadth and shape of the heterogeneity in MIPs by applying heterogeneous binding models. The resulting affinity distributions give a more accurate and complete measure of the binding properties of MIPs and enable a better understanding of the mechanism of the imprinting process. More recently, we have applied specific heterogeneous binding models such as the Freundlich and Langmuir-Freundlich, which significantly simplify the analysis so that affinity distributions can be readily generated from the corresponding experimental binding isotherms. These heterogeneous binding models also yield a quantitative measure of the heterogeneity, the total number of binding sites, and average binding affinity that allows ready comparison of different MIPs. Discussed will be the implications of the measured affinity distributions as to the mechanism of the imprinting process and for predicting their suitability in particular applications.

11:30 AM M1.5
MOLECULAR IMPRINTING. THE *DE NOVO* SYNTHESIS OF BINDING AND CATALYTIC SITES. Kenneth, J. Shea, Xian-Zhi, Zhou, Dolly Batra, Pete Conrad, Masanobu Naito, Dept of Chemistry, Univeristy of California, Irvine, Irvine, CA.

Molecular imprinting is a general protocol for the synthesis of cross-linked network polymers containing receptor and/or catalytic sites for small organic molecules. The imprinting process consists of a print molecule or template that is bound either covalently or non-covalently to functionalized monomers. The resulting pre-polymer complex is copolymerized with an excess of cross-linking monomer in the presence of an equal volume of inert solvent (porogen) and a free radical initiator. Thermal or photochemical initiated polymerization results in a highly cross-linked insoluble polymer. Removal of the template, in most cases by extraction or hydrolysis, leaves sites in the polymer that have incorporated the functionalized monomers. These sites are complementary in size and shape to the template molecule. Moreover, the functional groups are specifically positioned to converge on the template molecule in a reciprocal fashion. Molecular imprinting

has been used to create binding and catalytic sites for a wide variety of organic substrates. The resulting network polymers are mechanically and chemically robust materials that have been used as chromatographic packings and selective sorbents for the separation and isolation of organic compounds. Recently molecularly imprinted materials have been fabricated into thin films and free standing membranes for applications in membrane separation and chemical sensors. My talk will review the basic concepts of molecular imprinting and present recent developments in the area.

SESSION M2: MICROFABRICATION AND SILICA IMPRINTING
Chair: Borje Sellergren
Wednesday Afternoon, April 3, 2002
Concordia (Argent)

1:30 PM *M2.1
SENSORMATERIALS - DETECTING MOLECULES, MIXTURES AND MICROORGANISMS. Franz L. Dickert, Wolfgang Greibl, Oliver Hayden, Peter Lieberzeit, Vienna Univ, Inst of Analytical Chemistry, Vienna, AUSTRIA.

The needle eye in chemical sensors is the coating capable of chemical recognition, analyte enrichment and selectivity are performed in this way. An optimized design with respect to the transducer used can be accomplished by molecular imprinting. Quartz wafers for SAW fabrication can directly be coated with polystyrene/divinylbenzene copolymers imprinted with different organic solvents. These layers allow the differentiation e.g. between the xylene isomers at ambient humidity applying pattern recognition. These strategies can also be transferred to the liquid phase where even molecules without any functionality can selectively be detected. When two different print molecules are used, one as porogen and the other as template for cavity generation, two PAHs containing an equal number of aromatic rings can be distinguished by nearly two orders of magnitude in sensitivity. Printing with mixtures allows us to generate sensitive layers for the characterization both of degradation processes and quality assessment. Organic polymers and ceramics are able to extract oxidation and condensation products from engine or edible oils which is monitored by mass sensitive devices. Differential measurements between printed and non-imprinted sensors evaluate the chemical effects and those of viscosities. These printing processes are not restricted to molecular templates, however, since we were successful to extend them to microorganisms. A stamp with microorganisms preorganized on the surface can be used to create their image on prepolymerized materials. After hardening stable cavities with dimensions ranging from several nano- to some micrometers can be observed in these coatings. Selectivity is due to an optimized geometrical fit, but additionally the chemical surface properties are of great importance, since obviously organization processes occur between cell membranes and functional groups of the coating. Thus, the mass sensitive detection of yeast and bacteria cells, viruses and enzymes is possible.

2:15 PM M2.2
SOFT LITHOGRAPHY FOR THE FABRICATION OF MOLECULARLY IMPRINTED POLYMER MICROSTRUCTURES AND THIN FILMS. Mingdi Yan, Alika Lord, Tim Collins, Jennifer Brazier, Portland State University, Portland, OR.

This talk outlines the application of soft lithography for the fabrication of molecularly imprinted polymer (MIPs) micromonoliths and thin films. The technique employs crosslinked poly(dimethyl-siloxane) (PDMS) that contains relief structures as an elastomeric mold to define the shape and size of the polymer. It provides an excellent tool for chemists to generate micrometer-size polymer structures without the use of the expensive microfabrication facilities. MIPs could be made either as stand-alone microstructures on silicon wafers for applications such as sensing, or be isolated as free-standing micromonoliths. MIP films could also be generated using feature-less PDMS blocks. The technique has its limitation as the crosslinked PDMS swells in non-polar organic solvents that are widely used in the synthesis of many MIPs. The evaluation on the swelling of PDMS in acetonitrile and dimethylformamide will be presented.

3:00 PM *M2.3
ON ROUTE TO THE CHIRAL IMPRINTING OF BULK SILICA. Santiago Ini, Jessica Defreese, Alexander Katz, University of California at Berkeley, Dept of Chemical Engineering, Berkeley, CA.

The design, synthesis and characterization of amorphous silica with chiral pores containing functional groups immobilized therein is reported. Chirality is imprinted into the inorganic structure via condensation reactions of molecules containing a chiral center and tetraethylorthosilicate (TEOS). By removing a portion of the molecule surrounding the chiral center via chemical deprotection, stereospecific pores with functional groups in their interior are synthesized within a hybrid organic-inorganic sol-gel material. The deprotection process is followed by solid-state NMR, along with a variety of other potentiometric and spectroscopic methods. Probe molecule binding is used to characterize the remarkably specific regioselectivity exhibited by the active site, as well as its stereoselectivity in binding. Applications of using the imprinted silicates as specific adsorbents, in addition to catalysts, will be discussed.

3:45 PM M2.4
EXPERIMENTAL AND THEORETICAL INVESTIGATION OF THE GAS-SURFACE INTERACTION MECHANISM ON MOLECULARLY IMPRINTED SILICON USED AS GAS SENSOR MATERIAL. Dario Narducci, Patrizia Bernardinello, Istituto Nazionale per la Fisica della Materia and Dept. Materials Science, Univ. of Milano Bicocca, Milan ITALY; Giorgio Moro, Dept. Biotechnology, Univ. of Milano Bicocca, pzza della Scienza, Milan, ITALY.

Over the last years a growing interest has showed up towards the study of chemical systems characterized by weak interactions between molecules. Supramolecular chemistry has quickly extended its field of action to synthetic systems in which such interactions determine modifications of their chemical and physical properties. At the same time, the development of methodologies suitable to modify at an atomic scale the structure of condensed matter have offered horizons in which devising materials whose property were thought in connection with new functionality. This paper reports the results of an investigation aimed at using self-assembled monolayers to modify the supramolecular interactions between Si surfaces and gaseous molecules. Specific goal is that of employing molecularly imprinted silicon surfaces to develop a new class of chemical sensors capable to detect species with enhanced selectivity. Single-crystal p-type (001) silicon have been modified by grafting organic molecules onto its surface by using wet chemistry synthetic methods. Silicon has been activated toward nucleophilic attack by brominating its surface using a modified version of the purple etch, and aromatic fragments have been bonded through the formation of direct Si-C bonds onto it using Grignard reagents or lithium aryl species. Formation of Self-Assembled Monolayers (SAMs) was verified by using vibrational spectroscopy. Porous metal-SAM-Si diodes have been successfully tested as resistive chemical sensors toward NO_x, SO_x, CO, NH_3 and methane. Current-voltage characteristics measured at different gas compositions showed that the mechanism of surface electron density modulation involves a modification of the junction barrier height upon gas adsorption.
Quantum-mechanical simulations of the interaction mechanism, carried out using Density-Functional Theory, confirm that gas-SAM interaction leads to a change of the Si surface electron density. These results appear to open up new relevant applications of SAM techniques in the area of gas sensing.

SESSION M3: MEMBRANES AND NANOPARTICLES
Chair: Ken D. Shimizu
Thursday Morning, April 4, 2002
Concordia (Argent)

8:30 AM *M3.1
MOLECULARLY IMPRINTED MATERIALS. Klaus Mosbach, Lei Ye, Lund University, SWEDEN.

This brief abstract summarizes some recent developments from our Center for Molecular Imprinting related to the topic of this symposium. After a short presentation of the principle of molecular imprinting and recognition [1], the use of different materials including hybrids [2] for the formation of the host will be discussed, followed by examples given of different formats used such as small beads [3,4], membranes and microformats [5] summarized in a recent review [6]. In closing, potential directions for the next generation in molecular imprinting technology will be discussed [7-9].
References:
1. K. Haupt, K. Mosbach, Trends Biotechnol. 1998, 16, 468.
2. E. Yilmaz, K. Haupt, K. Mosbach, Angew. Chem. Int. Ed. Engl. 2000, 39, 2115.
3. L. Ye, R. Weiss, K. Mosbach, Macromolecules 2000, 33, 8239.
4. L. Ye, K. Mosbach, J. Am. Chem. Soc. 2001, 123, 2901.
5. I. Surugiu, B. Danielsson, L. Ye, K. Mosbach, K. Haupt, Anal. Chem. 2001, 73, 487.
6. K. Haupt, K. Mosbach, Chem. Rev. 2000, 100, 2495.
7. K. Mosbach, Anal. Chim. Acta 2001, 435, 3.
8. M. Yan, A. Kapua, Anal. Chim. Acta 2001, 435, 163.
9. K. Mosbach, Y. Yu, J. Andersch, L. Ye, J. Am. Chem. Soc. accepted.

9:15 AM M3.2
MOLECULAR IMPRINTING AT SURFACES USING IMMOBILISED MONOMERS, INITIATOR AND TEMPLATE, AND APPLICATIONS IN ANALYTICAL CHEMISTRY. Karsten Haupt, Dept. of Pure and Applied Biochemistry, Lund Institute of Technology, Lund, SWEDEN.

Novel imprinting approaches are presented allowing to obtain thin layers of molecularly imprinted polymers with binding sites situated at or close to the polymer surface. In a first approach, the template molecules were immobilised onto silica or glass as solid support materials. The pre-polymerisation mixtures consisting of monomer and cross-linker was then cast on these derivatised surfaces and polymerised. After polymerisation, the solid support was removed from the composite by chemical treatment. The resulting imprinted polymer layers carry surface binding sites, and were able to specifically rebind the template. When a short peptide was imprinted, longer peptides having the same terminal sequence were recognised as well by the polymer. In another approach, thin porous layers of imprinted polymer were formed at a solid surface by spin coating. Thereby, a linear soluble polymer was used as a porogen, which increased the viscosity of the solution and greatly facilitated spin coating. Following polymerisation, the linear polymer was extracted from the imprinted polymer leaving behind a porous structure. In a third approach, thin imprinted polymer layers were synthesised at surfaces after derivatising the latter with the polymerisation initiator. In this way, the polymer chains are at the same time covalently attached to the surface. These new approaches greatly increase the usefulness of molecularly imprinted polymers for immunoassays, sensors, and affinity separation.

10:15 AM *M3.3
MOLECULAR IMPRINTING OF POLYMERIC CORE-SHELL NANOPARTICLES. Natalia Perez and Andrew G. Mayes, School of Chemical Sciences, University of East Anglia, Norwich, UNITED KINGDOM.

Imprinted nanoparticles offer better access to ligand molecules and higher surface area than conventional ground 'bulk' imprinted polymers. An easy way to control the monodispersity and final size of the polymeric nanoparticles is by using a 2-stage emulsion polymerisation process to produce core-shell particles. Recently, it has been shown that core-shell surface imprinted particles rebind molecules of cholesterol in organic and aqueous solvents, based purely on hydrophobic interactions (1). Imprinting of such particles can also be achieved using the sacrificial spacer method which combines covalent and non-covalent interactions (2). So far they have never been tested using the more versatile non-covalent approach.
Non-covalent imprinting is a simple procedure applicable to a wider range of template molecules. In order to evaluate the compatibility of core-shell particles produced in aqueous systems with non-covalent imprinting procedures, core-shell particles with a small diameter have been synthesised in the presence and absence of a porogenic solvent, and their capacity to rebind template assessed by radioligand binding assay both in organic and aqueous media.
(1) N. Pérez, M.J. Whitcombe, E.N. Vulfson, Surface Imprinting of Cholesterol on Submicrometer Core-Shell Emulsion Particles, Macromolecules, 34; 830-836; 2001.
(2) N. Pérez, M.J. Whitcombe, E.N. Vulfson, Molecularly Imprinted Nanoparticles Prepared by Core-Shell Emulsion Polymerization, J. Appl. Polym. Sci., 77; 1851-1859; 2000.

11:00 AM *M3.4
MOLECULARLY IMPRINTED IONOMERS. George Murray, Johns Hopkins University Applied Physics Laboratory, Laurel, MD.

Ionomers have been defined as copolymers that have a certain proportion of ionic groups. The ionic groups have a significant effect on the mechanical properties of the copolymers. This is generally due to aggregation of ions in a low dielectric medium. The primary result is to restrict chain motion and raise the glass transition temperature. These are attributes that have relevance to molecular imprinting, since restricted chain motion should help preserve the integrity of the binding site. The connection between ionomers and molecular imprinting has come from the production of metal ion imprinted resins. Metal ions are used in the production of molecularly imprinted polymer ion exchange resins and ionically permeable membranes. The polymers have applications as separations media, sequestering media and as ion selective sensors. Metal ions are also being used to form imprinted polymers based on metal mediated imprint binding. We have prepared ion exchange resins, selectively permeable polymer membranes, ion selective electrodes and ion selective optical sensors using a modified version of the molecular imprinting technique. The modification is a reduction in the amount of covalent crosslinking used to form the polymers. This reduction may be justified by the presence of residual metal ion crosslinking in the immediate region of the imprinted binding site. The effects of metal ions on the thermal and mechanical properties of the polymers, as well their impact on binding selectivity, will be discussed.

SESSION M4: NANOSTRUCTURE AND MOLECULAR RECOGNITION
Chair: David A. Spivak
Thursday Afternoon, April 4, 2002
Concordia (Argent)

1:30 PM *M4.1
APPROACHES TO SURFACE CONFINED TEMPLATED BINDING SITES FOR MOLECULAR RECOGNITION AND CATALYSIS APPLICATIONS. Börje Sellergren, Claudia Sulitzky, Magdalena Titirici, Barbel Rückert, and Andrew J. Hall, Institut für Anorganische Chemie und Analytische Chemie, Johannes Gutenberg Universitat Mainz, Mainz, GERMANY.

Molecularly imprinted polymers (MIPs) are presently made and used in many laboratories to achieve highly selective separations of mainly small lipophilic molecules compatible with the conventional imprinting technique[1]. In order to widen the scope of the technique we are facing the typical challanges associated with the current imprinting procedure (i.e. to achieve recognition of very polar or nonpolar compounds or recognition of biological macromolecules in water, to reduce the nonspecific binding, to improve the mass transfer properties and to enhance the sample load capacity). Some of the problems may be overcome by the use of two new approaches to confine templated binding sites to accessible surfaces. In the first of these an optimised monomer formulation is used to graft polymers on non-porous or porous supports with well-defined particle size and shape, pore systems and pore size distributions[2]. These are based on the use of a surface immobilised initiators or iniferters with the objective of confining chain propagation to the vicinity of the support surface. This offers a means of fine tuning the layer thickness for either high efficiency (analytical) or high capacity (preparative) applications. An alternative technique makes use of template modified porous silica beads that after polymerisation and etching leaves behind porous polymer beads containing surface confined binding sites[3]
1. B. Sellergren (Ed.), Molecularly Imprinted Polymers. Man-made mimics of antibodies and their applications in analytical chemistry. Elsevier Science, 2001.
2. C. Sulitzky, B. Rückert, A.J. Hall, F. Lanza, K. Unger, B. Sellergren. Grafting of imprinted polymer films on silica supports containing surface bound free radical initiators. Macrmolecules 2001, in press.
3. M. Titirici, A.J. Hall, B. Sellergren, Hierarchically imprinted stationary phasesm, Mesoporous polymer beads containing surface confined binding sites for adenine. Chem. Mat. 2001, in press.

2:15 PM *M4.2
MOLECULAR IMPRINTING IN SELF-ASSEMBLED MATERIALS. Jun Liu, Biomolecular and Interfaces Department, Sandia National Laboratories, Albuquerque, NM.

Self-assembly of molecular building blocks, micelles and other colloidal materials have led to a wide range of 3-dimensionally organized nanostructural materials. In addition, applying self-assembled molecular monolayers in such materials provides amble opportunities to tailor the surface chemistry in the nanostructures. The objective of this presentation is to discuss the potential of combining molecular imprinting techniques and self-assembly approaches in the fabrication of novel functional nanoscale materials. A new class of ordered nanoporous materials, containing self-assembled molecular monolayers embedded with size-and-shape selective microcavities, will be discussed. The formation of such materials involves co-assembly of ceramics and surfactant liquid crystalline structures, molecular imprinting, and formation of self-assembled monolayers. Compared to 2-dimensional structures and amorphous materials, the organized nanostructures are desirable platforms for molecular imprinting because of the very large specific surface area and tightly controlled geometrical environments (pore dimension, curvature, etc). Besides the size-and-shape selectivity, other novel properties not commonly observed, such as tunable access, will also be discussed.

3:30 PM *M4.3
DIASTEREOSELECTIVE FLUORESCENT SENSING FOR CINCHONA ALKALOIDS BY METALLOPORPHYRIN-BASED IMPRINTED POLYMERS Co-ASSEMBLED WITH METHACRYLIC ACID. Toshifumi Takeuchi, Graduate School of Science and Technology, Kobe University, Kobe, JAPAN.

A diastereoselective molecularly imprinted polymer (MIP) for (*Å*E-cinchonidine (CD), PPM(CD), was prepared by the combined use of methacrylic acid and vinyl-substituted Zn(II) porphyrin as functional monomers. Compared to MIPs using only methacrylic acid

or Zn(II) porphyrin as a functional monomer, PM(CD) and PP(CD), respectively, PPM(CD) showed higher binding ability for CD in chromatographic tests using the MIPs-packed columns. Scatchard analysis gave a higher association constant of PPM(CD) for CD than those of PP(CD) and PM(CD). The MIPs containing a Zn(II) porphyrin in the binding sites, PPM(CD) and PP(CD), showed the fluorescence quenching according to the binding of CD and the quenching was significant in the low concentration range, suggesting that the high affinity binding sites contain the porphyrin residue. The correlation of the relative fluorescence intensity against log of CD concentrations showed a linear relationship. These results revealed that the MIP having highly specific binding sites was assembled by the two functional monomers, vinyl-substituted Zn(II) porphyrin and methacrylic acid, and they cooperatively worked to yield the specific binding. In addition, the Zn(II) porphyrin-based MIPs appeared to act as fluorescence sensor selectively responded by binding events of the template molecule. Fe(III) porphyrin based imprinted polymers will be also discussed.

1. T. Takeuchi, T. Mukawa, J. Matsui, M. Higashi, K.D. Shimizu, Anal. Chem. 2001, 73, 3869-3874.
2. J. Matsui, M. Higashi, T. Takeuchi, J. Am. Chem. Soc. 2000, 122, 5218-5219.

SESSION M5: POSTER SESSION
Chair: M. Joseph Roberts
Thursday Evening, April 4, 2002
8:00 PM
Metropolitan Ballroom (Argent)

M5.1
COMPUTATIONAL FLUID DYNAMICS MODELS OF MOLECULARLY IMPRINTED MATERIALS IN MICROFLUIDIC CHANNELS. Cynthia K. Webber, M. Joseph Roberts, Polymer Science and Engineering Branch, Naval Air Systems Command, NAWCWD, China Lake, CA.

Current research will lead to rapid-prototyping of chemical sensors that utilize microfabricated molecularly imprinted (MI) materials. CFD/CAD software may be used to model flow and chemical binding properties of MI materials in microfluidic channels. Use of this type of software expedites results when changes in properties are made. The surface concentration of bound analyte on a monolithic MIP within microfluidic channels can be modeled using its experimental binding kinetics. The time necessary to reach a detection limit is determined and optimized as a function of flow parameters.

M5.2
SELECTIVE RECOGNITION OF SMALL PEPTIDES USING Ni-NTA RECEPTOR SITES. Peter G. Conrad, II, Kenneth J. Shea, University of California, Irvine, Dept of Chemistry, Irvine, CA.

Molecular recognition of small molecules involves the selection of specific functional groups through multiple, weak interactions. Molecularly imprinted polymers (MIPs) provide a high degree of selectivity for specific analytes via the development of recognition sites during the polymerization process. Ordered interactions orient functional monomers in a pre-polymerization complex with template molecules. These complexes are incorporated into a macromolecular network polymer with cross-linking monomers. Following extraction of the template, the binding sites remain in the polymer matrix. These sites exhibit selectivity towards the template compound. The development of macromolecular receptors for small peptides using Ni-NTA technology has allowed both the polymerization and recognition processes to be carried out in an aqueous environment, which does not compromise the strong metal-ligand interactions primarily responsible for ligand recognition. The Ni(II) centers possess strong binding affinities towards histidine and N-terminus histidine containing peptides. This presentation will focus on polymers formulated with Ni-NTA receptor sites and the diverse applications associated with these MIPs.

M5.3
IMPRINTING OF STEROIDS USING BIFUNCTIONAL FLUORESCENT MONOMERS. Dolly Batra and Kenneth J. Shea, University of California, Irvine, Department of Chemistry, Irvine, CA.

Brevetoxin B is a marine neurotoxin associated with massive killings of fish and other marine life along coastal areas around the world. We wished to explore if molecularly imprinted polymers (MIPs) can be developed for the detection of this neurotoxin in the ocean. An approach would be the use of a fluorescent sensor within the polymer that would register a characteristic change (a quenching or a fluorescence shift) upon the binding of brevetoxin within the imprinted polymer. Our strategy for the imprinting of brevetoxin, or a surrogate steroid such as cholesterol, involves the use of a bifunctional monomer such as alkenoate **1**, which is covalently attached to both the template and the fluorescent probe. After polymerization with a crosslinking monomer such as divinyl benzene (DVB), the resulting polymer **2**can undergo an LAH reduction to give MIP **3**. With MIP **3** in hand, we hope to see a fluorescent change upon binding of the steroid due to a change in the microenvironment of the fluorescent probe. This poster will describe the synthesis of novel functional monomers of type **1** and subsequent fluorescent study of MIPs of type **3**.

M5.4
HIERARCHICALLY IMPRINTED STATIONARY PHASES: MESOPOROUS POLYMER BEADS CONTAINING SURFACE CONFINED BINDING SITES. M. Magdalena Titirici, Andrew J. Hall, Börje Sellergren, Institut für Anorganische Chemie und Analytische Chemie, Johannes Gutenberg Universität, Mainz, GERMANY.

Immobilisation of a template on the surface of a porous silica mold, polymerisation in the mold followed by dissolution of the silica results in a "mirror image" pore system containing binding sites residing uniquely at the pore walls.[1,2] We recently reported on the application of hierarchical imprinting to produce methacrylate based mesoporous beads useful for chromatographic applications, which featured surface confined binding sites for adenine or triamino-pyrimidine.[2] Here we report a detailed characterisation of these materials based on nitrogen sorption measurements, thermo-gravimetric analysis, energy dispersive X-ray analysis, fluorescence microscopy, scanning electron microscopy, IR and elemental analysis. Furthermore, the chromatographic selectivity of these hierarchically imprinted polymers has been evaluated, allowing conclusions concerning the nature of the binding sites to be drawn.

[1] E. Yilmaz, K. Haupt and K. Mosbach, Angew.Chem., Int.Ed., 2000, 39, 2115-2118.
[2] M.M. Titirici, A.J. Hall and B. Sellergren, Chem.Mat. (in press).

M5.5
DESIGN, SYNTHESIS AND APPLICATION OF NOVEL MONOMERS FOR MOLECULAR IMPRINTING TECHNOLOGY: BRINGING MOLECULES TOGETHER. Panagiotis Manesiotis, Andrew J. Hall, Jakob T. Mossing, Börje Sellergren, Institut für Anorganische Chemie und Analytische Chemie, Johannes Gutenberg Universitat, Mainz, GERMANY.

In the field of molecular imprinting the design and synthesis of novel monomers has been seen as a rather expensive and time consuming pursuit. However, the rewards far outweigh the effort required. We have synthesised novel monomers for the recognition of uracils, barbiturates and carboxylic acids, respectively, basing our designs on functional complementarity between the "host" monomer and the "guest" template, thereby "bringing the molecules together". The extent of monomer-template interaction has been studied via 1H NMR titrations and association constants have been determined. The monomers have then been incorporated into Molecularly Imprinted Polymers (MIPs), whose recognition properties have been evaluated in the chromatographic mode (HPLC) in comparison to Non-Imprinted Polymers (NIPs). Uracil is the only RNA base lacking an exocyclic amino- group and is thus difficult to imprint using commodity monomers, e.g. MAA. Using our novel monomers, we have observed a direct correlation between the hydrogen bond strength determined in solution and the discrimination and binding site fidelity observed in the subsequently prepared polymers. Additionally, materials with enhanced selectivity for barbiturates, commonly used as sedative and hypnotic drugs, could be used for isolation and purification of these drugs during their preparation and for the selective extraction and pre-concentration of samples containing them, simplifying any subsequent quantification process. Finally, effective targeting of carboxylic acid moieties should lead to recognition of biologically important molecules, such as amino acids and the C-termini of peptides.

M5.6
STUDIES OF THE PROCESS OF FORMATION, NATURE AND STABILITY OF BINDING SITES OF MOLECULARLY IMPRINTED POLYMERS. Francesca Lanza, Andrew J. Hall, Börje Sellergren Institut für Anorganische Chemie und Analytische Chemie, Johannes Gutenberg Universität, Mainz, GERMANY; Manuel Ruther, Polymer Research Unit, Physics Department, Trinity College, Dublin, IRELAND.

In Molecular Imprinting (1,2) the nature of the templated binding sites and their formation mechanism are poorly understood. For this reason our group is carrying out a series of fundamental studies concerning known imprinting protocols, with the primary aim of shedding some light on the role of the template in the different steps of the polymerisation process from the formation of the primary chains to the build-up of the porous structure. In this paper we are

reporting on the results of two different studies performed on the MAA/EDMA/9-ethyladenine (3) and MAA/EDMA/ametryn (4) model systems, concerning the effect of: (i) the presence of 9-ethyladenine on the kinetics of polymerisation of MAA/EDMA in different solvents (by in situ 1H NMR measurements); ii) a late addition of the template (ametryn) on the recognition properties (batch rebinding experiment on a small scale). The studies indicate that the template is playing a decisive role right from the start of the polymerisation, although the formation of the sites is a rather slow process. The results of a post-polymerisation curing on the porosity and the recognition properties of terbutylazine imprinted polymers will also be reported as an indirect method of investigating the nature and stability of the binding sites. In this context we will present data concerning dry state and swollen state pore size distributions for imprinted and non imprinted polymers.
The authors would like to acknowledge the support of the European Community in the Framework of the TMR Project MICA.
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M5.7
BINDING STUDIES ON RESINS IMPRINTED WITH (S)-NAPROXEN. Yue Hu, Robert A. Orwoll, Departments of Applied Science and Chemistry, College of William and Mary, Williamsburg, VA.

Resins were prepared in a free-radical polymerization of 4-vinylpyridine and ethylene glycol dimethacrylate in the presence of (S)-(+)-6-methoxy-α-methyl-2-naphtaleneacetic acid ((S)-naproxen). Initially (S)-naproxen, the imprinted molecule, i.e. template, was assembled with the monomer 4-vinylpyridine by non-covalent interactions. After the polymerization, continuous removal of the template left binding sites that retain complementary specificity and affinity. Calculated from the amount of template removed, the binding parameters including the number of binding sites and association constant were studied using a modified version of the Scatchard equation. Also a more sophisticated model that incorporates a distribution of association constants ("affinity spectrum") was tested for this system.

M5.8
PICOMOLAR DETECTION OF POLYCHLORINATED AROMATIC CONTAMINANTS IN WATER USING A QUARTZ CRYSTAL MICROBALANCE COATED WITH A MOLECULARLY IMPRINTED POLYMER THIN FILM. Kanad Das, Univ. of Mass. Dept of Chemistry, Amherst, MA; Jacques Penelle, Univ. of Mass. Dept of Polymer Science and Engineering, Amherst, MA; Vincent M. Rotello Univ. of Mass. Dept of Chemistry, Amherst, MA.

Hexachlorobenzene in aqueous solutions can be selectively and rapidly detected at picomolar concentrations using a quartz crystal microbalance (QCM) based sensor. This sensor is prepared by robustly coating a molecularly-imprinted polymer (MIP) thin film to the surface of a QCM chip. Obtained results indicate that a robust unit can be built able to measure the concentration of highly toxic, electron-poor organic pollutants in water at extremely low, environmentally significant levels. The use of a thin film coated to the surface of the QCM chip and the design of target specific electron-rich monomers results in real-time detection and appreciable sensor selectivity compared to a set of non-specific organic pollutants with varying size and electronic properties. In addition, a quantitative assessment and molecular understanding of the specific attributes arising from the imprinting process can be obtained by a Quantitative Structure Activity Relationship (QSAR) based methodology, allowing us to distinguish specific and non-specific binding events. This is accomplished by comparing the partition coefficient of each target to the sensor response, which results in a linear relationship. A deviation from the linearity indicates selectivity that is due to the imprinted molecule.

M5.9
AN EXAMINATION OF THE VARIABLES IN THE MOLECULAR IMPRINTING PROCESS WITH RESPECT TO THE HETEROGENEOUS DISTRIBUTION OF BINDING SITES. Robert J. Umpleby, II, Ken D. Shimizu, Univ of South Carolina, Dept of Chemistry and Biochemistry, Columbia, SC.

Variables in the molecular imprinting process were systematically examined for their effects on the heterogeneous distribution of binding sites in MIPs. Affinity distribution analysis enabled a more complete study of the effects of each variable on the shape of the distribution and percentages of high- and low-affinity sites in comparison to previous studies which applied homogeneous models to heterogeneous MIPs. Variables examined were concentration of template, polymerization initiation method (UV vs thermal), and apparent crosslinking density in a methacrylic acid/ethylene glycol dimethacrylate matrix imprinted with ethyl adenine-9-acetate. All the polymers were found to have binding properties consistent with an exponential distribution of binding sites and thus were readily analyzed by fitting the binding data with a Freundlich isotherm and calculating an affinity distribution using a newly derived distribution equation. In general, the quality of the MIPs improved with higher concentrations of template, lower temperatures, and higher apparent crosslinking densities.

M5.10
ENANTIOSELECTIVE RELEASE OF CONTROLLED DELIVERY GRANULES BASED ON MOLECULARLY IMPRINTED POLYMERS. Roongnapa Srichana, Teerapol Srichana, Trirut Rattananont, Dept of Pharmaceutical Sciences, Prince of Songkla University, Hatyai, Songkla, THAILAND.

The objectives of our study were to examine enantioselective release of controlled delivery granules based on molecularly imprinted polymers (MIPs) for various racemic drugs, including ibuprofen and ketoprofen (NSAIDs) and propranolol (β-blockers), and to evaluate the use of controlled delivery granule containing a combination of different MIPs for the multiple simultaneous enantioselective-controlled delivery of mixed racemic drugs. In this work, the MIP beads selective to S-Ibuprofen, S-ketoprofen as well as R-propranolol were prepared using multi-step swelling and thermal polymerization method. Afterward, the MIP beads were formulated with racemate of the chiral drugs and a binder and followed by granulation. Then, the enantioselective release of racemic drugs from the prepared MIP granules was investigated by in vitro dissolution test using a chiral HPLC for assays of enantiomers. The influences of drug/polymer ratio and medium pH on the selective enantiomeric release of MIP granules were explored. The release of the enantiomers of racemic ibuprofen and racemic ketoprofen from the granule containing two MIPs; S-ibuprofen MIP and S-ketoprofen MIP was also examined. The release profiles of both S-ibuprofen MIP granule and R-propranolol MIP granule exhibited differential release of enantiomers. Also, the finding indicated the stereoselective retardation of those controlled delivery granules as well as the influence of MIP formulation on enantioselective release mechanism. The enantioselective release of S-ibuprofen MIP granule and R-propranolol MIP granule appeared to depend on polymer loading and medium pH. In this case, the drug/polymer ratio of 1:25 showed the best enantioselective release with initial enantiomeric excess of 100%. On the other hand, the enantioselectivity of both granules was the greatest in buffer pH 7.4. Furthermore, the efficiency in enantioselective release of the combined MIP granule was higher than its corresponding single MIP granules, as a result of the cross-selectivities of the MIPs. In this study, controlled delivery granules based on MIPs demonstrated significant enantioselective release for several chiral drugs, and thus it may be developed to utilize as a tool for administration of a chiral pharmaceutical as single enantiomer.

M5.11
ATTEMPTS TO GRAFT "LIVING" MOLECULARLY IMPRINTED POLYMERS FROM HYDROPHILIC AND HYDROPHOBIC CHROMATOGRAPHIC SUPPORT MATERIALS. B. Rückert, C. Sulitzky, B. Sellergren Institut für Anorganische Chemie und Analytische Chemie, Johannes Gutenberg-University, Mainz, GERMANY.

Due to the increasing demand for drugs in enantiomerically pure form, chiral technologies are becoming increasingly important in the pharmaceutical industry. Therefore, the use of chromatographic preparative methods is becoming more widespread. These are based on chiral stationary phases (CSPs) that exhibit selectivity against one of the enantiomers and thereby allow enantiomer separations with high resolution and load capacity. The objective of our work is the synthesis of enantioselective molecularly imprinted chiral stationary phases (MICSPs) possesing high load capacities and improved mass transfer properties. We have focused on the "grafting from" technique, using dithiocarbamate iniferter molecules covalently bound to the surface of various support materials, e.g. hydrophobic poly(styrene)-based and hydrophilic silica-based particles. As this surface modification offers the possibility to obtain multiple functionalised layers differently imprinted via several successive polymerisation steps we concentrated on this opportunity for the targeted optimisation of the CSPs for specific applications as in pharmaceutical industry. The quality of the grafted copolymeric films has been investigated using a variety of techniques (IR spectroscopy, elemental analysis, nitrogen adsorption, SEM, TEM and HPLC) as we will present here.

SESSION M6: COVALENT AND NON-COVALENT IMPRINTING
Chair: Karsten Haupt
Friday Morning, April 5, 2002
Concordia (Argent)

8:30 AM *M6.1
CHEMICAL APPROACHES TO IMPRINTING.
Michael J. Whitcombe, Inst of Food Research, Norwich, UNITED KINGDOM.

The application of various "semi-covalent" protocols to the imprinting of small molecules will be described, including recent results utilizing the dimethylsilyl group as a sacrificial spacer. The synthesis of specialist monomers and templates for noncovalent imprinting will also be presented, along with their application to the imprinting of templates as diverse as inorganic crystals, antibiotics and steroids. In the latter case a novel surfactant approach was used to create imprinted sites at the surface of submicron particles. The use of covalently imprinted polymers in the regioselective acylation of polyols will also be described.
References:
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9:15 AM M6.2
REQUIREMENTS FOR MOLECULAR RECOGNITION BY IMPRINTED POLYMERS.
Ebru Oral[1], Nicholas A. Peppas[1,2], NSF Program on Therapeutic and Diagnostic Devices. [1]School of Chemical Engineering. [2]Department of Biomedical Engineering, Purdue University, West Lafayette, IN.

Biological molecules such as enzymes and antibodies have exceptional recognition capabilities. We investigated the properties that enable synthetic materials to recognize, select and bind specific compounds mimicking these biological molecules. We prepared crosslinked synthetic materials that show similar high molecular recognition capabilities for microfabrication and biosensor applications. We prepared and characterized molecularly imprinted polymers with the aim of identifying important material properties that render these materials specific. Polymer films and particles of 2-hydroxyethyl methacrylate and poly(ethylene glycol) dimethacrylate (PEGDMA) of various lengths were prepared by UV and thermally initiated free-radical polymerization, respectively. The effect of the type of crosslinking agent was also investigated by using 1,6-hexanediol dimethacrylate (HDDMA) and zinc dimethacrylate (ZnDMA). Poly(ethylene glycol)-star polymer networks (31 arms) were prepared by methacrylation of chain ends and crosslinking with PEGDMA by UV-initiated free-radical polymerization to investigate the effect of functional site density. Molecular imprinting was achieved by complexation and polymerization in the presence of biologically important templates such as glucose and cholesterol. The ratio of binding of glucose-imprinted films compared to non-imprinted films was 1.3-1.7. Moreover, selectivity of these polymers towards glucose was four-fold compared to galactose and methylglucopyranoside. The difference between imprinted and non-imprinted polymers increased as the crosslinking agent was increased from 5 mol% of polymer to 80 mol%. This, together with studies of HDDMA and ZnDMA, proved that the crosslinking agent was an integral part of the imprinting process as much as the monomers. Increased functional site density of the star polymers showed promising behavior in decreasing non-specific binding. Modeling of binding behavior showed faster binding of template to imprinted network. IR studies showed a decrease in rate of polymerization as a function of template concentration, which was an indication of complexation during polymerization.

10:15 AM M6.3
Abstract Withdrawn.

10:45 AM M6.4
MOLECULARLY IMPRINTED POLYMER HYDROGELS DISPLAYING ISOMERIC SUGAR BIORECOGNITION.
Paraskevi Parmpi, University of Maryland, College Park, Department of Materials and Nuclear Engineering, College Park, MD; Peter Kofinas, University of Maryland College Park, Department of Chemical Engineering, College Park, MD.

Molecular imprinting is an emerging technology which allows the synthesis of materials containing highly specific receptors sites, with an affinity for target compounds. We have developed methods to produce molecular imprinted polymer (MIP) hydrogels which selectively bind glucose over fructose even while in their water-swollen state. This synthetic methodology for MIPs might offer exciting avenues for novel biorecognition techniques. Glucose selective MIPs could lead to the development of a pharmaceutical, which would aid in the treatment of type II diabetes, and to the development of a glucose sensor. While methods of template fixation vary among research groups, the majority of studies to date have concentrated on synthesizing imprinted polymers from monomer, rather than crosslinking an existing polymer with functionality conducive to a biorecognizable imprint. This research employs molecular imprinting starting from a readily available polymer, which greatly simplifies the synthesis of the MIPs and may bring the technology closer to commercialization. The effect of polymer hydrogel synthesis parameters on glucose binding capacity and specificity will be presented, as well as experimental results demonstrating isomeric glucose biorecognition in aqueous and phosphate buffered solutions from mixed sugar media.

11:15 AM M6.5
MOLECULARLY IMPRINTED POLYMERS USED AS OPTICAL WAVEGUIDES FOR THE DETECTION OF FLUORESCENT ANALYTES.
Jennifer Brazier, Dr. Mingdi Yan, Portland State University, Dept of Chemistry, Portland, OR.

Molecularly imprinted polymers have found a niche in many sensor applications. The host-guest theory responsible for the sensitive and selective detection of imprint molecules has been applied to a combination of analytes and polymer systems. Furthermore, diverse fabrication techniques have created imprinted polymers ranging in design from bulk species to thin films. This project demonstrates the novel approach of fabricating imprinted polymers as fiber optic filaments in 50 micron dimension and incorporating these filaments into operational sensors. Filaments were comprised of polyurethane monomers, cross-linkers, and appropriate solvents to create a porous polymer matrix. Fluorescent polyaromatic hydrocarbons served as template molecules capable of interacting with the monomers through noncovalent, pi-pi forces. Fabrication of these filaments utilized the soft lithography technique of micro-molding in capillaries, MIMIC. In this process, a soft elastomeric stamp of poly(dimethylsiloxane) was used to create microchannels, which were filled with an imprinted solution by capillary action. Polymerization and stamp removal leave behind filaments used as optical waveguides. Binding characteristics of the fiber optic elements were measured and compared to those previously determined for 20 micron particles and films of the same imprinting system. The application of these filaments will be discussed.