Selected successful approaches in combinatorial materials research

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Combinatorial materials research (CMR) is still a relatively young field of research. Nevertheless, it already provides successful strategies for a fast and accurate evaluation of a large variety of different research problems. Some of these approaches in CMR considering polymeric materials will be discussed and highlighted within this contribution by focussing on three prominent literature examples: structure–property relationships in biomaterials research, material properties evaluation utilizing thin film polymer libraries as well as the parallel and automated study of polymer based reversed unimolecular micelles and their application possibilities. These examples are meant to demonstrate the almost unlimited possibilities of combinatorial approaches in polymer science rather than to provide an extended overview of the field.

Introduction

Combinatorial approaches in polymer science are on their way to maturing and recent research examples have shown that combinatorial materials research (CMR) can provide efficient and successful strategies for a large variety of research problems. These examples show that it is possible to address a broad range of different chemical and physical questions and include for instance high-throughput screening methodologies for the discovery of new polyolefin catalysts[1] or the evaluation of mechanical properties of novel materials in a combinatorial fashion.[2] The first example clearly demonstrates the feasibility and benefit of a three stage strategy with a primary (high-throughput, catalyst discovery, 384 experiments), secondary (intermediate-throughput, catalyst optimization, 96 experiments in a focused library) and tertiary (conventional-throughput, laboratory batch reactor, 2 reactions) screening to discover, optimize and evaluate new catalysts. The latter example shows that it is possible to automatically prepare discrete material libraries utilizing inkjet printing technology and that these libraries can subsequently be evaluated for their mechanical properties by nanoindentation experiments in an automated fashion. Moreover, recent technical reviews[3–7] have shown that it is possible to automate, miniaturize and/or

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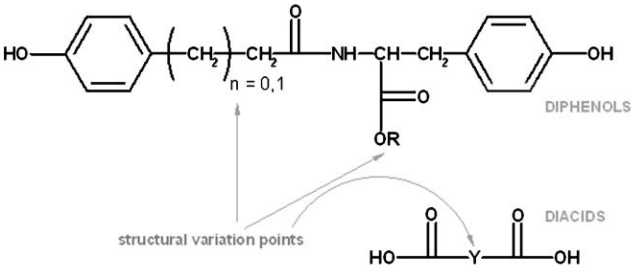
Ulrich S. Schubert was born in Tübingen in 1969. He studied chemistry at the Universities of Frankfurt and Bayreuth in Germany and the Virginia Commonwealth University, Richmond (USA). His PhD work was supervised by Prof. Eisenbach (Bayreuth, Germany) and Prof. Newkome (Florida, USA). In 1995 he obtained his doctorate with Prof. Eisenbach. After postdoctoral training with Prof. Lehn at the Université Strasbourg (France) he moved to the Technische Universität München (Germany) to obtain his habilitation in 1999 (with Prof. Nuyken). From 1999 to spring 2000 he held a temporary position as a professor at the Center for NanoScience at the Universität München (Germany). Since Summer 2000 he has been a full professor at the Eindhoven University of Technology (Chair for Macromolecular Chemistry and Nanoscience). His awards include the Bayerischen Habilitations-Förderpreis, the Habilitandenpreis of the GDCh (Makromolekulare Chemie), the Heisenberg-Stipendium of the DFG, the Dozenten-Stipendium of the Fonds der Chemischen Industrie and the VICI award of the Dutch Science Organization (NWO). His major research interests are: organic heterocyclic chemistry, supramolecular materials, combinatorial material research, nanoscience and tailor-made macromolecules.



Scheme 1 Starting materials for a library of 112 polyarylates derived from 14 tyrosine derived diphenols and eight diacids. For details about the structural variation points see Ref. 9.

parallelize all synthetic as well as analytical techniques known to the polymer chemist in order to speed up classical polymer research. Moreover, these special methods for the preparation as well as characterization of polymers are not only useful for the combinatorial chemist but are very beneficial to the polymer community as a whole. Generally, these systematic approaches allow the preparation of defined libraries with known variations in certain parameters (*e.g.* molecular weight, composition or architecture for polymeric materials) that can subsequently be utilized to evaluate structure–property relationships by applying the appropriate high-throughput screening (HTS) techniques. Moreover, the utilization of design of experiments (DoE) and other computational approaches[8] can significantly reduce the number of experiments required for *e.g.* optimization tasks and help to identify not only first order but also higher order structure–property correlations that would otherwise not be found.

Within this contribution we want to highlight several research approaches in CMR, including the study of biomaterials, thin film libraries as well as star-shaped polymer based reversed unimolecular micelles as prominent examples. Therefore, we will provide detailed overviews for these research examples and discuss their outcome and the benefits of CMR and HTS for these approaches while the recently published technical reviews[3–7] that cover the field more completely might act as a knowledge base for the reader.

Biomaterials research

Already, in 1997, Kohn and coworkers reported on a "combinatorial approach for polymer design".[9] These researchers were able to design and prepare a 112-membered library of strictly alternating A–B type copolymers with predictable and systematic material property variations by the co-polycondensation of 14 tyrosine-derived diphenols and eight diacids (see Scheme 1). Up to 32 parallel polymerizations were performed in a water bath in separate reaction vessels at a 0.2 g scale under the same reaction conditions since all monomers showed identical reactivities. After purification enough material could be isolated (0.1–0.2 g) to establish basic material properties as well as certain biological properties. It was shown that the glass transition temperature (T_g), as well as the air–water contact angle of the polymers, increased as the number of carbon or oxygen atoms in the polymer backbone and pendent chain decreased in a defined fashion, to only mention a few of the structure–property correlations found. Fig. 1 depicts the gradual variation of the T_g values of the whole polymer library as a function of the applied monomers. Moreover, a linear correlation was obtained between cell proliferation and air–water contact angles when polymers having an identical backbone structure but different pendent chains were grouped together. In general, cell proliferation significantly decreased as the polymer surface became more hydrophobic. In contrast, for those polymers having oxygen-containing diacids in the backbone, cell proliferation was far less sensitive to surface hydrophobicity. In fact, all polymers

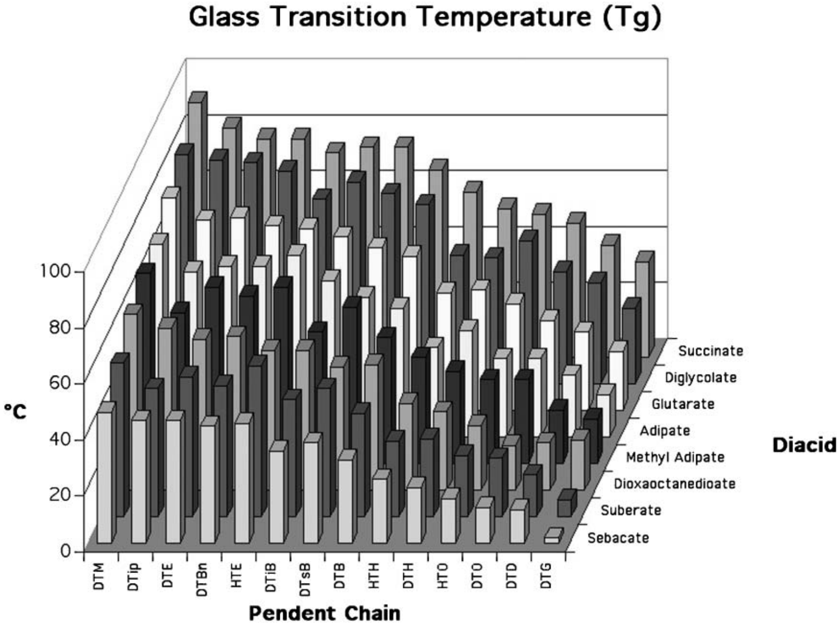


Fig. 1 Glass transition temperatures of a library of 112 polyarylates. Reprinted in part with permission from Brocchini *et al.*, *J. Am. Chem. Soc.*, 1997, **119**, 4553–4554.[9] Copyright 1997 American Chemical Society.

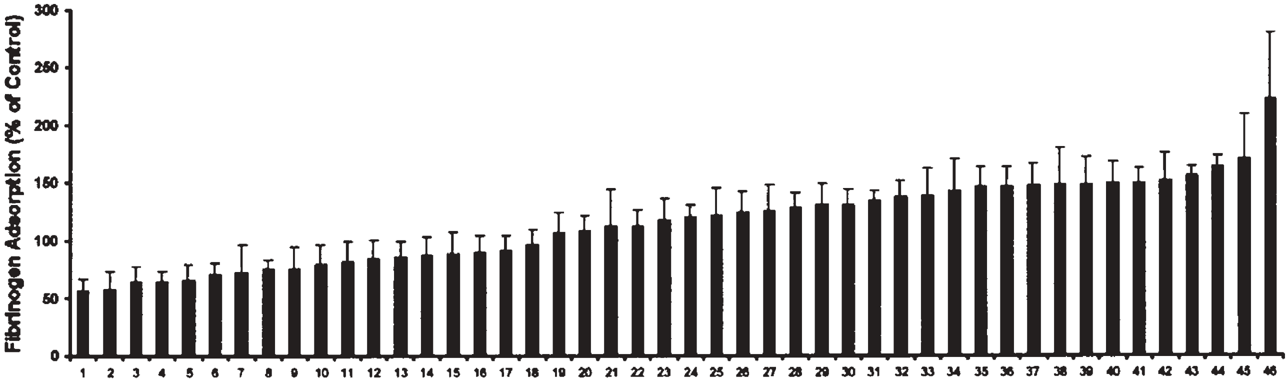
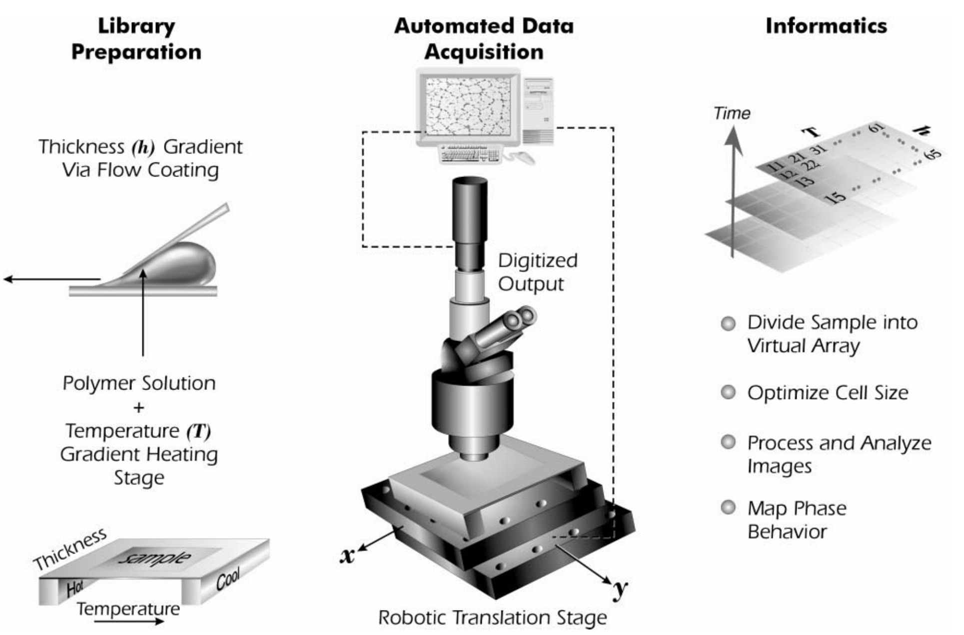


Fig. 2 Screening of human fibrinogen adsorption on 44 polyarylates, and two standard polymers. The statistical comparison of each of 10 low fibrinogen-binding polymers (No. 1–10) with each of 10 high fibrinogen-binding polymers (No. 37–46) showed significant differences between the polymers ($p < 0.001$). Taken from Weber *et al.*, *J. Biomed. Mater. Res., Part A*, 2004, **68**, 496–503.[11] Reprinted with permission of John Wiley & Sons, Inc.

having oxygen-containing diacids in their backbone were uniformly good fibroblast growth substrates irrespective of their air–water contact angle. In summary, the authors mentioned that the utilized combinatorial design of polymers will accelerate the progress for preparing and evaluating new polymers for specialty applications and might have the potential to accelerate the identification of important structure–property correlations, which is certainly true if the current success of combinatorial materials research is taken into account. Subsequently, it was shown that it is possible to derive models for both protein adsorption onto and cellular response to polymeric surfaces, which are derived from the discussed 112-membered library using computed descriptors that are only based on the polymer structure and the glass transition temperature (T_g).[10] Moreover, a subset of 44 polymers of this library was evaluated for its protein adsorption properties utilizing human fibrinogen as a model protein (see Fig. 2).[11] Therefore, protein adsorption and immunofluorescence assays were performed on polymer films that were deposited in microtiter plates. A polymer-dependent adsorption of fibrinogen was observed and this behavior could, for instance, be correlated to the air–water contact angle of the studied polymers. Moreover, the results indicated that it is possible to control the amount of adsorbed fibrinogen on a polymer surface through subtle changes of the chemical composition without necessarily changing the hydrophobicity/hydrophilicity of the polymer. Finally, a variety of other biologically important parameters, such as gene expression levels, were evaluated for this polymer library and it was attempted to correlate the outcome of these tests to the polymer structure.[12,13] These examples clearly demonstrate that a designed (targeted) library of polymeric materials is a very useful tool to evaluate structure–property relationships and to develop computational models. The obtained knowledge can subsequently be applied for the preparation of materials with certain designed properties with a reduced amount of effort and time.

Thin film polymer libraries

Researchers at the National Institute of Standards and Technology (NIST) developed preparation and characterization methods for thin film polymer libraries with gradients in thickness, composition, temperature, surface energy and others.[14–16] An overview of the possibilities of preparing these thin film libraries with different gradients was recently published by Meredith, Smith, Karim and Amis[17] and some of these possibilities are depicted in Scheme 2. In short, thickness libraries can be prepared with a special flow coating device (based on a velocity-gradient knife-edge coating device, see Scheme 2) capable of spreading drops of polymer solutions over the substrate at constant acceleration resulting in polymer films with a gradient in thickness. Moreover, a small modification of this technique, which utilizes an automated solution premixing setup, can be applied to construct composition libraries,[18] whereas temperature gradient libraries are easily obtained by utilizing gradient heating stages. The high-throughput investigation of these libraries enables the combinatorial scientist to evaluate certain structure–property correlations over a wide parameter range by applying, for instance, optical screening methods, such as microscopy (see Scheme 2), FTIR or others. Therefore, these techniques allow fundamental investigations to be performed and physical models for polymers to be developed in a straightforward and accelerated fashion. Prominent examples include the study of complete phase diagrams of polymers libraries with gradients in composition and temperature,[19] the efficient and accurate investigation of the effects of microstructure, roughness, and surface chemistry on cell adhesion and proliferation,[20] or the investigation of thin film dewetting depending on both film thickness and temperature.[15] Moreover, these approaches were applied for studying the polymer blend phase behavior.[18] It was for instance possible to reveal the cloud point of a polymer blend by using optical microscopy to detect phase separations on a two dimensional, orthogonal composition–temperature library. Fig. 3 displays a photograph of a two dimensional library (1. dimension: poly(styrene)/poly(vinyl methyl ether) composition; 2. dimension: temperature) after 2 h of annealing on a temperature gradient stage clearly revealing the lower critical solution temperature (LCST) cloud point curve. Moreover, the composition gradient along one dimension of this library could be confirmed by FT-IR spectroscopy and the cloud point curve observed by the



Scheme 2 Left: preparation of thickness and temperature combinatorial libraries. Middle: automated optical microscopy. Right: informatic data reduction. Reprinted in part from Meredith *et al.*, *Macromolecules*, 2000, **33**, 9747–9756.[15] Copyright 2000 American Chemical Society.

described combinatorial methods agreed well with cloud points measured by laser light scattering (circles in Fig. 3). Therefore, this new high-throughput approach to map physical properties of polymer blends was validated and offers significant advantages for a parallel investigation of interesting polymer properties.

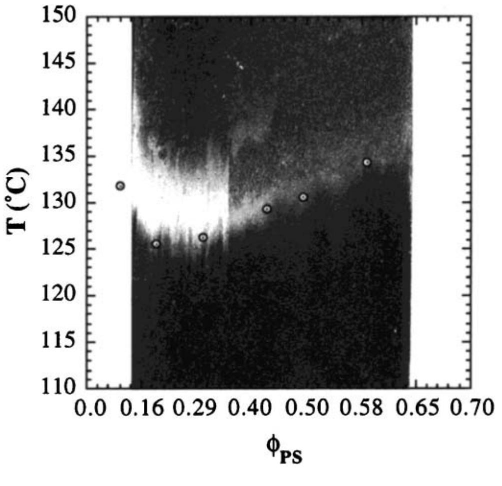


Fig. 3 LCST cloud point curve on a two dimensional polymer blend film library after 2 h of annealing on a temperature gradient stage. The overall sample dimensions are 30 mm by 40 mm. Reprinted in part from Meredith *et al.*, *Macromolecules*, 2000, **33**, 5760–5762.[18] Copyright 2000 American Chemical Society.

Reversed unimolecular micelles

Recently, efforts of the Dutch Polymer Institute led to the development of star-shaped block copolymer based reversed unimolecular micelles. The 5-arm star shaped block copolymers with a poly(ethylene glycol) (PEG) core and a poly(ε-caprolactone) (PCL) corona could be synthesized in a fully automated and reproducible fashion utilizing robotic synthesizer techniques.[21] The applied ring opening polymerization technique was found to be controlled and a series of polymers with different molecular weights and narrow molecular weight distributions could be synthesized, as revealed by high-throughput screening techniques (see Fig. 4 for size exclusion chromatography results). It was observed that these polymers can encapsulate and phase transfer methylorange, a pH indicator dye, from a water phase to a chloroform phase, indicating their unimolecular micellar behavior. This encapsulation behavior was subsequently evaluated by means of a parallel extraction assay in microtiter plate format revealing that the amount of dye that can be encapsulated was independent of the size of the corona (degree of polymerization of the outer PCL chains) of these unimolecular objects and that a branched core-shell architecture was a prerequisite for the observed encapsulation behavior.[21] Furthermore, additional high-throughput screening experiments in microtiter plate format revealed that this polymer class is capable of encapsulating a large variety of different guest molecules, including for instance fluorescent anthracene derivatives.[22] The screening was performed in an acidic as well as a basic environment in order to be able to detect specific changes in the potential guest's microenvironment upon encapsulation by UV/Vis and fluorescence spectroscopy. Fig. 5 depicts an optical picture as well as a schematic layout of the screening performed. This optical screening was validated by ^{1}H NMR techniques showing that 77% of all hits were identified by the screening and no false positives were identified. Furthermore, the very peculiar behavior of this class of polymers was exploited for the development of two application possibilities, namely a fluorescent transition metal sensor[23] and stabilized palladium nanoparticles for catalytic applications.[24] The sensoric system was based on the same

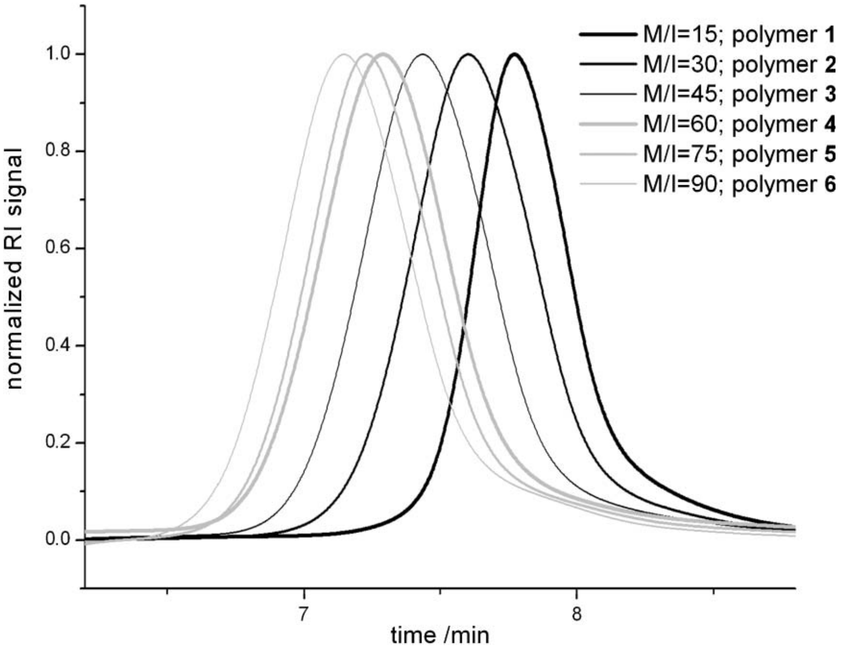


Fig. 4 Size exclusion chromatography traces of a series of 5-arm star-shaped block copolymers with PEO core (constant DP) and PCL shell (varying DP) obtained by automated robot techniques. Reprinted in part from Meier *et al.*, *J. Am. Chem. Soc.*, 2004, **126**, 11517–11521.[21] Copyright 2004 American Chemical Society.

5-arm PEG polymer that was end-group functionalized with terpyridine ligands. The resulting supramolecular polymer was able to encapsulate fluorescent anthracene derivatives in a similar fashion as the star-shaped block copolymers and the subsequent binding of transition metal ions resulted in a quenching of this fluorescence. Plate reader technology was also utilized here for a fast and accurate determination of interesting polymer properties revealing that the sensoric system was quite sensitive to transition metal ions in the micro-molar range of analyte, but not selective to a certain transition metal ion.[23] Moreover, it was observed that the studied star-shaped block copolymers are able to template and stabilize palladium[24] and gold nanoparticles.[25] Whereas the gold nanoparticles showed the expected surface plasmon resonance, the palladium particles could be utilized as efficient catalysts for the Heck coupling reaction. The catalytic activity of the palladium nanoparticles was evaluated in a fully parallel fashion utilizing robotic synthesizer techniques (Chemspeed ASW2000) in combination with an automated sample preparation for a GC-MS screening of the conversion of the reactions. Full conversion of the educts within 24 h reaction time at a catalyst loading of only 0.1 mol% was observed for the stabilized palladium nanoparticle catalysts. These high efficiencies were attributed to the small size (4 nm) and therefore high surface areas of the nanoparticles as well as their stabilization within the polymeric core shell architecture.[24] These examples demonstrate that CMR can offer solutions to a variety of different problems ranging from polymer synthesis and structure clarification to the evaluation of material properties in a similar fashion as classical approaches, but in a significantly reduced amount of time and effort.

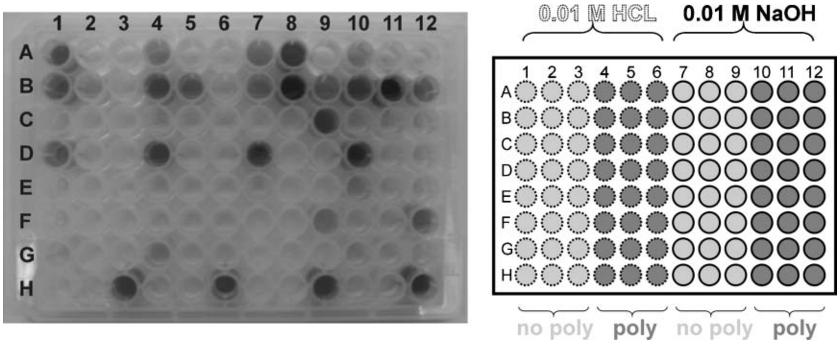


Fig. 5 Optical picture (left) as well as schematic layout (right) of a microtiter plate screening experiment to evaluate the host–guest chemistry of star-shaped block copolymers. 24 potential guest molecules were investigated in the presence and absence of star-shaped block copolymer in order to evaluate changes in the guest's microenvironment upon encapsulation. Reprinted in part from Meier and Schubert, *J. Comb. Chem.*, 2005, **7**, 356–359.[22] Copyright 2005 American Chemical Society.

Conclusion

We have described how combinatorial materials research (CMR) can offer solutions for a large variety of different chemical as well as physical research problems by discussing and highlighting three prominent literature examples. These examples clearly demonstrate the manifold possibilities available to the combinatorial material scientist that allow an accurate and accelerated discovery, optimization and/or material property evaluation.

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