A Combinatorial Approach for Polymer Design

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The design of polymers for specialty applications such as medical implants,[1,2] piezoelectric[3] and photonic materials,[4] or self-assembling systems[5] is challenging since such materials must meet multifaceted requirements. For example, the field of tissue engineering hinges on developing degradable scaffolds that promote cell proliferation and expression of desired physiologic behaviors through careful control of the polymer surface properties.[6] Here we report the concept of permutationally designed monomer systems to create libraries of structurally related polymers. To obtain libraries in which material properties vary in a predictable and systematic fashion, it is necessary to use carefully designed monomers and polymerization strategies. This can be achieved in strictly alternating A−B type copolymers in which the first monomer (A) contains a reactive group for the attachment of a series of pendent chains, while the second monomer (B) allows for systematic variations in the polymer backbone structure. The copolymerization of *n* different monomers A with *m* different monomers B gives rise to an array of *n*×*m* structurally related copolymers. Such libraries can be used to (1) increase the number of available polymeric candidate materials for any specific application and (2) systematize the study of correlations between polymer structure, material properties, and performance. As a first implementation of this concept, a library of 112 polyarylates **3** was prepared from 14 distinct tyrosine-derived diphenols **1** and eight aliphatic diacids **2** (Figure 1). These polymers are based on natural metabolites and are biodegradable and potentially useful as medical implant materials.[7]

In the set of tyrosine-derived diphenols **1**, the pendent group R and the number of methylene groups (*n* = 0, 1) were varied, while in the set of diacids **2**, the polymer backbone was varied via structural changes at Y. In combination, variations at R and Y provided incremental differences in polymer free volume, bulkiness, flexibility, and hydrophobicity. We found that the library of 112 polymers exhibited predictable changes in glass transition temperature (*T*g), surface wettability (as measured by the air−water contact angle), and cellular response (as measured by in vitro cell proliferation studies). On the other hand, since all polymers were derived from very similar monomers, they could be prepared under identical reaction conditions and shared important material properties such as solubility in organic solvents, thermal processibility, and amorphous morphology.

Up to 32 simultaneous reactions on a 0.2 g scale (based on the amount of diphenol **1**) were conducted in separate reaction vessels set up in a water shaker bath. Since the monomers used had almost identical reactivities at their respective functional groups, the same reaction conditions were employed and each polymerization was conducted and worked up in the same
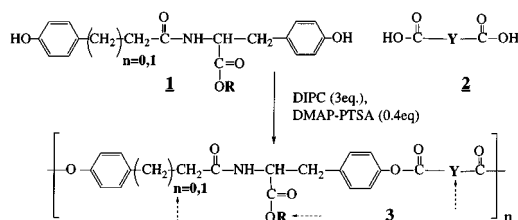
Figure 1. Library of 112 polyarylates **3** was derived from 14 tyrosine-derived diphenols **1** and eight diacids **2**. When *n* = 1, 11 of the 14 tyrosine-derived monomers were provided by R = methyl, ethyl, butyl, hexyl, octyl, 2-(2-ethoxyethoxy)ethyl, dodecyl, isopropyl, isobutyl, *sec*-butyl, and benzyl; when *n* = 0, the remaining three tyrosine-derived monomers were provided by R = ethyl, hexyl, and octyl. The diacids **2** were succinic, glutaric, diglycolic (HO$_2$CCH$_2$OCH$_2$CO$_2$H), adipic, 3-methyladipic, suberic, dioxaoctanedioic (HO$_2$CCH$_2$OCH$_2$CH$_2$OCH$_2$-CO$_2$H), and sebacic acid.
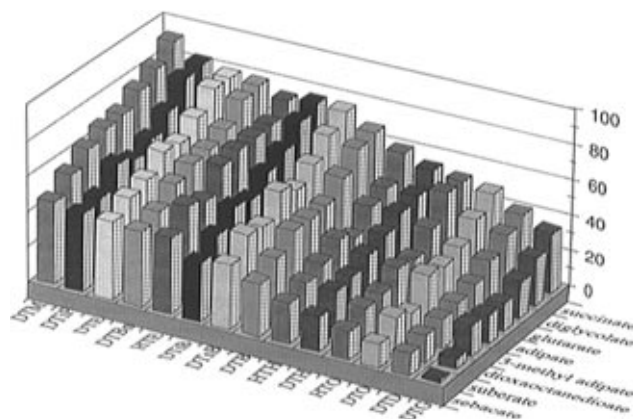
Figure 2. Polymer glass transition temperatures as function of the diacids present in the polymer backbone (*y* axis) and the diphenol alkyl esters which determine the structure of the polymer pendent chain (*x* axis). *T*g values ranged from 2 to 91 °C and increased in regular steps of about 1 °C from one polymer to the next. (Abbreviations: backbone diols, DT = desaminotyrosyl−tyrosyl diol, HT = 4-hydroxyphenylacetic acid−tyrosyl; pendent chains, M = methyl, iP = isopropyl, E = ethyl, Bn = benzyl, iB = isobutyl, sB = *sec*-butyl, B = butyl, H = hexyl, O = octyl, D = dodecyl, G = 2-(2-ethoxyethoxy)ethyl).

reaction vessel. About 0.1−0.2 g of each polymer was obtained after two precipitations from methanol. This methodology can be used for the automated synthesis of polymer libraries. The reaction scale provided sufficient polymer to establish basic material and biological property correlations.

Routine analysis using less than 40 mg of each polymer provided the molecular weight (GPC), *T*g (DSC), and air−water contact angle (sessile drop). Molecular weight averages ranged from 50 000 to 150 000 g/mol. Polydispersities ranged from 1.4 to 2.0. All polymers were sufficiently high in molecular weight and similar in polydispersity for evaluation and comparison of their respective material and biological properties. Several of the polyarylates were also prepared on a larger scale (5−50 g) by following a published procedure.[7] These materials were successfully extruded or compression molded into rods, ribbons, films, and fibers. Their properties matched those of polymers prepared in the simultaneous setup.

*T*g values increased in about 1 °C steps from 2−91 °C as the number of carbon or oxygen atoms in the polymer backbone and pendent chain was decreased (Figure 2). A similarly regular increase in the air−water contact angles was observed. Air−water contact angles ranged from 64 to 101° and increased in steps of about 0.5° from one polymer to the next.

The data provided several structure−property correlations including (1) *T*g increased and contact angle decreased with a

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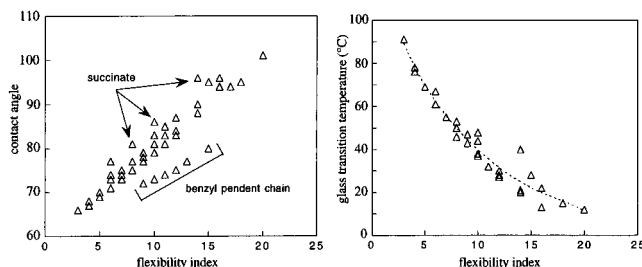
Figure 3. Correlations between the flexibility index (see text) and material properties for members of the polyarylate library. Each data point represents one specific polymer. (left) Air−water contact angle as a function of the flexibility index. Slight variation from a tight linear correlation was observed for polymers having a benzyl ester pendent chain and polymers having a succinic acid backbone. (right) Glass transition temperature as a function of the flexibility index. The dashed line represents a polynominal curve fit.

decreasing number of methylene groups in either the pendent chain or polymer backbone, (2) T_g decreased more due to backbone methylene substitution in the diacid portion than in the diphenol portion of the repeat unit, (3) T_g increased for polymers with alkyl branching in the pendent chain but the contact angle remained unchanged, and (4) contact angle values decreased when oxygen was substituted in place of methylene groups in either the pendent chain or the polymer backbone. To account more easily for changes in the polymer structure at both the pendent chain and the polymer backbone (R and Y in Figure 1), the "flexibility index" was defined as the total number of carbon atoms contained within R and Y. For those polymers that did not contain oxygen atoms in R and Y, the "flexibility index" was tightly correlated with fundamental material properties such as the polymer glass transition temperature and the surface air−water contact angle (Figure 3).

A fundamental hypothesis of this work is that more meaningful biological correlations can be derived when the test materials exhibit systematic variations in structure while sharing a range of common features. Surface properties such as wettability, charge, rigidity, and surface structure have been widely studied and are known to profoundly influence polymer−cell interactions.[8−12] However, many of these studies compared structurally unrelated materials, e.g. Teflon, nylon, and polystyrene.[9] To establish *in vitro* correlations between polymer structure and the cellular response, the proliferation of rat lung fibroblasts was studied in a group of 42 test polymers using the MTS colorimetric assay (Promega, Madison, WI). Cell growth data were normalized to the cell growth observed on tissue−culture polystyrene control surfaces.

When polymers having an identical backbone structure but different pendent chains were grouped together, a linear correlation was obtained between cell proliferation and air−water contact angles (data summarized in Table 1). Cell proliferation on polymers having no oxygen atoms in the backbone was tightly correlated with surface contact angle (surface hydrophobicity); 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 as illustrated by the significantly less negative slope of the linear curve fit (Table 1). In fact, all polymers having oxygen-containing diacids in their backbone were uniformly good fibroblast growth substrates irrespective of their

Table 1. Linear Regression Analysis of Cell Proliferation on Groups of Polymers as a Function of Air−Water Contact Angle

polymer backbone[a]	oxygen present in backbone	slope	r^2
succinate	no	−3.82	0.96
adipate	no	−3.33	0.81
glutarate	no	−2.58	0.98
suberate	no	−2.60	0.88
sebacate	no	−3.15	0.92
diglycolate	yes	−0.066	0.84
dioxaoctanedioate	yes	−0.060	0.50

[a] In each backbone group, six polymers were tested having either a methyl, ethyl, butyl, hexyl, octyl, or dodecyl pendent chain.

Table 2. Selected Polymer Subgroups Illustrating the Tailoring of Material Properties to Specific Applications

polymer	contact angle (deg)	T_g (°C)
poly(DTG diglycolate)[a]	**70.1**	27
poly(DTBn dioxaoctanedioate)[a]	**71.1**	55
poly(DTiP succinate)[a]	**70.7**	82
poly(DTG succinate)[b]	70.3	**34**
poly(DTsB sebacate)[b]	82.1	**36**
poly(DTD diglycolate)[b]	97.5	**36**

[a] Example polyarylates which exhibit comparable contact angles over a wide T_g range (27−82 °C). [b] Polymers with T_g close to body temperature that span a wide range of contact angles (70−97°).

air−water contact angle. This agrees with the literature where incorporation of oxygen species into the surface by plasma glow discharge has been shown to improve cell growth.[11,13]

The availability of this library facilitates the selection of polymers for biomedical applications in ways not previously possible; e.g., polymers with an air−water contact angle around 70° often lead to optimum cell attachment and proliferation.[8,9] From this polymer library it is possible to choose polymers having a 70° contact angle that span a wide T_g range, including polymers that would be either glassy or rubbery at body temperature (Table 2). In other subgroups of polymers, the glass transition can be kept constant while the air−water contact angle can be varied over a wide range (Table 2).

In summary, the design of two sets of monomers having small but systematic structural variations and their copolymerization to yield strictly alternating A−B type copolymers can lead to the rapid preparation of extensive polymer libraries. This combinatorial design of polymers will accelerate progress for preparing and evaluating new polymers for specialty applications and has the potential of accelerating the identification of important structure−property correlations. Results reported here indicate that this approach may be particularly useful in biomaterials research. Although cell response screening studies of biomedical polymers have been conducted in the past,[9] the lack of common structural features among test materials made it difficult to identify correlations between chemical structure and cellular responses. The further study of combinatorial polymer libraries will facilitate the identification of new biomaterials that are optimally matched to the requirements of a specific medical application.

Supporting Information Available: Procedures and data for desaminotyrosyl−tyrosyl diols **1** and polymerization, characterization, and cell assay procedures along with tables listing T_g, contact angle, and percent fibroblast proliferation for the library of polyarylates **3** (11 pages). See any current masthead page for ordering and Internet access instructions.

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