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Polymers derived from the amino acid L-tyrosine: polycarbonates, polyarylates and copolymers with poly(ethylene glycol)

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Abstract

The natural amino acid L-tyrosine is a major nutrient having a phenolic hydroxyl group. This feature makes it possible to use derivatives of tyrosine dipeptide as a motif to generate diphenolic monomers, which are important building blocks for the design of biodegradable polymers. Particularly useful monomers are desaminotyrosyl-tyrosine alkyl esters (abbreviated as DTR, where R stands for the specific alkyl ester used). Using this approach, a wide variety of polymers have been synthesized. Here, tyrosine-derived polycarbonates, polyarylates, and polyethers are reviewed with special emphasis on recent developments relating to cellular and in vivo responses, sterilization techniques, surface characterization, drug delivery, and processing and fabrication techniques. The commercial development of tyrosine-derived polycarbonates is most advanced, with one polymer, poly(DTE carbonate) (E = ethyl), being under review by the USA Federal Drug Administration.

Keywords: Tyrosine-derived polymers; Desaminotyrosyl-tyrosine alkyl esters; Biodegradable polymers; Polycarbonate; Polyarylate; Cell–material interactions; Sterilization techniques; Surface characterization; Drug delivery; Polymer processing

Contents

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1. An historic overview of amino-acid-derived polymers

Over the last 25 years, significant efforts have been devoted to the development of polymeric biomaterials. Historically, the vast majority of these efforts were focused on identifying 'off the shelf' polymers that were biologically inert and stable under physiological conditions. These materials were used as permanent prosthesis such as bone and joint replacements, dental devices and cosmetic implants. However, the emerging field of tissue engineering and the need for advanced drug and gene delivery systems have resulted in an increasing need for resorbable polymers.

A new approach in the development of polymeric biomaterials is to custom design the polymer to tailor its properties for the desired application. Since poly(amino acid)s are structurally related to natural proteins, the synthesis of amino-acid-based polymers was explored as a potential source of new biomaterials. Starting from about 1970, the use of both homo- and copolymers of amino acids was studied for a variety of biomedical applications [1–5]. Several excellent, comprehensive reviews are available for developments prior to 1987 [3,6–9]. The early studies revealed that most poly(amino acid)s could not be considered as potential biomaterials due to their immunogenicity and unfavorable mechanical properties. So far, only a small number of poly(γ-substituted glutamates) and copolymers thereof [3,10–12] have been identified as promising candidate materials for biomedical applications.

To improve the unfavorable physicomechanical properties of most poly(amino acid)s, amino acids have been used as monomeric building blocks in polymers that do not have the conventional backbone structure found in peptides. Collectively, these materials are referred to as 'non-peptide amino-acid-based polymers' or as 'amino-acid-derived polymers with modified backbones'. These materials have previously been classified into four major groups by Kenmitzer and Kohn [13], as described below.

1.1. Synthetic polymers with amino acid side chains

These polymers consist of amino acids or peptides which have been grafted as side chains onto a synthetic polymer backbone. Some of these materials exhibit polyelectrolyte and metal complexation behavior [14–17].

1.2. Copolymers of α-L-amino acids and non-amino acid monomers

Copolymerization of α-L-amino acids with non-amino acid monomers has been achieved through a variety of reaction schemes, leading to polymers with a wide range of structures and properties [18–23].

1.3. Block copolymers containing peptide or poly(amino acid) blocks

These polymers mostly consist of A–B or A–B–A block copolymers, where A is poly(ethylene glycol) and B is a conventional poly(amino acid) or a peptide. Such systems represent promising materials for the delivery of therapeutic agents by control of supramolecular solution structures [24–30].

1.4. Pseudo-poly(amino acid)s

Naturally occurring amino acids are linked by non-amide bonds, such as ester, iminocarbonate and carbonate bonds. The resulting polymers contain the same monomeric building blocks as conventional poly(amino acid)s, but do not have a peptide-like backbone structure. They were first described in

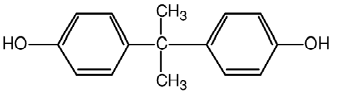
1984 [31,32]. A number of tyrosine-derived pseudo-poly(amino acid)s have been extensively studied and have found practical, biomedical applications.

This article focuses on the design, synthesis, characterization and applications of two families of tyrosine-derived polymers: the polycarbonates and polyarylates. We will also briefly introduce new copolymers with poly(ethylene glycol) (PEG), the tyrosine-containing poly(DTR–PEG carbonate)s and poly(DTR–PEG ether)s. For more information on other types of amino-acid-derived polymers, the reader is referred to several publications [3,20,33–38] and to the many publications cited in the preceding paragraphs.

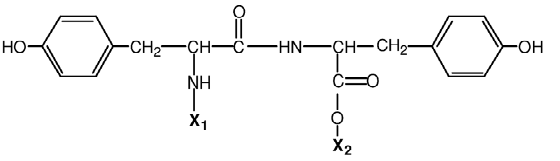
2. Design and synthesis of tyrosine-derived diphenolic monomers

Diphenols, such as Bisphenol A, are frequently used in industry, since their aromatic backbone structures can significantly increase the stiffness and mechanical strength of polymers. However, Bisphenol A and other industrially used diphenols are cytotoxic and can therefore not be used as monomers in degradable biomaterials. There was a significant need for a non-cytotoxic, diphenolic monomer that could be used as a building block in the design of degradable implant materials. This need was addressed by the development of several tyrosine-based monomers. Tyrosine is the only major, natural nutrient containing an aromatic hydroxyl group. In view of the non-processibility of conventional poly-(L-tyrosine), which cannot be used as an engineering plastic, the development of a tyrosine-based pseudo-poly(amino acid) was envisioned. In this context, derivatives of tyrosine dipeptide can be regarded as diphenols and may be employed as replacements for the industrially used diphenols in the design of medical implant materials (Fig. 1). This approach led, for the first time, to tyrosine-derived polymers with favorable engineering properties.

The protecting groups used to block the N- and C-termini of tyrosine dipeptide (Fig. 1) have a significant impact on the properties of the resulting polymers. The challenge of the early studies was to identify suitable protecting groups that will lead to non-toxic, fully degradable polymers with good engineering properties. The combination of these different properties within one single design proved to be a difficult task and early investigations did not lead to readily processible materials [32,39]. Later, it was recognized that the number of inter-chain hydrogen bonding sites per monomer unit had to be minimized [40]. These studies led to the replacement of one tyrosine molecule by desaminotyrosine [3-(4′-hydroxyphenyl)propionic acid] and the identification of desaminotyrosyl-tyrosine alkyl esters (Fig. 2) as fully biocompatible replacements for Bisphenol A



Bisphenol A (BPA)



protected tyrosine dipeptide

Fig. 1. Chemical structures of Bisphenol A and tyrosine dipeptide. In the dipeptide structure, the amino terminal group and the carboxylic acid terminal group are shown with appropriate chemical protecting groups attached (X_1 and X_2). The nature of these protecting groups affects the chemical synthesis of the polymer as well as the final physicomechanical properties of the polymer.

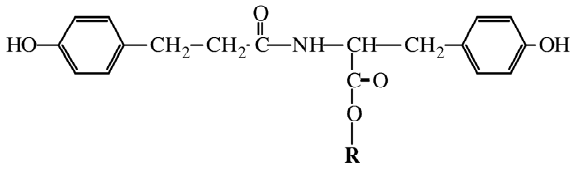


Fig. 2. Chemical structure of desaminotyrosyl-tyrosine alkyl esters, abbreviated 'DTR'. The carboxylic acid terminal group is protected by an alkyl ester which can be regarded as a pendent chain after polymerization. The structure of the alkyl esters is indicated by the following nomenclature convention: DTE, desaminotyrosyl-tyrosine ethyl ester; DTB, desaminotyrosyl-tyrosine butyl ester; DTH, desaminotyrosyl-tyrosine hexyl ester; DTO, desaminotyrosyl-tyrosine octyl ester; DTD, desaminotyrosyl-tyrosine dodecyl ester. These particular monomers are most commonly used in the synthesis of tyrosine-derived polymers.

and other industrial diphenols in a wide range of polymers [41–43].

Monomer synthesis from 3-(4′-hydroxyphenyl)propionic acid and tyrosine alkyl esters was accomplished by carbodiimide-mediated coupling reactions, following known procedures of peptide synthesis [44,45], giving typical yields of 70%. Monomers carrying an ethyl, butyl, hexyl, or octyl ester pendent chain have been investigated extensively [45,46].

3. Properties of tyrosine-derived polymers

The basic design, synthesis, and material properties of tyrosine-derived polycarbonates and polyarylates have been reviewed in detail [13,47–49]. These properties are therefore reviewed here only very briefly.

3.1. Tyrosine-derived polycarbonates

Tyrosine-derived polycarbonates are a group of ‘homologous’ carbonate–amide copolymers differing only in the length of their respective alkyl ester pendent chains (Fig. 3). The diphenolic monomers were polymerized using either phosgene or the more easily handled bis(chloromethyl) carbonate triphosgene. Polymers with weight-average molecular weights (M_w) of up to 400,000 [44,45] were obtained, although for practical applications, M_w values around 100,000 are usually preferred. Polymer properties, such as glass transition temperature, surface free energy, and mechanical properties, can be easily

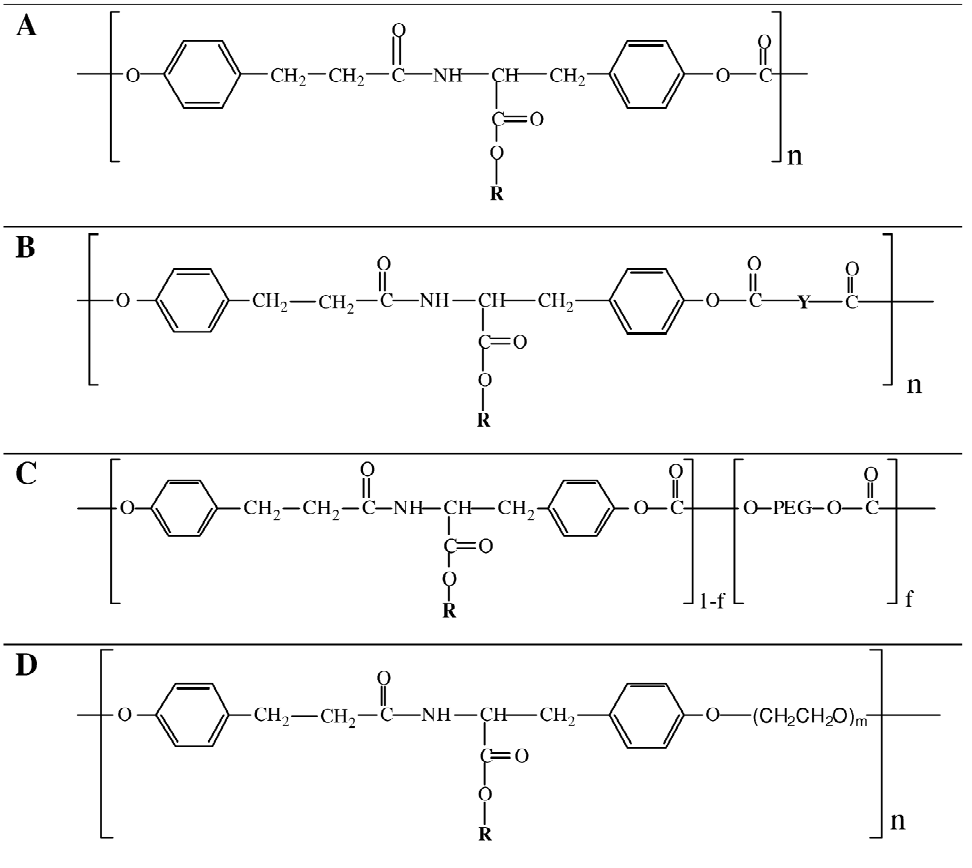


Fig. 3. Chemical structures of (A) tyrosine-derived polycarbonates, (B) tyrosine-derived polyarylates, (C) tyrosine-containing poly(DTR–PEG carbonate), and (D) tyrosine-containing poly(DTR–PEG ether). See Fig. 2 for more details of the structure of ‘DTR’.

Table 1
Physicomechanical properties of tyrosine-derived polycarbonates[a]

Polycarbonate derived from	Molecular weight (weight average)	Poly-dispersity	Glass transition temp. (°C)	Decomposition temp. (°C)	Contact angle (deg)
DTE	176,000	1.8	81	290	73
DTB	120,000	1.4	66	290	77
DTH	350,000	1.7	58	320	86
DTO	450,000	1.7	53	300	90

[a] From Ertel and Kohn [45].

controlled by varying the length of the alkyl ester pendent chain (Table 1). Surprisingly, the degradation rate is not a sensitive function of the length of the alkyl ester pendent chain, therefore all poly(DTR carbonate)s can be easily handled under ambient conditions and degrade only slowly under physiological conditions. In vivo studies confirmed the absence of enzymatic involvement in the degradation process [52–54].

The physicomechanical properties and potential applications of tyrosine-derived polycarbonates were studied by Ertel and Kohn [45]. Briefly, the polycarbonates are amorphous polymers. Because of their high hydrophobicity, they do not swell in aqueous media or during the degradation process. Their equilibrium water content is about 2 to 3% and remains below 5% even at advanced stages of degradation. Glass transition temperatures (T_g) range from 52 to 93 °C and decomposition temperatures exceed 290 °C, providing a wide temperature window for thermal processing. Thorough evaluations of enthalpy relaxation kinetics [50,51] determined that storage of polycarbonates at a temperature of $T_g - 15$ °C for only a few hours is sufficient to bring the physical aging process to completion. Even in an unoriented stage (thin solvent cast or compression molded films), tyrosine-derived polycarbonates are characterized by their high mechanical strength (50–70 MPa) and stiffness (1–2 GPa) [45]. These values can be further increased by processing conditions that induce molecular orientation.

Recently, the degradation mechanism was studied in detail by Tangpasuthadol et al. [55,56] utilizing a series of small model compounds that mimic the repeat unit of the polymer, followed by a thorough 3-year degradation study. These results indicated that the backbone carbonate bond is hydrolyzed at a faster rate than the pendent chain ester bond. Only under very acidic conditions (pH ≤ 3) did the acid-catalyzed hydrolysis of the ester bond become a dominant factor and pendent chain ester hydrolysis outpaced the rate of hydrolysis of the backbone carbonate bonds. Increasing the length of the pendent chain from ethyl to octyl reduced the rate of hydrolysis of both the ester and carbonate bonds, possibly by hindering the access of water molecules to these bonds. The mechanism of polycarbonate degradation is shown schematically in Fig. 4. According to this mechanism, the final degradation products in vitro are desaminotyrosyl-tyrosine and the alcohol used to protect the carboxylic acid group. In vivo, it is reasonable to expect the enzymatic degradation of desaminotyrosyl-tyrosine to desaminotyrosine and L-tyrosine.

3.2. Tyrosine-derived polyarylates

The combinatorial approach used in the design of the polyarylate library was described in detail by Brocchini et al. [57]. Briefly, a permutationally designed monomer system was used for the synthesis of 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 gave rise to an array of $n \times m$ structurally related copolymers. The first five structurally related polyarylates were reported by Fiordeliso [58] and this initial group of polymers was further extended to 112 synthesized polyarylates by Brocchini et al. [57]. Polymerization was achieved by reaction with 1,3-diisopropylcarbodiimide according to a procedure first published by Moore and Stupp [59].

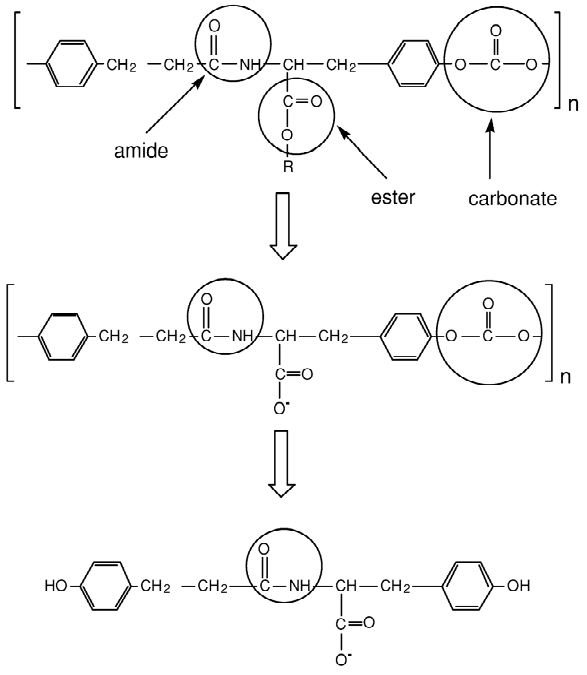


Fig. 4. Schematic summary of the mechanism of degradation of tyrosine-derived polycarbonates. Proceeding via two alternate pathways, the final degradation products in vitro are desaminotyrosyl-tyrosine and the alkyl alcohol used to protect the carboxylic acid group. In vivo, it is reasonable to expect that desaminotyrosyl-tyrosine will be further degraded into desaminotyrosine and L-tyrosine.

A total of 18 publications [54,58,60–75] have heretofore been published describing the properties and potential applications of this first library of combinatorially designed biomaterials (Table 2). One of the most significant features of this library of polymers is the fact that important polymer properties and polymer performance characteristics follow predictable patterns. For example, changes in the glass transition temperature (Fig. 5) increase in about 1 °C steps from 2 to 91 °C as the number of carbon or oxygen atoms in the polymer backbone and pendent chain decreased [57]. Similarly, the air–water contact angle ranged from 64 to 101° and increased in steps of about 0.5° from one polymer to the next (Fig. 6). X-ray scattering and DSC data indicate that these tyrosine-derived polyarylates range from amorphous to liquid crystalline. The polyarylates are thermally stable polymers with thermal decomposition temperatures in the range of 300 °C. The mechanical properties range from soft, elastomeric materials, e.g. poly(DTO sebacate), to fairly tough and strong materials, e.g. poly(DTE succinate). In vitro and in vivo degradation studies of a limited number of polyarylates indicate that polyarylates have a faster degradation rate than polycarbonates [54].

3.3. Tyrosine-containing poly(DTR–PEG carbonate)s and poly(DTR–PEG ether)s

There is a growing need for hydrophilic, soft, and fast degrading biomaterials. Some applications that may benefit from these materials are drug delivery, non-thrombogenic coatings for stents and vascular grafts, degradable membranes for the prevention of surgical adhesions, and scaffolds for wound healing and artificial skin. To address these needs, tyrosine-derived diphenolic monomers were copolymerized with blocks of poly(ethylene glycol) (PEG), resulting in a new class of poly(DTR–PEG carbonate)s (Fig. 3C) [76]. The chemical structure of the copolymers, referred to as poly(DTR-co-f% PEG_{M_w} carbonate)s, supports the optimization of material properties through variation of three independent structure parameters: the percent mole fraction of PEG (f), the average molecular weight of the PEG blocks (M_w), and the pendent alkyl group (R) present in each tyrosine-derived diphenol. Synthesis of this copolymer was achieved by reacting desaminotyrosyl-tyrosine alkyl ester with a pre-determined molar ratio of PEG in the presence of phosgene at room temperature by a condensation copolymerization reaction. General structure–property correlations for glass transition and melting temperatures were established [76]. The introduction of PEG significantly increased water uptake. As the PEG content was increased, the rate of water uptake and the equilibrium water content increased. At PEG contents above 15 mol%, the copolymers behaved increasingly like hydrogels, and at PEG contents over 70 mol%, the polymers became water soluble.

The incorporation of PEG into the backbone of tyrosine-derived polycarbonates had a significant impact on their mechanical properties. At low PEG content, the polymers were strong and tough and had tensile stiffness (1.8 GPa) and strength (36 MPa)

Table 2
Overview of publications describing tyrosine-derived polyarylates

Authors	Year	Title
S. Bron and J. Kohn [60]	1993	The effect of small changes in the chemical structure on the chain mobility in the glassy state of a new series of polyarylates
J. Fiordeliso, S. Bron and J. Kohn [58]	1994	Design, synthesis, and preliminary characterization of tyrosine-containing polyarylates: new biomaterials for medical applications
J. Kohn [61]	1994	Tyrosine-based polyarylates: polymers designed for the systematic study of structure–property correlations
J. Fiordeliso, S. Bron and J. Kohn [62]	1995	Design, synthesis, and preliminary characterization of tyrosine-containing polyarylates: new biomaterials for medical applications
J. Kohn and S. Brocchini [63]	1996	Pseudo-poly(amino acid)s
V. Tangpasuthadol, A. Shefer, C. Yu, J. Zhou and J. Kohn [64]	1997	Thermal properties and enthalpy relaxations of tyrosine-derived polyarylates
K.A. Hooper, N.D. Macon and J. Kohn [54]	1998	Comparative histological evaluation of new tyrosine-derived polymers and poly(L-lactic acid) as a function of polymer degradation
M. Puma, N. Suarez and J. Kohn [65]	1999	Conductivity and high-temperature relaxation of tyrosine-derived polyarylates measured with thermal stimulated currents
D.M. Schachter and J. Kohn [66]	1999	A new approach to the control of peptide drug release using novel polymer blends
A.M. Belu, S. Brocchini, J. Kohn and B.D. Ratner [67]	2000	Characterization of combinatorially designed polyarylates by time-of-flight secondary ion mass spectrometry
F. Bouevich, S. Pulapura and J. Kohn [68]	2000	Microscopic analysis of porous biodegradable scaffolds for tissue engineering
E.A.B. Effah-Kaufmann and J. Kohn [69]	2000	Correlations of osteoblast activity and chemical structure in the first combinatorial library of degradable polymers
J. Kohn [70]	2000	The use of combinatorial approaches for the design of biomaterials
J. Kohn, E.A.B. Effah Kaufmann, E. Tziampazis and P.V. Moghe [71]	2000	Combinatorial approaches in the design of degradable polymers for use in tissue engineering
D.M. Schachter and J. Kohn [72]	2000	Design of a polymer matrix for the programmable delayed release of a water-soluble model peptide
E. Tziampazis, J.A. Cassaday, J. Kohn and P.V. Moghe [73]	2000	Dynamic control of cell adhesion and migration behavior on protein-adsorbed, PEG-variant polymer surfaces
N. Suarez, S. Brocchini and J. Kohn [74]	2001	Study of relaxation mechanisms in structurally related biomaterials by thermally stimulated depolarization currents
D.M. Schachter and J. Kohn [75]	2002	A synthetic polymer matrix for the delayed or pulsatile release of water-soluble peptides

within the range observed for the corresponding tyrosine-derived homopolymers. As the PEG content was increased, the polymers lost their stiffness and strength. Generally, copolymers containing more than 5 mol% of PEG were flexible and soft elastomers in the wet state (UTS ~20 MPa, Young's moduli 37–500 MPa; up to 1000% strain) [76].

Increasing PEG content also increased the degra-

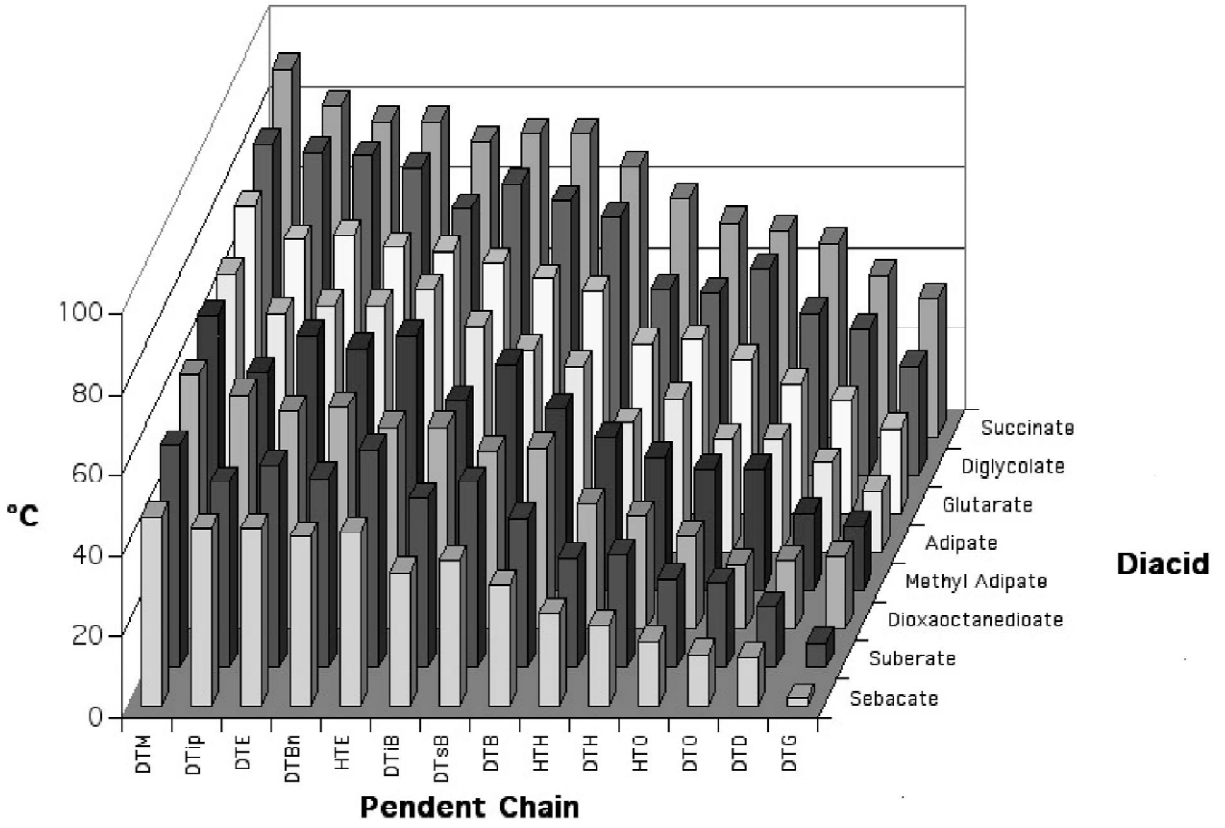


Fig. 5. Pattern of glass transition temperatures in the library of polyarylates.

dation rate compared to films of the homopolymer. The hydrolytic cleavage of the homopolymer backbone is limited by the low water content within the polymeric matrix. Thus, the introduction of PEG into the copolymer structure increases the degradation rate by increasing the availability of water within the matrix [76]. An inherent property of the high PEG content, marginally water-soluble poly(DTR–PEG carbonate)s is that they exhibit inverse temperature transitions, e.g. the polymers are more soluble in cold water and tend to precipitate when the temperature is increased. By changing the polymer structure, the transition temperature could be varied from 18 to 58 °C [77]. Since the polymer structure can be tailored to undergo an inverse temperature transition slightly below body temperature, these materials have a wide range of potential applications in medicine.

While the above described poly(DTR–PEG carbonate)s are random copolymers, a corresponding family of strictly alternating copolymers, poly(DTR–PEG ether)s (Fig. 3D), were synthesized by copolymerization of DTR monomers with methylsulfone-activated PEG. This strategy resulted in alternating multiblock copolymers containing approximately four to eight repeat units [78]. PEG blocks of molecular weights ranging from 1000 to 8000 and alkyl pendent chains (R) ranging from ethyl (C2) to dodecyl (C12) were used to vary the molecular structure of the multiblock copolymers. These copolymers have a high tendency to self-assemble and to form polymeric micelles in aqueous solution [79]. The increased tendency of the poly(DTR–PEG ether)s to form supramolecular structures in aqueous solutions is most probably a direct consequence of their higher molecular order compared to the random poly(DTR–PEG carbonate)s. In the future, these two families of polymers may be used as an interesting

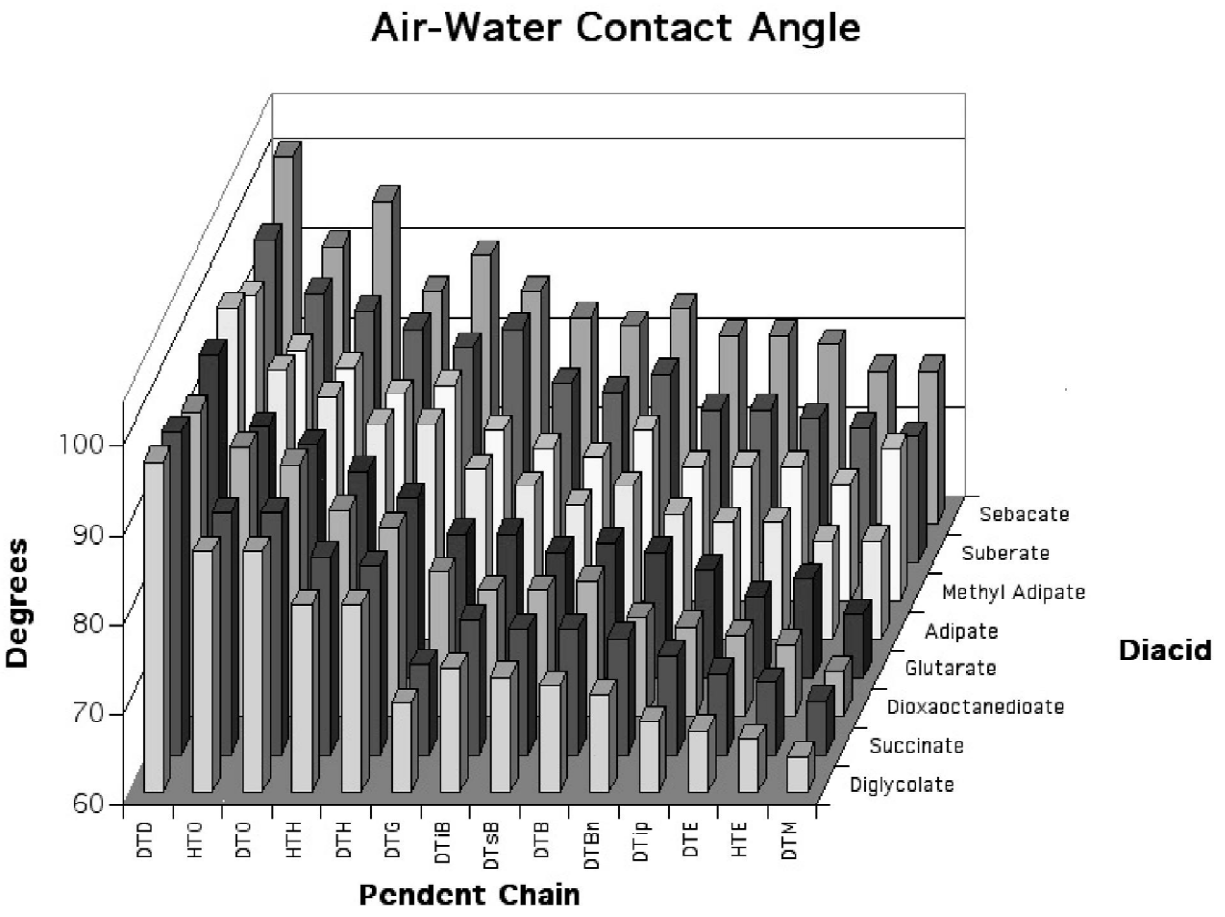


Fig. 6. Pattern of air–water contact angle in the library of polyarylates.

tool in studies relating molecular structure to various performance measures.

4. Cellular and in vivo response

The cellular responses to polycarbonates and polyarylates indicate no sign of cytotoxicity. The ability of cells to attach and proliferate on these polymer surfaces was strongly correlated with the hydrophobicity of the polymers [45,61,80]. Tyrosine-containing poly(DTR–PEG carbonate)s are also non-cytotoxic. However, the presence of PEG leads to low or no cell attachment in short-term cell culture [76]. It is reasonable to assume that poly(DTR–PEG ether)s are also non-cytotoxic, but, at the current time, these studies have not yet been completed.

The tissue response to fracture fixation pins made of various tyrosine-derived polycarbonates, such as poly(DTE carbonate), poly(DTB carbonate), poly-(DTH carbonate) and poly(DTO carbonate), was evaluated in a rabbit transcortical model [53,81,82]. The test polymers had identical chemical backbone structures and varied only in the structure of the alkyl ester pendent chain which was increased in length from ethyl (two carbons), to butyl (four carbons), hexyl (six carbons) and octyl (eight carbons), as shown in Figs. 2 and 3. Identical, extruded pins of poly(DTE carbonate), poly(DTB carbonate), poly(DTH carbonate), and poly(DTO carbonate) were implanted transcortically in bone defects in the

rabbit's distal femora and proximal tibiae permitting histological comparisons of the bone–implant interface as a function of incremental changes in polymer structure and time. The transcortical implants were followed over a period of 1090 days (3 years).

The experimental details of this study were recently published [81]. Great care was taken to control the study and to account for possible artifacts or effects that were independent of the chemical structure. After implant retrieval from the hard tissue sites, samples were prepared for undecalcified light microscopy analysis. The histological sections were evaluated for general material biocompatibility. Next, the bone–implant interface around the circumference of each implanted pin was evaluated in light of whether (a) a fibrous tissue layer separated the implant from the surrounding bone or (b) direct bone apposition was the dominant feature of the bone–implant interface.

Upon histological evaluation of pin cross sections, at time points as early as 90 days (3 months) and as late as 1090 days (3 years), all the polymeric implants were found to be surrounded by bone without any obvious deleterious effects such as bone resorption or large concentrations of inflammatory cells at the implant site. Poly(DTE carbonate), poly(DTB carbonate), poly(DTH carbonate), and poly(DTO carbonate) were all osteocompatible according to traditional definitions [83,84]

However, fundamental differences were observed at the bone–pin interface—some pins were encapsulated with fibrous tissue (an encapsulation response), whereas others exhibited predominantly direct apposition of bone to the implant surface. The encapsulation response was distinguished by an organized fibrous capsule that ranged between three and 30 cell layers. The capsule lined the entire circumference of the implant and effectively separated the implant from the surrounding bone. In contrast, at those implant sites where bone apposition was observed, the circumference of the implant was devoid of an organized fibrous capsule.

Table 3 lists the frequency with which the encapsulation or bone apposition responses were observed. Most striking was the bone response to poly(DTE carbonate) where direct bone apposition to the implant was the defining feature in 73% of the retrieved implants (22 of 30 pins). Those poly(DTE carbonate) implants that did exhibit an encapsulation response tended to have thin capsules of less than 10 cell layers. In contrast, as the length of the pendent chain was increased to butyl and octyl, less bone apposition was observed and the predominant response was the formation of a fibrous capsule. Particularly noteworthy is the dramatic difference between poly(DTE carbonate) and poly(DTB carbonate) as these two polymers have very closely matched chemical structures and material properties. Poly(DTB carbonate) elicited direct bone apposition at only 21% of the implant sites. Clearly, in this family of tyrosine-derived polycarbonates, the predominant response elicited at the bone–implant

Table 3
Frequencies of direct bone apposition and encapsulation responses at the bone–implant interface[a]

	Poly(DTE carbonate)		Poly(DTB carbonate)		Poly(DTO carbonate)	
	Bone apposition[b] (%)	Encapsulation[c] (%)	Bone apposition[b] (%)	Encapsulation[c] (%)	Bone apposition[b] (%)	Encapsulation[c] (%)
Short-term[d]	60	40	30	70	20	80
Long-term[e]	80	20	17	83	16	84
Total[f]	73	27	21	79	17	83

[a] From James et al. [82].
[b] Bone apposition responses were reported when an organized fibrous tissue layer could not be identified at the light microscopic level at the bone–implant interface.
[c] Encapsulation responses were reported when a fibrous capsule encompassed the implanted pin.
[d] 0–180 days ($n=10$).
[e] 270–1090 days ($n=26$).
[f] Overall results ($n=36$).

interface was significantly influenced by a relatively minor modification of the polymer structure.

The unique osteocompatibility of poly(DTE carbonate) has been confirmed in a canine model [52]. This particular polymer has a wide range of applications as orthopedic implant material and is currently under review by the US Food and Drug Administration.

In general, serum proteins such as fibrinogen, or extracellular matrix proteins such as fibronectin adsorb strongly onto surfaces of tyrosine-derived polycarbonates. These polymers therefore tend to be strongly adhesive to cells in tissue culture. Fortunately, it is possible to modulate protein and cell adhesiveness by copolymerization with PEG. For tyrosine-containing poly(DTR–PEG carbonate)s containing more than 10% of PEG, dramatically reduced levels of cell attachment were observed in short-term cell culture [76]. The use of DTR–PEG copolymers as a tool for the study of cell–biomaterial interactions is particularly attractive. For example, Tziampazis et al. [85] used a series of poly(DTE-co-*f*% PEG_{1000} carbonate)s ($f=0$, 2, 4, 6, 8 and 10) as a model system to understand the role of small molar fractions of PEG in the regulation of cellular responses in tissue culture. They analyzed the effect of low concentrations of PEG on the amount, conformation and bioactivity of fibronectin, and then related the data on protein adsorption to the attachment, adhesion strength, and motility of L929 fibroblasts. It was observed that the ability of cells to attach to the polymer surface was related to fibronectin *bioactivity* and not to the total *amount* of fibronectin present. However, the strength of cell adhesion was correlated with the total amount of fibronectin present on the polymer surface. Additionally, the rate of cell migration was inversely correlated with PEG concentration over a narrow range of PEG concentrations. This work demonstrated the utility of incorporating very small amounts of PEG into the surface of a biomaterial to study cell attachment, adhesion strength and motility. These types of studies are relevant to the development of tissue engineered scaffolds.

Heretofore, less work has been published on the responses of cells and tissues to tyrosine-derived polyarylates. The earliest study is a report by Hooper et al. [54] comparing the degradation and tissue responses to poly(DTE carbonate), poly(DTE adipate) (a representative member of the library of polyarylates), and poly(L-lactic acid).

The study employed extruded pins of the test polymers in a subcutaneous rat model. The tissue response at the implant sites was followed histomorphometrically for 570 days. In this study, poly(DTE adipate) consistently elicited the mildest tissue response, as judged by the width of the fibrous layer and the lack of cellularity of the fibrous tissue formed around the implant. The tissue response to poly(DTE carbonate) was mild throughout the 570 day study. However, the response to PLLA fluctuated as a function of degradation, exhibiting an increase in the intensity of inflammation as the implant began to lose mass. At the completion of the study, tissue ingrowth into the degrading poly(DTE adipate) pins was evident, while no comparative ingrowth of tissue was seen for PLLA.

This study represents the first comprehensive, comparative study of the degradation and tissue compatibility of tyrosine-derived polycarbonates, polyarylates and PLLA. The results of this study indicate that complete resorption of poly(DTE adipate) implanted in a non-load-bearing, soft tissue site will require 1 to 2 years depending on the device configuration. In correspondence with this resorption rate, poly(DTE adipate) pins have a useful device lifetime of about 200 days. The complete resorption of pins of poly(DTE carbonate) may require more than 3 years. This long resorption time is associated with an extended ‘use life’ of over 1 year, making this material most suitable for long-term applications similar to those of high-molecular-weight PLLA.

There were significant differences between poly(L-lactic acid) and the tyrosine-derived polymers, poly(DTE adipate) and poly(DTE carbonate). The tyrosine-derived polymers did not take up more than 5% of water even at the most advanced stages of degradation. This is in contrast to the known tendency of lactic- or glycolic-acid-derived polymers, which swell significantly due to water uptake toward the end of their useful life time. The lack of water uptake also means that implants of tyrosine-derived polymers will maintain their shape for longer periods than PLLA. Another important difference between tyrosine-derived polymers and lactide- or glycolide-derived polymers relates to the onset of mass loss:

since the tyrosine-derived monomers are not readily water soluble, mass loss occurs very slowly and only at the very end of the degradation process. In contrast, PLLA starts to lose mass when the molecular weight decreases to about 20,000. Another key difference between tyrosine-derived polymers and lactide- or glycolide-derived polymers relates to the amount of acidic degradation products produced per gram of device. The values for poly(glycolic acid), poly(lactic acid), poly(DTE adipate), and poly(DTE carbonate) are 15.5, 11.4, 6.4, and 2.6 meq of acid per gram of polymer, respectively. The dramatic reduction of the amount of acidic degradation products being formed in tyrosine-derived polymers relative to the commonly used poly(lactic acid) and poly(glycolic acid) may contribute to their better tissue compatibility, especially in bone.

As described before [57,86], tyrosine-derived polyarylates were designed as part of an extended library of structurally related polymers. The development of a combinatorial approach to biomaterials resulted in a large number of polymeric biomaterials becoming available for screening and exploration. This, in turn, requires the development of new techniques for the systematic study of correlations between polymer structures, material properties and biological performance. Studies are, therefore, underway to develop rapid screening methods for the evaluation of biological properties and performance characteristics for multiple polymers.

5. Sterilization

To further evaluate tyrosine-derived polycarbonates for clinical use, the ability of selected polycarbonates and PLLA to maintain their properties after ethylene oxide or γ-irradiation sterilization was determined by Hooper et al. [87]. Ethylene oxide was found to induce less structural damage to the polymers than γ-irradiation based on measurements of molecular weight, surface composition, mechanical properties, and in vitro degradation rate. Ethylene oxide was determined to be a feasible method of sterilization, except for poly(DTO carbonate), which exhibited a higher degradation rate after exposure to ethylene oxide than the non-exposed control. Due to the presence of aromatic groups in the backbone, tyrosine-derived polycarbonates were significantly more resistant to γ-irradiation than PLLA. Thus, contrary to PLLA, tyrosine-derived polycarbonates can be sterilized by γ-irradiation.

The effects of both ethylene oxide and γ-irradiation sterilization were also investigated for the copolymers with PEG. Specifically, a series of copolymers from the group of poly(DTR-co-PEG carbonate)s were studied [76]. No noticeable change in color or physical appearance was observed for any of the copolymers after their exposure to ethylene oxide. However, for copolymers containing high weight fractions of PEG (PEG content $\geq$70%), an increase in the molecular weight after exposure to ethylene oxide was observed, possibly caused by crosslinking. This observation indicates that ethylene oxide should be used with caution when sterilizing polymers containing a high PEG content.

Three doses of γ-irradiation (0.3, 1.1, 3.9 Mrad) were used to evaluate the effect of γ-sterilization. The copolymers retained their initial molecular weight after exposure to 0.3 Mrad of irradiation but, when the irradiation dose was increased to 1.1 and 3.9 Mrad, the molecular weight decreased. The higher the PEG content of the copolymer, the more pronounced was the decrease in molecular weight following irradiation. Since for the sterilization of medical plants a 2.5 Mrad dose is required, only copolymers with PEG content below 30 mol% should be considered for γ-irradiation. These observations are readily explained: the aromatic structure of DTR is highly resistant to radiation damage, while the aliphatic structure of PEG is highly sensitive to radiation damage. Therefore, the higher the fraction of PEG within the copolymer composition, the more susceptible the polymer becomes to radiation damage.

6. Surface characterization

The surface properties of polymeric biomaterials are of interest because they play a significant role in the cell, blood, and tissue responses observed both in vitro and in vivo. Therefore, Pérez-Luna et al. [88] characterized the surface of five tyrosine-derived polycarbonates (pendent chain: DTE, DTB, DTH, DTO and DT-benzyl) by using contact angle mea-

surements, electron spectroscopy for chemical analysis (ESCA) and static secondary ion mass spectrometry (SIMS).

Results showed that the wettability, critical surface tension, and polarity of these polymers decreased with increasing chain length of the pendent alkyl groups. The surface elemental composition, as determined by ESCA, was consistent with the stoichiometry of the repeat unit of the polymers. Additionally, high-resolution C 1s, O 1s, and N 1s ESCA spectra also showed results consistent with the specific bonding states of these elements in the polymer repeat unit. SIMS experiments showed fragment ions characteristic of the pendent groups in the negative-ion SIMS spectra only, while the positive SIMS spectra provided a characteristic fingerprint for each polymer. Because of the reproducibility of the spectra and the high cleanliness of the polymer surface, Pérez-Luna et al. suggested the use of tyrosine-derived polycarbonates as reference standards for surface characterization studies.

In a similar study, Belu et al. [67] used a series of 16 tyrosine-derived polyarylates to test the ability of time-of-flight secondary ion mass spectrometry (TOF-SIMS) to identify structurally very closely related polymers. The tyrosine-derived polyarylates were selected for this study since they exhibit well-controlled and systematically varying chemistry, and individual polymers are structurally identical except for the incremental additions of C_2H_4 units to either the backbone and/or the side chain. From the spectra, peaks characteristic of all polyarylates could be identified. Furthermore, evaluation of the spectra and identification of unique signals allowed the unambiguous classification of the polyarylates according to side chain and backbone chemistry.

7. Drug delivery

Poly(DTH carbonate) was selected for the design of a long-term controlled-release device for the intracranial administration of dopamine [89,90]. The potential advantages of poly(DTH carbonate) over other degradable polymers include the ease with which dopamine can be physically incorporated into the polymer (due to its relatively low processing temperature and the structural similarity between the drug and the polymer), the apparent protective action of the polymeric matrix on dopamine, the prolonged release of only about 15% of the total load of dopamine over about 180 days, and the high degree of compatibility with brain tissue. Results indicated an average release of about 1 to 2 μg/day, a dosing rate that falls within the therapeutically useful range.

In Europe, tyrosine-derived polyarylates [58,91] and polycarbonates [92] were tested as haemocompatible coatings for blood-contacting devices. Techniques were developed to incorporate anticoagulants into coatings made of tyrosine-derived polyarylates, polycarbonates or lactide/glycolide copolymers. These coatings were then applied to carbon fibers. Without coating, the fibers were covered within minutes by a coagulation plug rich in fibrin and platelets. Degradable coatings without anticoagulants reduced the thrombogenicity of the test materials, but coatings releasing hirudin and prostacyclin inhibitors prevented the formation of thrombin at the coated surfaces.

In a low-molecular-weight drug release model study, the adipic acid series of polyarylates consisting of poly(DTE adipate), poly(DTH adipate), and poly(DTO adipate) [58,93] exhibited a diffusion controlled release mechanism, as indicated by the linear correlation between the cumulative release and the square root of the release time.

Schachter and Kohn [75] developed a release formulation for the delayed or pulsatile release of water-soluble peptides. In general, water-soluble peptides are difficult to release without bursts. This problem was addressed by using polymers that have a peptide-like backbone structure and that can provide strong hydrogen bonding interactions with the peptide drug. Tyrosine-derived polyarylates were particularly useful in this context, since it is possible to screen the library of polyarylates for those polymers that provide a high level of peptide–polymer interactions for any given target peptide. Using the development of a delayed release system for the heptapeptide Integrilin™ as a ‘test study’, Schachter and Kohn screened the library of polyarylates and identified poly(DTE adipate) as a polymer that had particularly strong hydrogen bonding interactions with Integrilin™. In fact, when up to 30% by weight of the water-soluble Integrilin™ was incorporated into a poly(DTE adipate) matrix, virtually no peptide

was released during a 50 day incubation period under physiological conditions (pH 7.4, 37 °C). Next, small amounts of fast degrading poly(lactide-co-glycolide) (PLGA) were blended into the formulation. Upon incubation, PLGA degraded, releasing acidic degradation products within the poly(DTE adipate) matrix which weakened the peptide–polymer hydrogen bonds. Consequently, the fast degrading PLGA copolymers acted as 'delayed-action' excipient. The initial molecular weight of PLGA controlled the length of time before degradation occurred. As the initial molecular weight of PLGA was varied from 12,000 to 62,000, the duration of the delay period prior to release increased from 5 to 28 days. These results demonstrate the development of a novel approach for the formulation of delayed-release peptide delivery systems. It is easy to envision multiple release phases or even pulsatile release behavior with multiple preprogrammed lag periods when a combination of different film sets is used. The timing of the release phase was controlled to a very high degree of accuracy by the selection of the initial molecular weight of PLGA. This system can easily lend itself to such applications as antigen delivery (vaccination) where a pulsatile release rate is often more effective than a sustained release rate.

Tyrosine–PEG-derived poly(DTR–PEG carbonate)s have been explored for drug release from a microsphere configuration [76]. *p*-Nitroaniline (*p*NA) and fluorescein isothiocyanate–dextran (FITC–dextran) were used as models for low-molecular-weight hydrophobic and high-molecular-weight hydrophilic drugs, respectively. With increasing PEG content in the polymer, a significant increase in the release of *p*NA was observed. For FITC–dextran, the release was characterized by a short burst during the first hour, followed by a long lag period of about 14 days during which very little additional FITC–dextran was released.

8. Processing and fabrication

Polycarbonates and polyarylates have sufficient thermal stability to be processed by conventional polymer fabrication techniques such as extrusion, compression molding and injection molding. Additionally, high solubility in a wide range of organic solvents allows for the use of solvent casting to fabricate films, fibers, sponges and coatings. So far, films [45], rods [94], porous scaffolds (sponges) [56,95], pins [56,81] and fibers [96–98] have been processed by one or more of the above-mentioned methods.

Conventional solvent casting/salt leaching techniques produce scaffolds with low pore interconnectivity. Consequently, Levene et al. [95] developed a fabrication process which creates porous scaffolds with novel architectures for guided bone regeneration and other tissue engineering applications. The scaffolds were fabricated from tyrosine-derived polycarbonates using a well-controlled phase separation process added to the salt leaching technique. This method resulted in scaffolds containing a highly interconnected pore network with porosity greater than 90%. The morphology of these scaffolds is illustrated in Fig. 7, where a bimodal distribution of

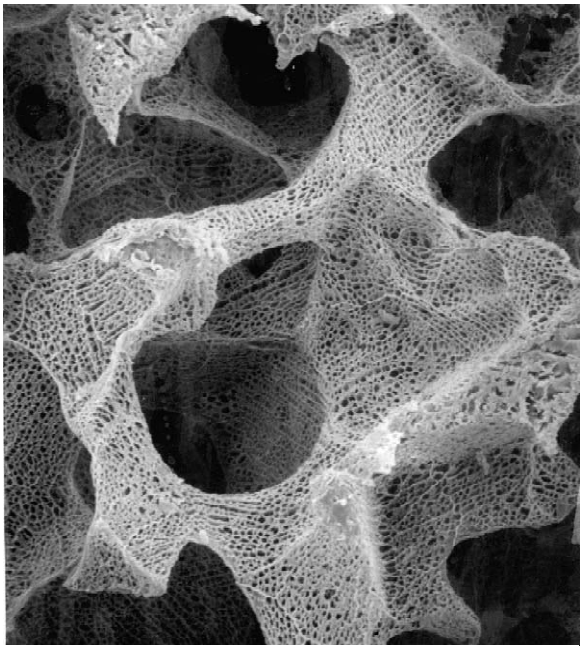
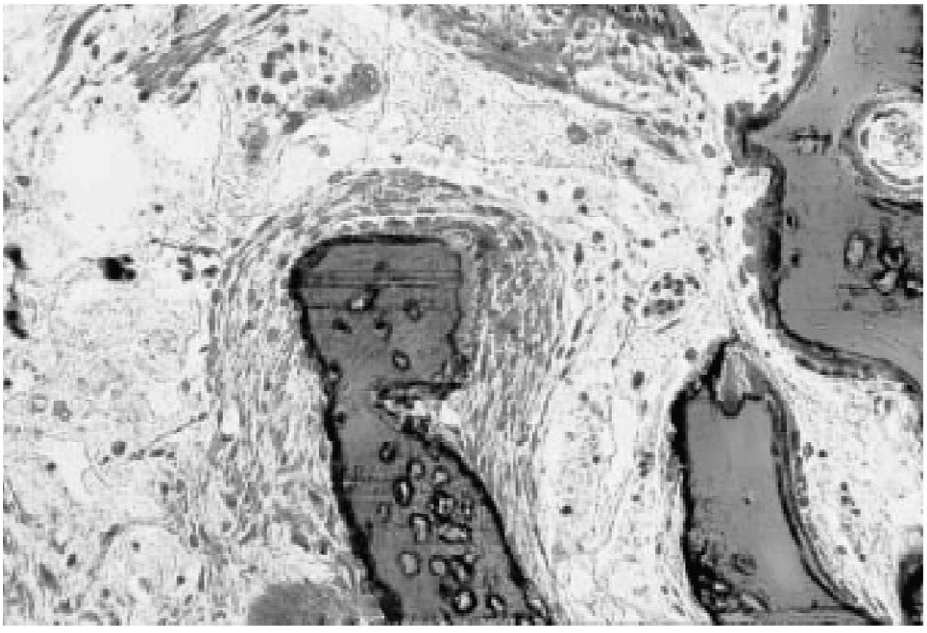


Fig. 7. Porous scaffold fabricated from poly(DTE carbonate). A bimodal distribution of macro- and micro-pores can be easily distinguished. The macropores (212–425 μm) are the impressions of the salts on which the solution is cast. The macropores (212–425 μm) are the impressions of the salt crystals used as porogens, while the micropores (about 1 to 10 μm) are caused by the formation of frozen solvent crystals during cooling.



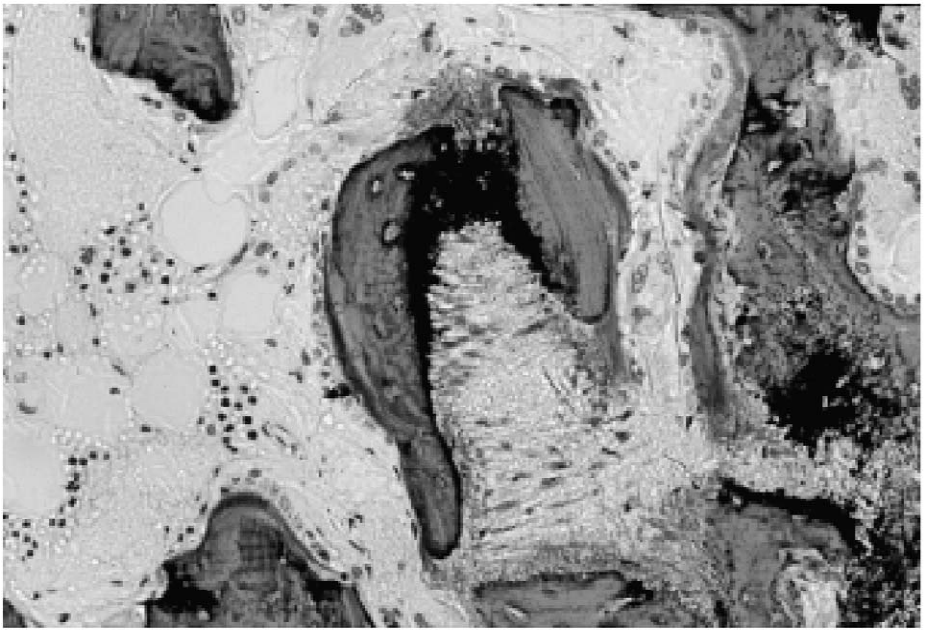


Fig. 8. A comparison of histologies from scaffolds without micropores (a) at 3 weeks and scaffolds with micropores (b) at 4 weeks. The area within the circle shows directed collagen ingrowth only in the scaffold with micropores. Both samples are viewed at 62.5× and stained with Stevenel's Blue and Van Geison's Picrofuchsin.

macro- and micro-pores can be easily distinguished. The macropores (212–425 μm) are the impressions of the salt crystals used as porogens, while the micropores (about 1 to 10 μm) are caused by the formation of frozen solvent crystals during cooling. These highly porous scaffolds provide a large surface area and internal volume which may be ideal for cell seeding, growth and production of extracellular matrix by attached cells. The small pores, created in the walls of the larger pores, are oriented in linear arrays. This very specific microstructure may affect cell–matrix interactions, as illustrated in Fig. 8, where the micropores provide a template for directed collagen ingrowth.

Bourke et al. [99] produced poly(DTE carbonate) fibers with ultimate tensile strength (UTS) values of 230 MPa and Young Moduli of 3.1 GPa by a one-step melt extrusion. When compared in strength retention to poly(L-lactic acid) fibers, poly(DTE carbonate) performed significantly better. UTS values for poly(DTE carbonate) remained above 200 MPa (87% strength retention) after 30 weeks of incubation, while UTS values for poly(L-lactic acid) dropping to 20 MPa (7% strength retention) within 2 weeks.

Recently, fibers having yield stress values above 200 MPa combined with lower modulus values (1–2 GPa) have been fabricated from poly(DTD dodecanoate) (Bourke and Kohn, unpublished results). These fibers may be useful in applications where compliance with soft tissue is important.

9. Conclusions and outlook

The amino acid L-tyrosine was shown to be a versatile building block for biodegradable and biocompatible polymers. The incorporation of derivatives of tyrosine dipeptide, such as the desaminotyrosyl-tyrosine alkyl esters (DTR), into the backbone of different polymer systems results in versatile polymers with interesting properties. Contrary to most conventional poly(amino acid)s, tyrosine-derived pseudo-poly(amino acid)s exhibit excellent engineering properties and polymer systems can be designed whose members show exceptional strength (polycarbonates), flexibility and elastomeric behavior (polyarylates), or water-solubility and self-assembly properties (copolymers with PEG). In particular, the tyrosine-derived polycarbonate, poly(DTE carbonate), has been shown to have a high degree of tissue compatibility and is currently being evaluated for possible clinical uses by the USA Federal Drug Administration (FDA). Poly(DTE carbonate) is expected to be the first tyrosine-derived polymer to become commercially available for clinical use.

The main driving forces for the development of new, degradable biomaterials are (i) the need of the pharmaceutical industry to develop advanced drug delivery systems for the many new peptide and protein drugs that will become available through biotechnology and genomics, (ii) the need of the medical device industry to develop degradable implants (scaffolds) for tissue regeneration and tissue engineering applications, and (iii) the need to improve the biocompatibility of biosensors and implantable medical devices. This last application calls for new materials with surfaces that prevent scarring and/or protein adsorption at the implant/tissue interface.

While in the past the vast majority of all commercial research involving degradable polymers was limited to the use of poly(lactic acid), poly(glycolic acid) or copolymers thereof, it is obvious that, in the future, a wider range of new materials will be needed. Tyrosine-derived pseudo-poly(amino acid)s represent one of many new ‘second generation biomaterials’ that will enter into clinical use over the next decade.

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