Aliphatic Polyesters: Great Degradable Polymers That Cannot Do Everything[†]

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Nowadays the open and the patent literatures propose a large number of polymers whose main chains can be degraded usefully. Among these degradable polymers, aliphatic polyester-based polymeric structures are receiving special attention because they are all more or less sensitive to hydrolytic degradation, a feature of interest when compared with the fact that living systems function in aqueous media. Only some of these aliphatic polyetsers are enzymatically degradable. A smaller number is biodegradable, and an even more limited number is biorecyclable. To be of practical interest, a degradable polymer must fulfill many requirements that depend very much on the targeted application, on the considered living system, and on living conditions. It is shown that aliphatic polyester structures made of repeating units that can generate metabolites upon degradation or biodegradation like poly(β-hydroxy alkanoate)s and poly(α-hydroxy alkanoate)s are of special interest. Their main characteristics are confronted to the specifications required by various potential sectors of applications, namely, surgery, pharmacology, and the environment. It is shown that degradation, bioresorption, and biorecycling that are targets when one wants to respect living systems are also drastic limiting factors when one wants to achieve a device of practical interest. Finding a universal polymer that would be the source of all the polymeric biomaterials needed to work in contact with living organisms of the various life kingdoms and respect them remains a dream. On the other hand, finding one polymeric structure than can fulfill the requirements of one niche application remains a big issue.

Introduction

For the last 60 years, synthetic polymeric materials have grown progressively up to forming one of the most attractive domains in materials science. This success is primarily due to their low cost, their reproducibility, and their resistance to physical aging and biological attacks. However, the resistance of synthetic polymers to the degrading action of living systems is becoming more and more problematic in several domains where they are used for a limited period of time before becoming wastes. It is the case in surgery, in pharmacology, in agriculture, and in the environment as well. In these domains, time-resistant polymeric wastes are less and less acceptable. From this viewpoint, sutures, bone fracture fixation devices, mulch films, and packagings are philosophically comparable.

Ideally, all these time-limited applications require the elimination of the artificial material after use to restore the surrounding living medium as it is in a normal organism.

Historically, materials of natural origin, namely, minerals and biopolymer-based compounds such as proteins and cellulose and their complex natural derivatives such as bone, wood, leather, and so forth, were exploited first. People learn how to take advantage of the natural organic compounds as material and more recently to modify them chemically to enlarge the range of properties that could be covered. However, the chemical modification of biopolymers minimizes or eliminates their inherent degradability and it is difficult to control. Biomedical researchers were the first, in the early 1960s, to look for polymeric devices or macromolecules that could replace materials of natural origin as sources of degradable devices such as CATGUT sutures made of denaturated collagen.[1] At that time, synthetic fiber-forming polymers such as nylon or aromatic polyesters were capable of fulfilling the requirement of suturing monofilament or threads. However, they could not fulfill the requirement of elimination after use because of their outstanding resistance to biochemical processes.[2]

Basically any artificial polymeric device or macromolecule that is to be used as material in contact with a living system for a limited period of time only should be eliminated and ideally biorecycled after use to avoid storage as a waste. This is true in the case of the animal and human bodies where high-molecular-weight polymeric compounds are entrapped between skin and mucosa and cannot cross cell-made parenteral physiological membranes such as the blood−brain barrier or the vascular walls. It is also true in the environment, although storage of nonbiorecyclable organic matter was not a matter of concern, at least until recently. To achieve biorecycling, mother nature had to find processes to get rid of proteins or polysaccharide-type biopolymers. Indeed, these polymers are, and had to be, chemically stable under the

Table 1. List of Specifications Typical of a Biomaterial To Be Developed at the Clinical and Commercial Levels

biocompatibility	biofunctionality
nontoxic	adequate properties
nonimmunogenic	mechanical
noncarcinogenic	physical
nonthrombogenic	chemical
	thermal
	biological
	appropriate rate of degradation
	elimination of residues after use
	resistance to sterilization
	resistance to aging on storage
	easy use
	approved by regulatory agencies

conditions ensuring life. Therefore, the choice of the complex enzymatic and cell machineries is remarkable. Indeed enzymatic degradation is outstandingly efficient, selective, and appropriate to ensure the turnover of living systems. However, in the world of degradable polymers, one must have in mind that enzymes can be present in nature only if living cells are present and that bioactive enzymes can be present only if the right cells are present. These requisites are sometimes ignored in the search for natural or artificial polymers and polymeric matters that could serve as material and be eliminated and recycled via natural pathways when they become waste. The fact that poly(glycolic acid) does not require an enzyme to be degraded in the human body was one of the reasons for it to become the first artificial degradable polymer to be developed as suturing material in the early 1960s.[2] Since then, thousands of scientific papers and patents have described so-called "biodegradable" polymeric compounds.[3−8] However, the number of contributions that take into account the requisites related to effective use (biofunctionality) and the respect of living systems (biocompatibility and bioresorption or biorecycling) is much smaller. If biocompatibility and biofunctionality include the major criteria in the biomedical field (Table 1), similar criteria can be defined for the environment. As examples, let us mention nonecotoxicity, nondecrease of fertility, and nonmodification of living systems and populations regarding biocompatibility (ecocompatibility) and cost-effectiveness instead of sterilization regarding biofunctionality. This last point implies that monomers are available on a large scale and rather cheap, conditions that are not critical in the biomedical field. For all these restrictive reasons, one can predict that the number of biocompatible and biofunctional artificial polymers of effective practical use will be limited, a situation that nature faced too since all life is based on three and only three major polymeric backbones, namely, polynucleotide, poly(α-amino acid), and polysaccharide. For the same reasons, aliphatic polyesters, especially those that can generate metabolites during degradation like poly(β-hydroxy butyrate), PHB, poly(β-malic acid), PMLA, poly-(ε-caprolactone), PCL, or poly(α-hydroxy acids derived from glycolic and lactic acids), PLAGA, show the highest potential for replacing biostable polymers in time-limited applications, at least basically. In practice, the human or animal body and the environmental world are two different living media where enzymes, cells, and tissues are different, even if the

ingredients are similar, namely, water, minerals, lipids, phospholipids, enzymes, and other proteins, polysaccharides, polynucleotides, and so forth.

Biomedical Field and Corresponding Applications

Figure 1 shows the schematic representation of some of the therapeutic devices relevant to the concept of elimination after use that are presently clinically used or that are still only at the level of scientific investigation in human or animal.

Surgical implants are therapeutic devices that are introduced within one of the parenteral compartments (vascular, intraperitoneal, cerebral, etc.) for surgical purposes (temporary prostheses), for pharmacological ones (drug delivery and targeting systems), or for both (medicated prostheses). Such devices can have different sizes, that is, be large (bone screw or bone plate or contraceptive reservoir) or small (suture, staple) and different shapes or structures (plain membrane, monofilament, multifilament thread, mesh, or porous scaffold in the case of tissue engineering).

Regarding pharmacology and polymer-based controlled drug delivery, the advantages expected from therapeutic devices are multiple: protect the bioactive drug from the aggression of the host, protect the host from the toxicity of the drug, increase the therapeutic index (or drug efficiency for a given dose), avoid repeated administrations, increase the solubility of hydrophobic drug molecules in water, deliver the drug at predetermined doses and rates, target some cells or organs, and so forth. The number of devices or systems that are presently under investigation in pharmacology is large (Figure 1). The two types that have been investigated first and the only having received commercial applications are solid implants and microparticles made of tiny plain spheres or hollow capsules. In terms of polymer science, the entrapped bioactive molecules to be delivered behave like plasticizers or fillers depending on their compatibility with the polymeric matrix. Therefore, they can perturb the behavior of this matrix according to rules that are well-known in polymer science. Presently nanoparticles are being investigated to allow intravenous injections that are precluded when particle sizes are over 7 μm because of the risk of blood capillary embolization. Their very small sizes raised other problems at the level of loading and retention of the entrapped low-molecular-weight compounds. They also raise problems at the degradation level as a result of their enormous surface (fast enzymatic degradation) or their small size (low rate of autocatalyzed hydrolytic degradation).[9] Beside these solid particles, various systems based on self-assembled amphiphilic macromolecules are being studied, namely, micelles of diblock copolymers, aggregates of hydrophilic macromolecules with pendant hydrophobic substituents, and the particular case of monomolecular globules that resemble transport proteins.[10] Polyelectrolytic complexes are composed of electrostatically interacting polyanion and polycation, the polyanion being a segment of genes occasionally. Macromolecular prodrugs or polymer therapeutics are more sophisticated systems where drug molecules are bound to a water-soluble or dispersible polymeric carrier to which a specific ligand of a receptor can also be attached to

- # Implant

- # Injectables

  - **Microparticles (> 1000 nm)**

  - **Nanoparticles (< 1000 nm)**

  - **Self assemblies**

    - **Micelles (~ 50-150 nm)**

    - **Aggregates (~ 50-200 nm)**

    - **Monomolecular globule (~ 5-8 nm)**

    - **Polyelectrolyte complexes**

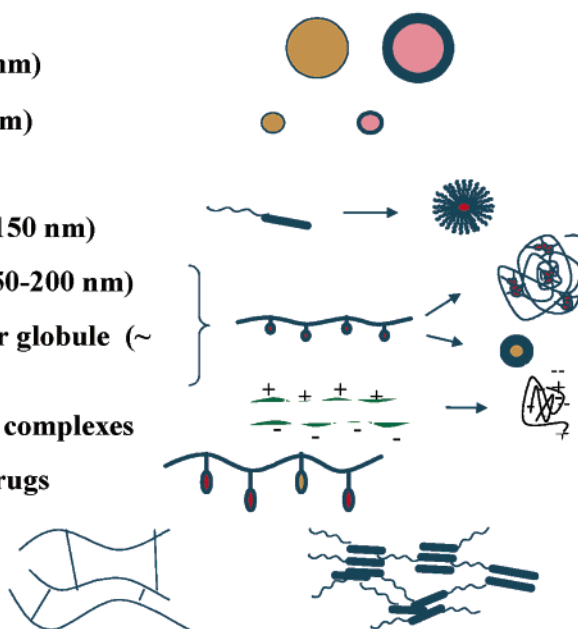 - **Macromolecular prodrugs**

  - **Hydrogels**

Figure 1. Schematic representation of the various therapeutic systems that are relevant to the use of bioresorbable polymeric items in temporary therapy based on the outstanding self-healing capacity of living systems, here the human body.

target this receptor and the corresponding cells or organ. Last but not least, chemically cross-linked hydrogels and physically cross-linked hydrogels where the cross-linking is due to reversible thermo-sensitive, pH-sensitive, ionic-strength-sensitive, or solvent-sensitive hydrophobic interactions are smart systems regarded as promising to deliver large molecules such as proteins or even large hydrophilic molecules and lipophilic small molecules at the same time when the cross-linking lipophilic microdomains entrap the small drug molecules and the hydrophilic network the large biopolymers.[11]

Because they are to be used for a limited period of time, all these systems require degradable polymers to fulfill the criterion of elimination after use. They also have to fulfill many other requirements related to the respect of the human body and specific regulations. The biostable polymers that are to be replaced are poly(methyl methacrylate), silicones, and so forth.

Environmental Domain and Corresponding Applications

In the field of the so-called environmental applications of polymers, a parallel can be found with the biomedical field. Indeed, applications such as packaging, mulching films, agricultural staples, coatings to protect seeds, chewing gums, cigarette filters, cartridge and cartridge wax, and so forth can be compared with biomedical implants (Table 2). They are to be used for a limited period of time, they generate wastes, and they must be ideally biorecycled because they cannot be eliminated from the globe, so far. The parallel can be extended to the fields of pharmacology and agronomy with the use of polymeric systems to deliver pesticides,

Table 2. Main Applications of Polymers Relevant to Resorbable and Biorecyclable Polymers and Comparison between the Biomedical and the Environmental Fields

biomedical	environnement
surgery	packaging
sutures	washing products
osteosynthesis devices	cartridge for guns
tissue engineering	cartridge wad
wound dressings	cigarette filters
pharmacology	agriculture
controlled drug delivery	sustained delivery of pesticides, insecticides, pheromones, and fertilizers
bioactive macromolecules	seed protection
packaging	mulching films

insecticides, fertilizers, and so forth, with similar (higher relative efficiency; lower overall toxicity; localization, time, and rate control of the delivery; etc.). For all these applications, degradable polymers are basically necessary. Obviously, it is not a single backbone, or the few degradable backbones proposed in the literature, that is going to provide solutions to the listed potential applications. Polymer scientists and industrials have developed sciences and technologies to take advantage of the outstanding possibility offered by polymeric systems to match material properties and application requirements, namely, copolymerization and formulation with additives. Basically the same strategies can be applied to degradable polymers. However, degradation phenomena introduce complications that are partly due to the complexity of natural processes and partly due to the complexity of chemical and physicochemical phenomena found when one deals with macromolecules or solid matrixes.

Situations in the Case of Aliphatic Polyesters

Aliphatic polyesters are members of a large family of polymers that are either from natural origin [bacterial poly-(β-hydroxy acid)s, β-PHA] or from chemical origin (polycondensation of hydroxy acids and of diacids and dialcohols or polymerization of lactone-type heterocycles).[6,8−12]

Bacterial β-PHA-type Polyesters. PHB was recognized as a biopolymer in the first quarter of the 20th century.[13] Because it is well-known, this family was very much enriched thanks to the versatility of bacterial biosynthetic processes and the various members of the family, β-PHA, have been presented as biodegradable and biorecyclable for many years.[14] β-PHAs do biodegrade in the environment when proper and active microorganisms are present. Whether they biodegrade in the human or animal body is still a matter of debate.[15] So far, one cannot consider β-PHAs as biodegradable in the human body because of the absence of active enzymes, in agreement with the absence of this polymer in the animal kingdom. Of course, like most of the polymers, β-PHAs can be degraded hydrolytically but the process is very slow and the rate of degradation depends on the length of the alkyl chains. The longer this chain the slower the degradation rate. In particular, it has been shown that poly(β-hydroxy octanoate) was not significantly degraded after two years in an animal body.[16] In the field of natural aliphatic polyesters, one family of degradable polymers has received rather little attention compared to non-functional β-PHAs, namely, PMLA.[17] PMLA is an analogue of PHB where pendent methyl groups are replaced by carboxyl ones. Microorganisms make the poly-R-isotactic isomer whereas the whole family of polstereomers can be made by chemical routes.[18] In terms of degradability, the family raises problems because if PMLA itself is water soluble and degrades very rapidly, its ester derivative poly-(benzyl β-malate), PMLABz, is very stable in water. Copolymers are the worse case because degradation affects preferentially the acid repeating units to leave the rather biostable PMLABz segments as residues.[19]

These findings raise the question of the correlation between the rate of degradation and the expected lifetime of a useful and exploitable degradable device. This is the reason poly-(α-hydroxy alkanoate)s that are much more sensitive to chemical hydrolysis are presently regarded as compounds of high potential to replace other biostable materials and, thus, polymers, in time-limited applications involving living systems.

Chemistry-Derived Aliphatic Polyesters. Aliphatic polyesters synthesized either by polycondensation of hydroxy acids or diacids and diols or by polymerization of lactone-type heterocyles are not biopolymers.[20] Indeed, they are not found as such in living systems. The confusion comes from an improper use of the word biodegradable that must be reserved for cell-mediated degradation and not applied to abiotic enzymatic degradation. The fact that a synthetic polymer can be enzymatically attacked under lab conditions does not imply that the same polymer is going to be biodegradable in the real world. The presence of the right cells and life-permitting conditions are mandatory. From this viewpoint, PCL, like PHAs, is biodegradable in the environment whereas it is only hydrolytically degradable in the human body.[21−22]

Poly(α-hydroxy acid)-type polyesters are now well-known to degrade hydrolytically in both the environment and in an animal body as shown by many recent reviews.[23−26] However, they degrade via simple chemical hydrolysis and not enzymatically, despite the fact that some exotic enzymes can cleave their main chain, like proteinase K.[12,27] It is only at the last stages of the hydrolytical degradation processes that oligomeric degradation byproducts become small enough to be processed via biochemical routes by microorganisms and indirectly by animals of the food chain like earthworms.[28−30]

Basically, the degradation of polymers that can be degraded via nonenzymatic chemical routes is easier to control by chemists. However, the special features of hydrolytic degradation of aliphatic polyester-based matrixes is a source of complications that render control difficult. For many years, their degradation in aqueous media, that is, in vitro as well as in vivo, was regarded as homogeneous although surface erosion was claimed in a few cases. This was primarily due to the fact that degradation was monitored either visually or through molecular weight changes measured by viscometry. Since then, size exclusion chromatography has revealed that two populations of macromolecules are often observed when rather large size devices are allowed to degrade in liquid media and in an animal body as well. When such a device made of a lactic acid-based polymer is placed in contact with an aqueous medium, water penetrates into the specimen and the hydrolytic cleavage of ester bonds starts as well as autocatalysis. Water absorption is, thus, a critical factor. For a time the partially degraded macromolecules remain insoluble in the surrounding aqueous medium, and the degradation proceeds homogeneously according to autocatalysis rules. However, as soon as the molecular weight of some of the partially degraded macromolecules becomes low enough to allow dissolution of the formed oligomers in the surrounding aqueous medium, the diffusion of these oligomers starts within the whole bulk, with the soluble compounds moving slowly to and off the surface while they continue to degrade. This process, that combines diffusion, chemical reaction, and dissolution phenomena, results in a differentiation between the rates of degradation at the surface and interior of the matrix.[31,32] In vivo, where the medium is buffered, neutralization of terminal carboxyl groups might also contribute to discriminate the surface degradation rate.

Basically there are four main factors which condition the diffusion−reaction−dissolution phenomena: (i) the hydrolysis rate constant of the ester bond; (ii) the diffusion coefficient of water within the matrix; (iii) the diffusion coefficient of chain fragments within the polymeric matrix; and (iv) the solubility of degradation products, generally oligomers, within the surrounding liquid medium from which penetrating water is issued.[33] During degradation, hollow structures can be observed depending on the initial configurational structures of polymer chains and on the existence of initially present or degradation-induced semicrystalline domains. The formation or not of crystalline residues was mapped and discussed in detail, at least for zinc-derived PLAX, where

X stands for the percentage in L-units in PLA stereocopolymer chains, and copolymers with glycolic acid.[34]

The mechanism of heterogeneous degradation contributed very much to the understanding of the effects of many other factors on the degradation of chiral lactic acid-based aliphatic polyesters, namely, matrix morphology, size, shape, presence of chemically reactive compounds within the matrix, and nature of the degradation medium. The heterogeneous degradation mechanism provided fruitful information on the behavior that can be expected from matrixes where additives or foreign molecules (oligomers, drug, initiator, solvent residues, plasticizer, absorbed molecules from the outer media, etc.) are present or have been introduced.[12] In particular, it has been shown that the smaller the size of a polymer device, the slower the hydrolytic degradation rate.[35] From the same logic, porous systems generally degrade at a slower rate than plain ones because the release of soluble degradation byproducts, that are responsible for the autocatalysis, can escape more easily from the polymer mass as a result of the higher surface.

Recently, attention was paid to the effects of the initiator on the degradation characteristics of some PLAX polymers. It has been shown that dramatic differences in repeating unit distribution can be observed in the case of stereocopolymers such as PLA polymerized in the presence of stannous octoate or zinc metal. Later on it was suggested that, in bulk polymerization of lactides, stannous octoate causes more or less chain-end modifications by esterification of alcoholic end groups by octanoic acid and generates hydrophobic residues which resists purification by precipitation from an organic solution with ethanol or water. Such modifications do not occur in the case of zinc metal or zinc lactate initiations.[36] These findings well explained the differences of behavior between PLA polymers derived from stannous octoate and those derived from zinc lactate ring-opening polymerizations.[37] Whether similar effects can be observed in the case of PLA polymers obtained using other initiating systems, through solution polymerization, or in the presence of alcohols is still unknown. Indeed, the effect of the structural differences on degradation characteristics are difficult to identify from literature data, generally because of the lack of precise characterization of the investigated polymers, especially nowadays when commercial polymers of different origins and history are considered.

Whereas in the biomedical field the temperature is generally fixed around 37 °C, in the environment rather large variations of temperatures can be observed and a poly(L-lactic acid) that degrades totally under composting conditions where the temperature can go up to 70 °C[25] will degrade in 2−3 years in vivo[38] (depending on many other factors as recalled above) and will remain almost stable in water at 20 °C. Another shortcoming of PLA polymers is the sensitivity to heat. In particular, they become rapidly deformable under low stressing when the temperature of use goes above their glass transition temperature that is around 60 °C depending on the origin and the characteristics of the polymer. Of course, this particularity is not critical in vivo at 37 °C, nor for outdoor applications at ambient or at refrigerator temperatures. In contrast, it can be dramatic for mechanical
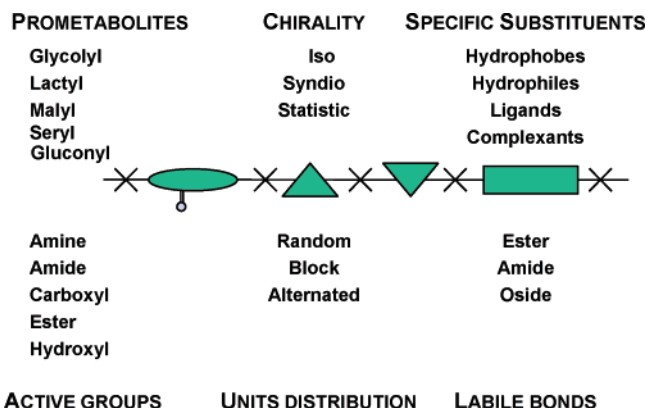
Figure 2. Schematic representation of the strategy to make artificial biopolymers aimed at making polymers composed of prometabolite building blocks able to generate biocompatible and bioprocessable degradation byproducts.

Scheme 1. DIPAGYL and Poly(DIPAGYL) as a Source of Hydroxyl-Bearing Poly(α-hydroxy acid) Degradable Polymer Chains
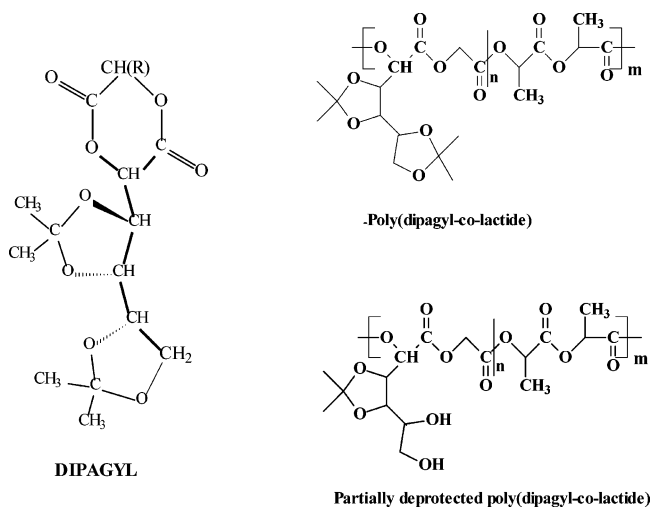
properties and lifetime if a PLA-based device comes in contact with a hot liquid or hot atmosphere. It is worth noting that any uptake of water in a liquid medium like in vivo or because of local humidity increases with the advance of the degradation reaction or with aging although this is a slow process at ambient temperature. As a result, T_g decreases and, thus, can modify the initial mechanical characteristics.

All these degradation characteristics should hold for the aliphatic polyesters that are sensitive to water. However, the actual behavior of a given compound will depend basically on the effects of the structures on the four parameters mentioned above.

Despite the complexity of their degradation mechanism, bioresorbable (degradable with proved elimination from the human body) and biorecyclable (environment) lactic acid-based devices are presently at the commercial stages as matrixes to make surgical devices (sutures, bone plates, and screws and filling material for bone reconstruction or plastic surgery), controlled drug delivery particulate systems in pharmacology, and packaging even if the market is still limited.[25,26] Indeed, below T_g, these polymers are rigid and exhibit rather good mechanical properties that can be compared with those of some commodity polymers. How-

Scheme 2. Serine and Serine-Based Primary Amine Aliphatic Polyesters

Serine   Poly(aminoserinate) copolymers   Poly(aminoserinate)

ever, they cannot provide alternatives to functional polymers satisfactorily because of the absence of functional groups to enlarge the range of properties and to generate properties such as hydrophilicity, chemical reactivity, and even smartness that are available in the families of biostable polymers and are necessary for some of the applications mentioned in Table 2 and Figure 1.

Concept of Artificial Biopolymer

In attempts to take into account and combine all these remarks into a strategy to design aliphatic polyesters that could cover the specifications of applications requiring biocompatibility, biofunctionality, and bioresorbability, we have introduced, many years ago,[39] the concept of the so-called artificial biopolymers, that is, polymers made to generate only metabolites upon degradation. Lactic acid-based aliphatic polyesters are the archetype of artificial biopolymers because they are issued from renewable resources and are bioresorbable in the human body and biorecyclable in the environment. The principle of making artificial biopolymers is to take bi- or multifunctional metabolites such as hydroxy acids and amino acids present in biochemical pathways or in petrochemistry eventually and use them to make polymers with nonnatural chemically degradable backbones. The aim is to promote engineer-controlled bioresorption or biorecycling instead of nature-controlled biodegradation. All the resources offered by polymer science to modulate the properties provided by a given backbone can then be exploited such as repeating unit and molecular weight distributions, copolymerization, chirality in connection with tacticity, chemistry and nature of subtituents, and so forth, as schematically suggested in Figure 2).

Hydroxyl-Bearing Aliphatic Polyesters. According to the artificial biopolymer strategy, we synthesized and characterized, a few years ago, a novel functionalized 1,4-dioxane-2,5-dione, namely, 3-(1,2,3,4-tetraoxobutyl-diisopropylidene)-dioxane-2,5-dione or DIPAGYL, that is composed of a glycolyl and a D-gluconyl unit derived from a metabolite, namely, gluconic acid. This monomer paved the route to PLAGA polymers with OH groups in side chains after elimination of some of the protecting groups necessary to allow ring-opening polymerization.[40−43] Scheme 1 shows the structure of DIPAGYL and of its copolymers with lactide. The presence of the bulky pendent groups issued from the gluconyl moieties is able to cause an interesting increase of T_g that depends on the composition of the copolymers that are actually terpolymers of glycolyl, chiral gluconyl, and chiral lactyl units.[44] Partial deprotection of the OH groups leads to poly(DL-lactic acid-*co*-glycolic acid-*co*-gluconic acid) with OH groups present in the side chains (Scheme 1).[44] It

Scheme 3. Basic Reactions Involved in the Anionic Activation of Aliphatic Polyester Chains via Carbanion Formation Using LDA Followed by the Coupling of an Electrophile

was shown that such copolymers, that are more hydrophilic that PLA or PLAGA polymers, are water-sensitive and can degrade hydrolytically up to forming the expected metabolites.[45] The presence of OH groups was used to bind various compounds such as a fluorescent dye or even poly(ethylene glycol) (PEG) segments.[46] Mixing naphthoyl chloride and PEG−COCl coupled to PLA$_{90}$DIPAGYL$_{10}$ and PLA$_{95}$DIPAGYL$_5$ copolymers led to simultaneous coupling of the two reagents.[47] Cross-linking can also be achieved using difunctional metabolites such as diacids like succinic or maleic acids to generate degradable hydrogels. Of course the degradation rate can be modulated according to the chemical and physicochemical characteristics.

Amino Group-Bearing Aliphatic Polyesters. In polymer applications, synthetic water-soluble polycations of the acrylic or methacrylic types or poly(ethylene imine)s are compounds of practical interest. In the field of degradable polycations, chitosans and poly(L-lysine) are currently investigated for their biodegradability. According to the concept of artificial biopolymers, we have found a practical route to make an aminated aliphatic polyester derived from serine (Scheme 2).[48] The presence of amino pendent groups along the polyester chains provides basicity and hydrophilicity and even hydrosolubility depending on the degree of deprotection of the amino groups. Again the presence of pendent groups paves the route to biorecylable hydrogels, bioresorbable polymeric drug carriers, and amphiphilic polymeric aggregates. Interestingly enough, basic poly(amino serinate)s can be combined with acidic PMLAs to form bioresorbable or biorecyclable polymeric complexes that can be use to entrap small molecules or even polynucleotides.

Versatile Route to Functional Aliphatic Polyesters. A few years ago, a novel and versatile method was introduced that allows one to chemically modify aliphatic polyesters. The modification is based on the activation of a polyester chain by proton extraction on the carbon atom located in the α position with regard to the main-chain carbonyl using lithium *N,N*-di-isopropylamide (LDA) in tetrahydrofuran. The activated polymer chains bearing carbanion sites can then be combined with an electrophile to generate novel aliphatic polyester copolymers quite easily (Scheme 3). The method was first described in the case of PCL.[49] Despite

Functionalisation

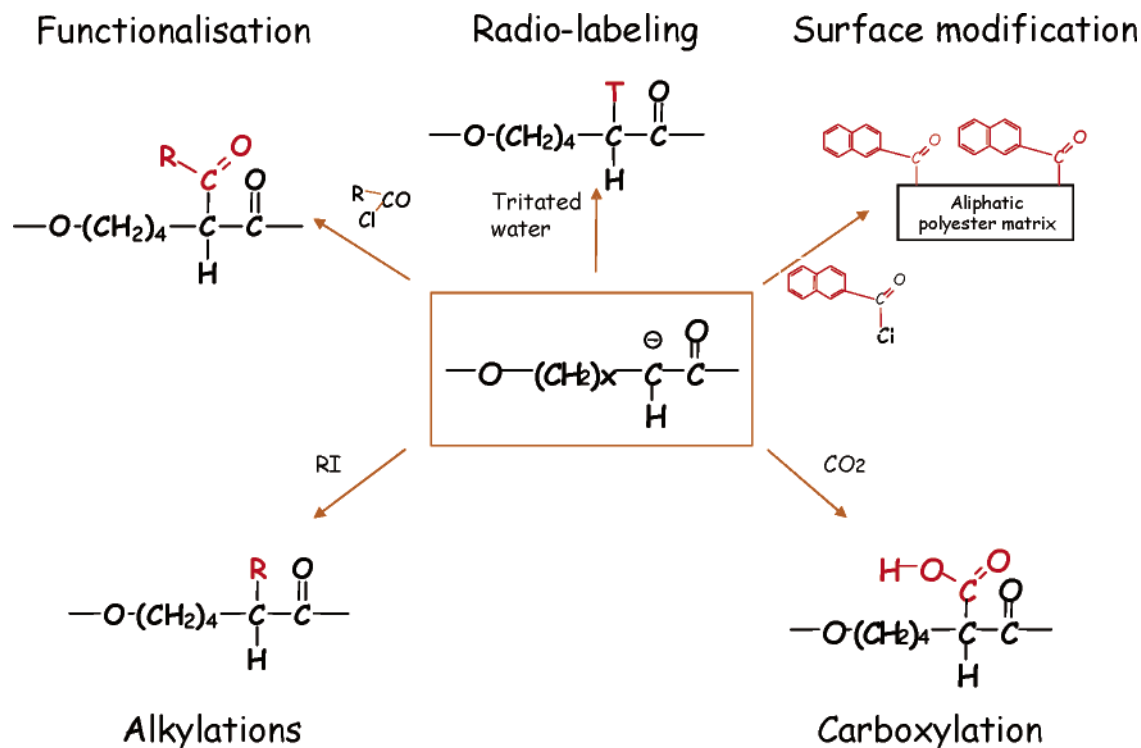## Radio-labeling

Surface modification

Figure 3. Examples of chemical modifications of aliphatic polyesters allowed by the versatile anionic activation by LDA and coupling of electrophiles.
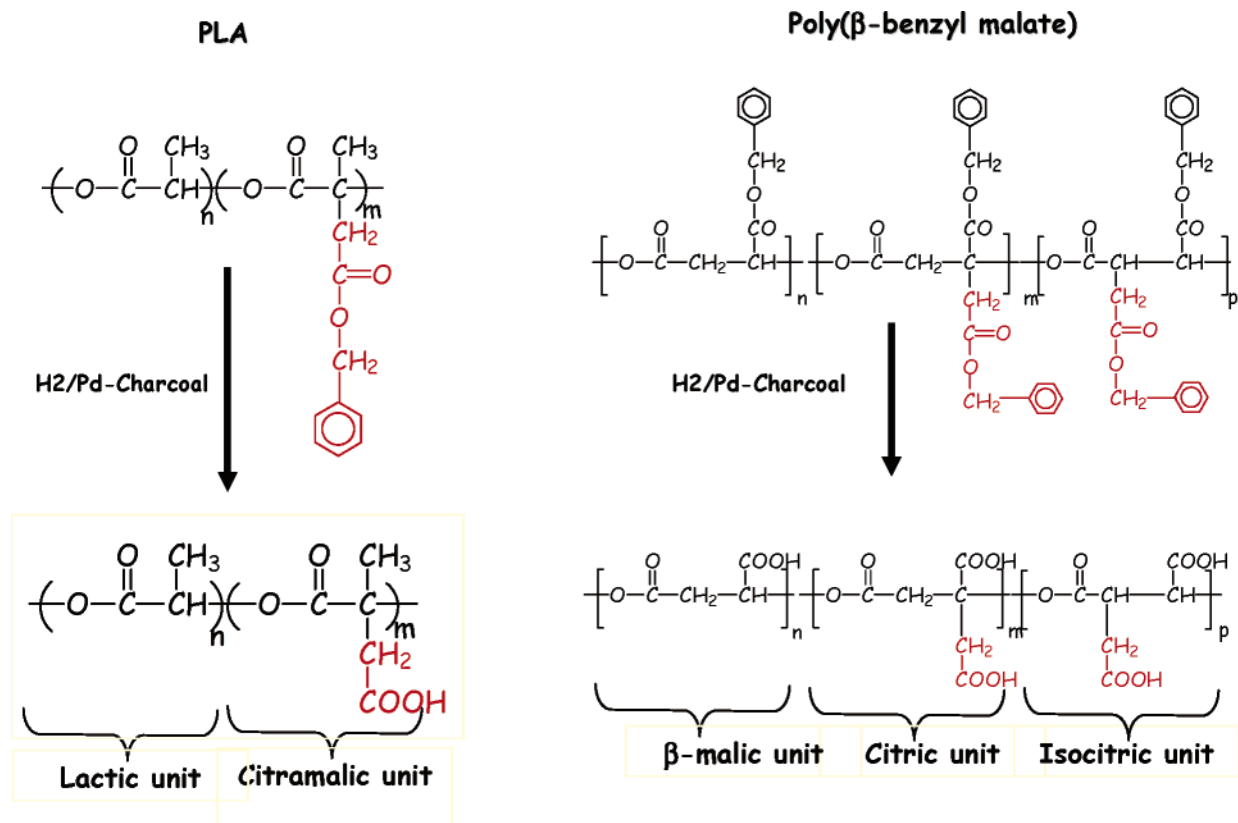
PLA

Poly(β-benzyl malate)

Figure 4. Examples of chemical modifications of aliphatic polymers using the anionic activation method that match the artificial biopolymer strategy.

the fact that partial degradation of polymer chains occurred during the first step, various functionalized PCLs of rather high molecular weights were obtained. The method is very easy to handle and very versatile because many electrophiles can be bound onto the carbanionic sites generated along the aliphatic polyester chains. In the case of lactic acid-based aliphatic polyesters, the chain degradation was rather dramatic. However, the method was used to chemically modify the surface and allowed the binding of many electrophiles to aliphatic polyesters (Figure 3).[50,51] The method was applied

to other aliphatic polyesters,[52,53] despite the fact that the concomitant chain degradation was more or less dramatic depending on the polymer backbone. It is worth noting that, basically, adequate choice of the electrophile can lead to polyesters composed of other prometabolite units such as citramalic, citric, or isocitric acids (Figure 4).[53]

Conclusions

In this contribution, it has been shown that aliphatic polyesters, especially those derived from lactic acid, are compounds of rather great potential for many applications requiring elimination or biorecycling after temporary use. The actual problems are multiple. First, the polymeric backbone has to be biocompatible, degradable, or biodegradable and able to generate degradation byproducts that are also biocompatible and that can be eliminated or bioassimilated (animal and human body) or bioassimilated and biorecycled (environment). Second, the polymer must be able to generate devices with properties analogous to those of the biostable material to be replaced. Last but not least, degradation characteristics have to be in harmony with the function characteristics and requisites imposed by the living system. Presently, the literature is full of polymers that are regarded as biodegradable because the molecular weight of corresponding macromolecules decreases under certain conditions. However, insufficient attention is paid to the nature and the fate of the degradation byproducts and to the matching of the other characteristics of the polymers to the specifications of the targeted applications. Aliphatic polyesters, especially lactic acid-based polymeric systems, have a potential to provide bioresorbable and biorecyclable matrixes and devices of practical interest beyond existing biomedical applications.[54] However, they cannot provide solutions to all the applications requesting life-respecting polymeric systems. As we attempted to show, the route to enlarge and modulate the range of accessible properties is not close because slowly degradable aliphatic polyesters can be made to degrade faster by suitable chemical modification. The facts that life is possible in the presence of water only and that aliphatic polyesters are basically water-sensitive are favorable factors with respect to chemically controlled degradation as compared with the very structure-sensitive enzymatic degradation. However, the requirements related to bioresorption and biorecycling limit very much the possibility of property adjustment based on copolymerization and formulation presently exploited by common polymers and polymeric devices. The range of aliphatic polyesters that are presently available and that do not fulfill the criteria of the potential applications yet might appear acceptable (biocompatible, biofunctional, and bioresorbable or biorecyclable) in the future provided the right tests are applied to show the pertinence of their performances and the absence of harmful effects onto relevant natural living systems.

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