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How do Specialty Polymers Modify the Chemical and Pharmaceutical Industries?

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HOW DO SPECIALTY POLYMERS MODIFY THE CHEMICAL AND PHARMACEUTICAL INDUSTRIES?

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ABSTRACT

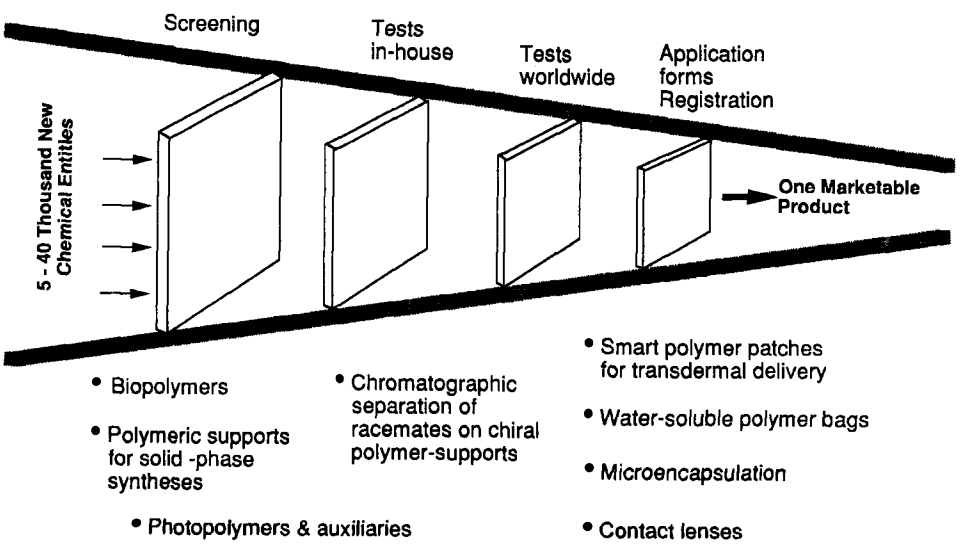
Specialty polymers play an increasingly important role in all stages of the enormously complex development process of new biologically active products. They widen and facilitate the *discovery stage*. For example, the use of solid polymer supports for automated peptide and oligonucleotide synthesis (the application of "Affymax" technology) enables the light-directed parallel chemical synthesis of a highly diverse set of oligopeptides. The chiral DNA and RNA backbones of antisense oligonucleotides can be replaced by synthetic archiral ones. In the *testing stages* the rapid chromatographic separation of racemates on chiral polymer supports has been established as an invaluable tool. The search for better *application methods* has led to the development of smart polymer patches that often provide excellent transdermal delivery of pharmaceutical drugs; water-soluble bags and microencapsulation technology have greatly improved the environmental safety of agrochemicals. Finally, the diverse synthetic activity within a large research organization brings to light compounds which can unexpectedly be utilized as new monomers, initiators, or crosslinkers; for example, for the design of high-performance photopolymers.

INTRODUCTION

The search for modern drugs and plant protection agents and especially their development to superior commercial products requires the joint efforts of natural scientists from virtually every discipline. It is an enormously complex and costly process [1]. To bring one single new chemical entity to the point where it can be launched on the market, 5000 to 40,000 compounds have to be thoroughly tested and moved through various stages of a development pipeline (Scheme 1). Such a passage takes from 6 to 12 years to complete. Besides investments, it costs up to US$200 million for a new plant protection agent and up to US$300 million for a new pharmaceutical drug.

No wonder that in a biooriented industry all kinds of emerging modern techniques and tools are eagerly used in order to facilitate all activities in the development pipeline. It is the purpose of this paper to demonstrate and to emphasize the increasing importance of specialty polymers, both natural and synthetic, in discovery, testing, and delivery of innovative new products for human and animal health, as well as products for weed, disease, and insect control.

In addition, the market itself creates a lot of users needs for all kind of specialty polymers. It is a distinct feature of big chemical and pharmaceutical companies like Ciba-Geigy that during the very extended synthetic and testing efforts, compounds which prove unsuitable for the envisaged application can reveal otherwise highly interesting properties and thus open novel business opportunities. This role of serendipity will be exemplified by three examples from the field of photopolymers.



SCHEME 1. Schematic representation of the development pipeline in the biooriented industry and the role of specialty polymers therein.

DISCOVERY STAGE

Proteins

In the three classes of natural polymers (Table 1), proteins are still the most important ones as far as the possibility of therapeutically relevant intervention is concerned. Intimate knowledge of the sequence of the constituent amino acids as well as their 3-D structure is essential for a rational design of enzyme inhibitors, for their expression by recombinant methods, for advances in immunology, etc. This has led to immense demands for larger amounts of synthetic peptides. Accordingly, peptide chemistry is currently witnessing a tremendous upswing in technological progress [3].

A breakthrough in the total synthesis of peptides was achieved by Merrifield in 1963 [4]. His sequential synthesis utilized chloromethylated polystyrene, crosslinked by 1% divinylbenzene as a solid support (Scheme 2). Typically, beads of 50–100 μm diameter are used. Under the reaction conditions which demand dimethylformamide as a solvent for the activated amino acids, the polymer matrix is highly swollen. It makes the Merrifield method rather slow, in spite of robots. Washing must be repeated in every cycle of deprotection and coupling steps. Typically after 1 to 3 weeks of automated operations, peptides of rather uniform length and constitution are formed.

Three decades ago, this was progress. However, for systematic structure–activity correlation studies, the speed of this synthetic method is not at all satisfactory.

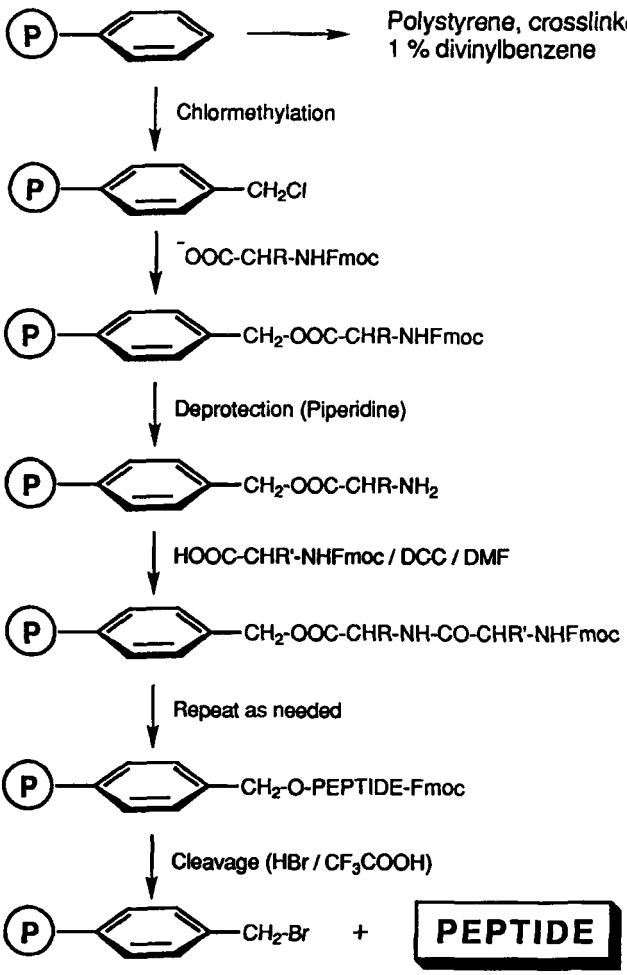
In 1985 Houghten [5] introduced a multiple peptide synthesis, the so-called "tea-bag" method. With the help of robots and computers, his method is suitable for preparing up to 150 different peptides at the same time.

The key is the sealing of small portions of the polymeric support in a labeled polypropylene net (tea-bag) before the solid-phase synthesis starts. In principle, the same crosslinked polystyrene as in the Merrifield synthesis can be used, but other

TABLE 1. Three Classes of Important Biooligomers and Biopolymers

	Biopolymer[a]		
	Proteins	Nucleic acids	Carbohydrates
Therapeutic intervention	Established	Novel	Exploratory
Approach	Enzyme inhibitors	Antisense oligonucleotides	Inhibitors of carbohydrate synthesis
	Receptors	Antiviral compounds Gene replacement	Modulators of carbohydrate/protein interaction
Focus	Industry	Universities/venture capital companies	

[a]Other biopolymers, the high molecular weight polyhydroxy acids, are presently the subject of lively interdisciplinary investigations [2]. Although the low molecular weight poly[(*R*)-3-hydroxybutyrate] occurs in the cell membranes of procaryotic and eukaryotic organisms, this type of biopolymer has not been a target of any therapeutic intervention and therefore will not be dealt with here.



SCHEME 2. Polymer-supported synthesis of peptides according to Merrifield [4].

polymeric supports may also be employed. For the coupling, the tea-bags are sorted according to the coupling amino acid and allowed to react in parallel with different amino acids in separate reaction vessels. Then they are washed and reunited for the next cycle of deprotection and washing.

The variability and efficiency of this method is remarkable, as solvents and protecting groups can easily be altered during one coupling cycle. However, the search for enzyme inhibitors based on oligopeptides makes it imperative to prepare thousands of oligopeptides with different sequences on a micromolar scale and in a very short time.

This has been made possible by an ingenious technique, developed by the Affymax Research Institute [6a], which is called VLSIPS (very large-scale immobilized polymer synthesis). This technique combines synthetic chemistry and photolithography to create up to 250,000 different oligopeptides per square centimeter

[6b]. To achieve synthesis on this microdimension, the traditional synthetic polymer support has been replaced by materials well known from microelectronics, such as a silica chip or a glass surface. The key steps of this method are illustrated in Scheme 3. The surface is first treated with 3-(aminopropyl)-triethoxysilane. The amino groups, thus covalently bound to the surface through a spacer, are then protected with the photolabile group nitroveratryloxycarbonyl (NVOC). For practical reasons about 1000 fields containing different oligopeptides are made on a chip of 1 cm^2 size.

For the affinity tests, the chip covered by areas of different oligopeptides is simply held in a solution of an enzyme and rinsed. The enzyme binds only where a randomly synthesized oligopeptide possessing a "correct" substrate sequence for that particular enzyme is present. Areas containing such affinity sequences can be detected by using a fluorescence labeled antibody specific for that particular enzyme. This fantastic new method is slowly settling down in pharmaceutical research laboratories despite involving large investments in both equipment and personnel.

Nucleic Acids

In order to achieve a desired therapeutic effect, the direct predecessors of proteins (peptides, enzymes), that is, DNA or mRNA, can be addressed and modulated (blocked, cleaved) in the cell.

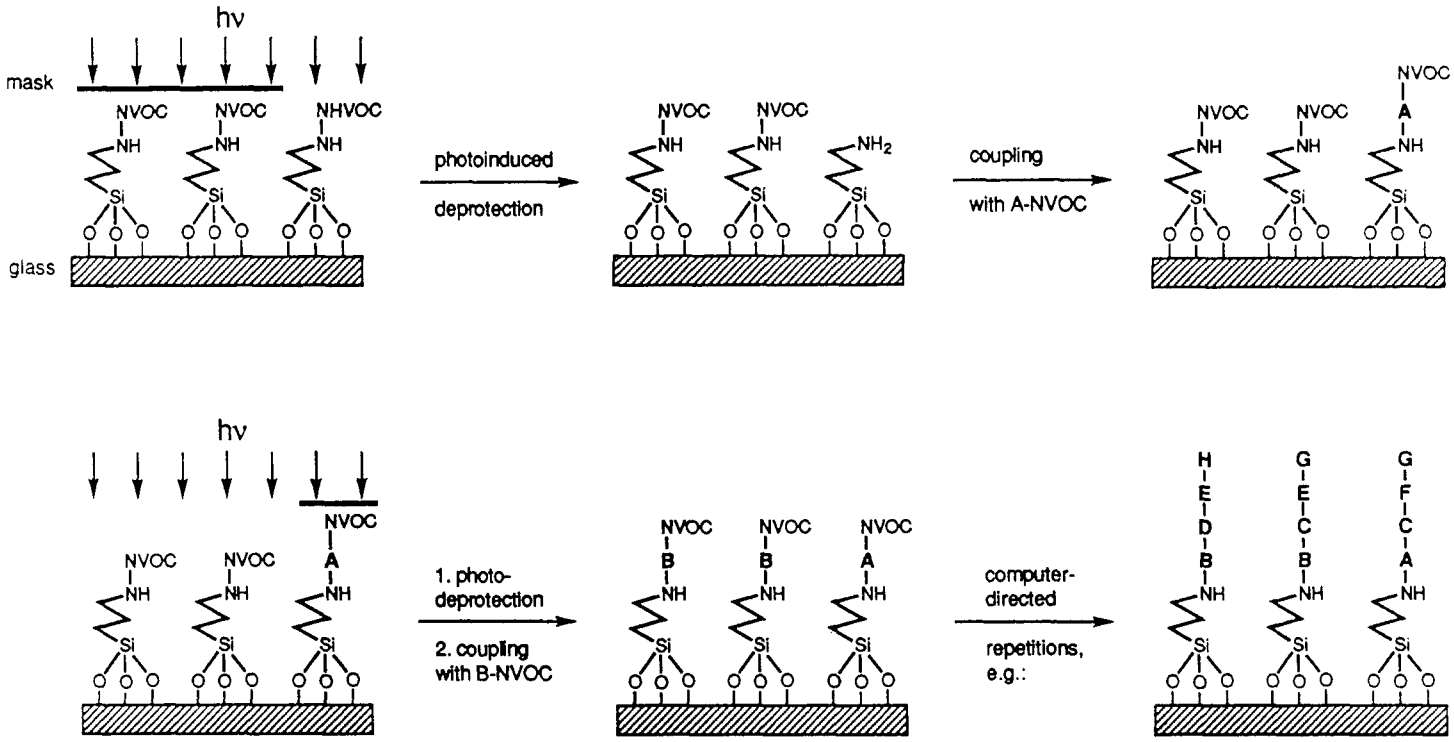
The antisense strategy uses as a target the single strand of natural polymeric mRNA [7]. For a certain sequence of this natural "sense" mRNA, which is functionally responsible for the expression of a disease-related protein, a complementary "antisense" oligonucleotide can be designed according to the well-known Watson–Crick base pairing rules and then synthesized. When offered to a "sense" strand of mRNA, a spontaneous recognition and hybridization to a double helix takes place. In this way the expression of the undesired protein from the mRNA is rendered impossible (Scheme 4).

According to statistics, an oligonucleotide with a specific sequence of 17 nucleosides (a 17mer) would find only one single, exact complementary sequence within the whole human genome. This fact underlines the enormous potential of the antisense strategy for the selective fighting of diseases.

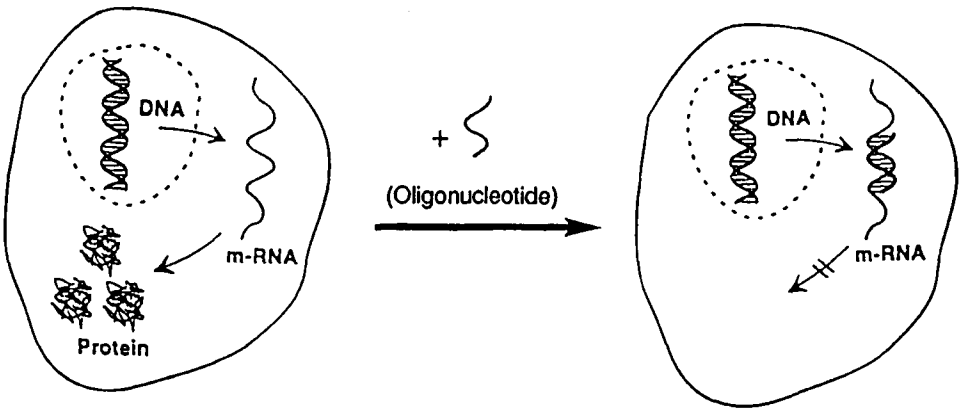
For the preparation of the target sequences of mRNA as well as antisense nucleosides, polymer-supported synthesis is quickly gaining in importance [8]. While the approach resembles those employed in the synthesis of peptides, there are some significant differences (Table 2). The removal of the dimethoxytrityl protection group in each cycle from the 5′-terminus of ribose requires the use of a rather strong acid. The acid must be removed as soon as possible, otherwise considerable degradation of the acid-sensitive ribose would occur (Scheme 5). In highly swollen, low-crosslinked polystyrene beads of 50–100 μm diameter, as used in the Merrifield synthesis of peptides, sufficiently fast washing cycles cannot be achieved, thus polystyrenes crosslinked by up to 50% of divinylbenzene must be used.

Oligonucleotides prepared by this method exhibit good molecular weight uniformity.

However, in order to achieve greater resistance of the synthetic "antisense" DNA- or RNA-like oligonucleotides toward cleavage by hydrolytic enzymes, it is necessary to prepare unnatural nucleosides. Typical modifications include the intro-



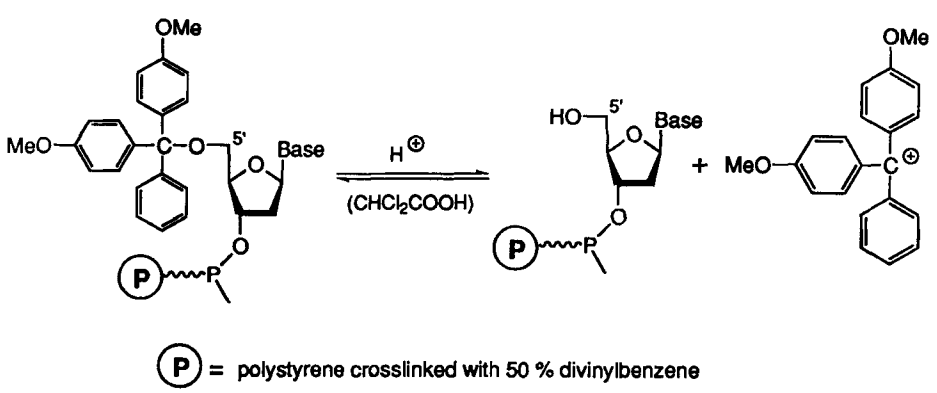
SCHEME 3. Light-directed spatially addressable parallel chemical synthesis of oligopeptides. A spacer containing a terminal amino group protected by a photochemically removable group (NVOC) is selectively illuminated through a mask. As a result, amino groups in distinct regions are selectively deprotected. The first of a set of NVOC-protected amino acids, i.e., A-NVOC, is exposed to the entire surface of the glass chip. Chemical coupling occurs at those regions which were exposed to UV light. A different mask is then used to selectively deprotect different amino groups. A second protected amino acid, i.e., B-NVOC, is added and reacts with free amino groups. The computer-directed process is repeated to obtain the desired large array of oligopeptides possessing different amino-acid sequences.



SCHEME 4. Schematic interference of oligonucleotide with mRNA within the cell (antisense approach) according to Moser [7b].

TABLE 2. Comparison of Polymer-Supported Synthesis of Peptides versus Oligonucleotides

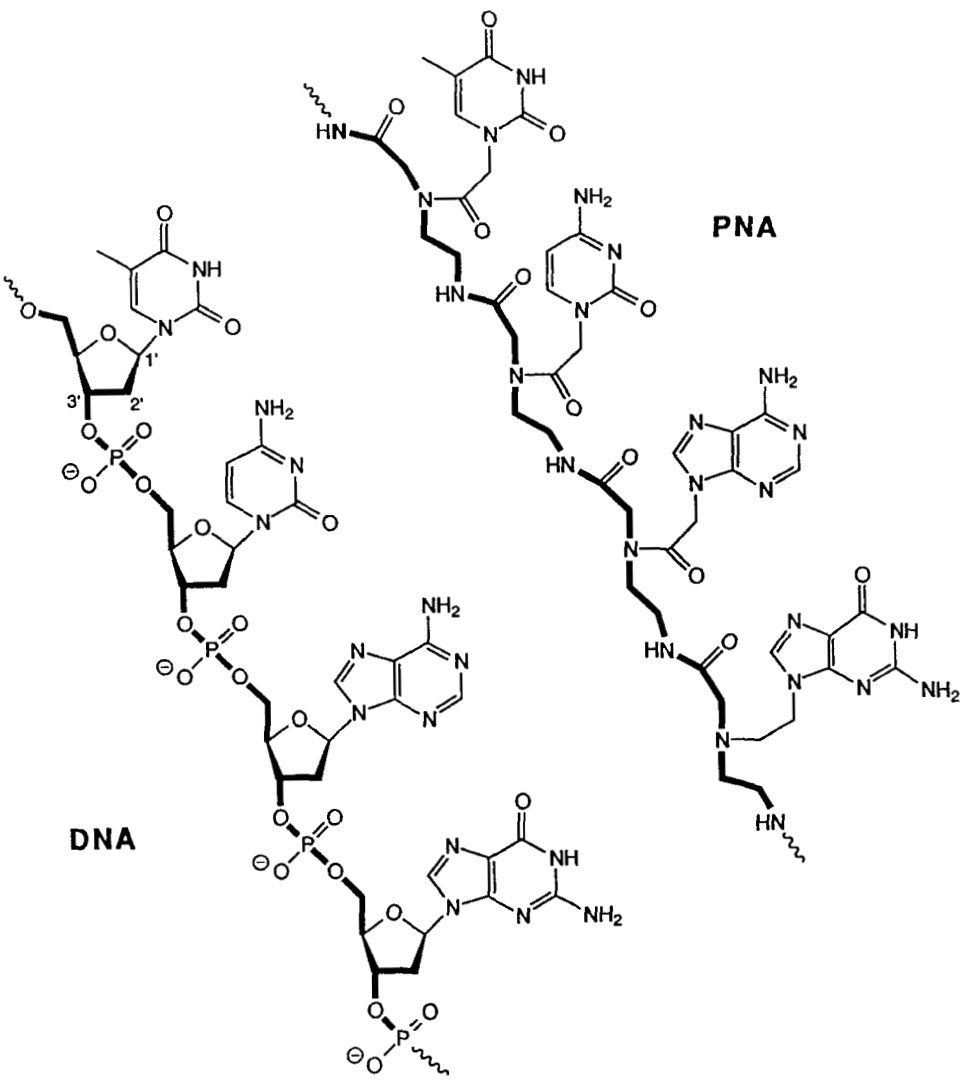
Conditions	Peptides	vs	Oligonucleotides
Polystyrene, typically crosslinked by	1% divinylbenzene		50% divinylbenzene
Swelling	High in CH_2Cl_2, DMF		Low in CH_2Cl_2
Allows automatic instrumentation	Yes		Yes
Purification time	Long		Short
Molar excess of monomer	≥ 10		2.5–5



SCHEME 5. Acid-catalyzed deprotection of a polymer-fixed, 5′-protected nucleoside, a critical step of the polymer-supported synthesis of oligonucleotides.

duction of small substituents instead of 2′- or 3′-OH groups or the replacement of the ribose tetrahydrofuran ring by a cyclopentane ring. The hybridization requires, however, that the absolute configuration at C-1′ and C-3′ in synthetic nucleosides is the same as that of the natural ribose. For this reason their synthesis represents a significant challenge.

A total turn away from the concept of modifying the ribose ring was recently published by Egholm and coworkers [9]. They made use of an achiral polyamide backbone (PNA) as shown in Scheme 6 to replace the phosphodiester linkage in DNA or RNA as well as to gain increased resistance toward hydrolytic enzymes



SCHEME 6. Schematic comparison of DNA and PNA backbones.

(nucleases). Instead of the chiral C-1′ of ribose, an achiral nitrogen atom serves for the attachment of pyrimidine or purine bases to the polymeric backbone.

This is an amazingly simple approach. Astonishing binding results obtained with these PNAs (peptide nucleic acids) has inspired many laboratories all over the world to investigate this new approach. As PNAs contain peptide bonds in the backbone, they could easily be prepared by the polymer-supported Merrifield synthesis from the corresponding δ-amino acids.

In conclusion, the whole field of synthetic oligonucleotides is highly interesting, full of high-flying expectations, and, at the same time, hard-to-master experimental difficulties.

Carbohydrates

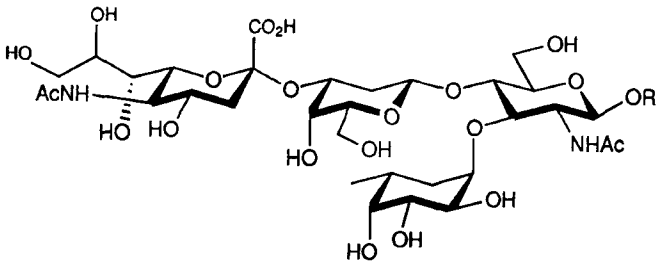
The trickiest class of natural polymers are carbohydrates. On the one hand they are structurally very complex, on the other hand they are ubiquitous in nature, certainly for good reasons.

Today, the so-called adhesion polymers, consisting of membrane-bound glycoproteins with complex sugars like the tetrasaccharide Sialyl Lewis^x (Scheme 7) at the free end, are among the hottest topics in drug companies [10]. They are seen as contributors to just about everything that happens in our bodies, wherever cells are moving and interacting; for example, in inflammation, cancer metastasis, septic shock, thrombotic disorders, etc. These complex sugars are seen to act as "ZIP codes" in order to deliver and bind the cells selectively to the proper receptor.

One possibility to avoid such binding would be a blocking of the protein receptors by oligomeric synthetic analogues of natural saccharides, which are constituents of glycoproteins.

Such a strategy is feasible. However, due to the multifunctionality and multichirality of monomeric building blocks of sugars, i.e., hexoses, one encounters a completely new dimension of enormous synthetic difficulties. Not surprisingly, the polymer-supported solid-phase synthesis of oligosaccharides is still in its infancy [11].

Therefore, a number of other strategies are under investigation. One of them uses true "specialty polymers," copolymers of acrylamides bearing the Sialyl Lewis^x attached to the side chain. There is a good experimental indication [12] that the polyvalent interaction of such "poly-Sialyl Lewis^x" with some natural receptors



SCHEME 7. Cell-surface tetrasaccharide Sialyl Lewis^x. R = Glycoprotein.

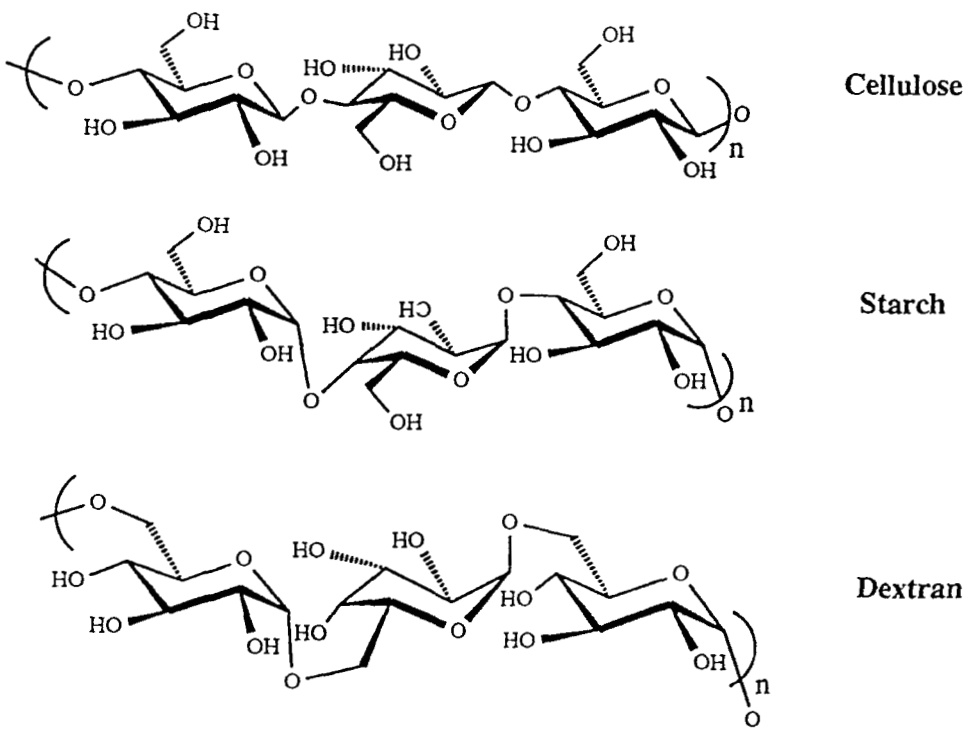
(membrane proteins) can competitively inhibit the undesired binding of certain viruses having a surface rich in Sialyl Lewis^x.

An interdisciplinary approach like this one, merging polymer chemistry, organic chemistry, biochemistry, and glycobiology, is really one of the major reasons why the design of carbohydrate-based drugs is starting to grow exponentially.

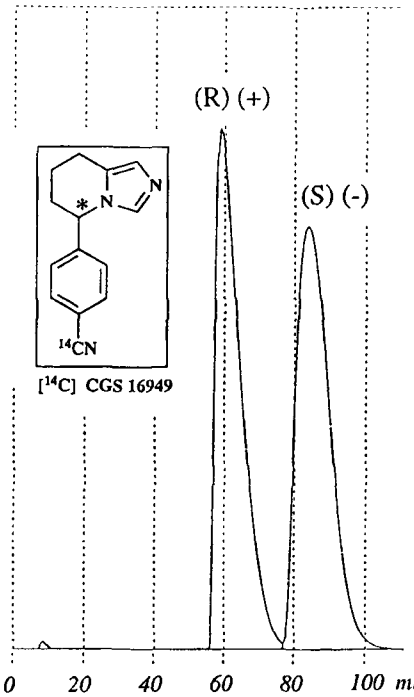
TESTING STAGES

In addition to the very modern inclusion of oligosaccharides into the discovery stage of the development process, as described in the preceding section, the potential of "classical" naturally occurring polysaccharides (Scheme 8) for the chromatographic separation of enantiomers on a preparative scale as a tool for the isolation of optically pure compounds is gaining increasing recognition in biooriented industry [13].

In the discovery phase, scientists in the biooriented industry have a common aim, namely the discovery of novel compounds that exhibit desired biological properties by virtue of highly selective molecular recognition between them and the three-dimensional receptors of living organisms. These receptors consist of enantiomerically (that is, optically) pure building blocks of DNA/RNA, proteins/enzymes, and carbohydrates. The common denominator, which is at the heart of all molecular



SCHEME 8. Structures of naturally occurring polysaccharides: cellulose, starch, and dextran.



SCHEME 9. Preparative (1 g) resolution of racemic ^{14}C-labeled CGS-16949 (Fadrozole) on cellulose triacetate.

recognitions, is chirality. Chirality is not a requirement for biological activity per se, but in those cases in which the bioactive compound contains one or more chiral centers, the desired biological property is often related to a single isomer [14].

When a racemic or diastereomeric lead compound possessing a promising activity is identified, the optically pure isomers have immediately to be made available in larger amounts in order to enable a careful testing of both of them separately. One powerful method the chemists have at their disposal is the chromatographic separation of racemates on polymers containing repeating optically active units [13].

The best results in terms of versatility and resolution are achieved with cellulose. However, two prerequisites for a high resolving power have to be fulfilled. First, the cellulose must be acetylated in order to break down strong intra- and interchain hydrogen bonds, and, at the same time, the cellulose must remain microcrystalline in order to preserve the large number of regular cavities surrounded by the same chiral environment.

The great value of cellulose triacetate as a polymeric chiral stationary phase is illustrated by Scheme 9. In the testing stage of the development of Ciba-Geigy's experimental anticancer drug Fadrozole (CGS 16949) [15], it became necessary to possess sizable amounts of both of its ^{14}C-labeled enantiomers for metabolic studies. Racemic Fadrazole could be perfectly separated on a gram scale within 2 hours on a cellulose triacetate column [16]. This represented an enormous benefit, because the

total asymmetric synthesis of both single enantiomers would require 10 to 20 times more resources than the synthesis of racemic Fadrozole.

In conclusion, preparative and semipreparative chromatographic resolutions on polymeric chiral stationary phases have become an absolutely indispensable, cost-saving tool in modern drug development.

ADVANCED STAGES (APPLICATION METHODS, REGISTRATION)

After a promising bioactive compound has been found, separated into optical isomers (if necessary), thoroughly tested and scaled-up, an appropriate delivery form must be established. Sophisticated use of both well-known and new polymers can help a lot in this stage.

Polymer Patches for Rate-Controlled Transdermal Delivery of Drugs

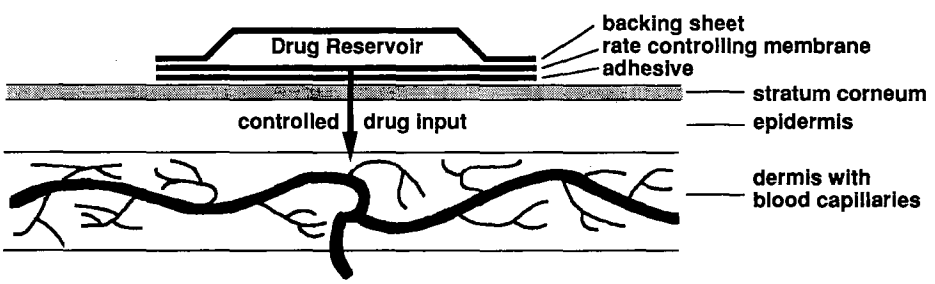
In recent years transdermal drug delivery became a great success story and big business in many pharmaceutical companies. For example, three out of six of Ciba-Geigy's top drugs in 1992, with combined sales in excess of US$1 billion, were sold as polymer patches: Nicotinell TTS, containing nicotine for smoking cessation; Nitroderm TTS, containing nitroglycerine which provides effective prophylaxis for heart diseases, e.g., angina pectoris; and the Estraderm TTS patch, containing estradiol for the prevention or the treatment of the postmenopausal syndrome.

Most procedures for the design and development of transdermal patches [17] have not yet been disclosed to the public. There is a general reluctancy to do so for two major reasons:

1. The technology involved is very new. Potentially patentable innovations are kept closely guarded.
2. The successful design of a useful and convenient multilevel polymeric skin patch contains a lot of know-how. Its premature disclosure could bring a high monetary reward to any imitators and pirates.

Nevertheless, the general framework of a patch is usually composed of five functional elements (Scheme 10):

1. A backing membrane which prevents the drug from migrating outward—it can be polyethylene, paper, etc.



SCHEME 10. Transdermal patch on skin.

2. A drug reservoir with the drug as an emulsion or suspension.
3. A rate controlling membrane—microporous, macroporous, semipermeable. Here is where the know-how is hidden!
4. A pressure-sensitive adhesive which secures the patch to the surface of the skin. It must not represent a rate-limiting barrier to diffusion of the drug. Medical-grade rubber, acrylate, or silicone are usually employed.
5. A peel-off strip for mechanical protection of the patch during storage and handling. All kind of films are used, especially those derived from fluorinated polymers.

All patches have one common obstacle to overcome: the outermost layer of the skin, the stratus corneum. It represents another rate-limiting barrier to prolonged drug delivery. For this reason, all therapeutic agents in successful transdermal systems have to be biologically active in daily doses of less than 2 mg.

The patch design secures a nearly constant rate of drug diffusion into blood capillaries; for example, the nitroglycerine-containing patch guarantees a constant dosage for 24 hours.

Water-Soluble Packages and Microencapsulations

Some problems with agrochemicals are connected with their packaging and handling. Especially difficult is the situation in less developed countries: nice plastic bottles which served for the distribution of agrochemicals are sometimes misused for the storage of food, etc. Education and instructions alone do not prevent misuse. Accordingly, new regulation policies are expected to require the use of agrochemical packages that do not end up in the solid waste stream.

For the above reasons all environmentally responsible agrochemical companies are busily involved in developing premeasured and water-soluble packages that minimize waste and practically eliminate the opportunities for users to come in direct contact with the agrochemical. A typical *water-soluble bag* is made from polyvinyl alcohol (PVA). When added to water, it dissolves within 3–5 minutes at 10–15°C, forming an emulsion ready for application.

PVA is an old polymer. However, only in the last 6 years have PVA polymers with the required properties become commercially available. The appropriate PVA must possess the following qualities:

Soluble in cold water
Resistant to most solvents
Grease and oil barrier
Flexible at low temperatures
Heat sealable
Excellent film transparency
Antistatic
Biodegradable

Useful PVAs contain about 13% of a polyol plasticizer, the exact chemical composition of which is a secret of the producer. A typical degree of polymerization is around 1800.

Biodegradable jugs made from PVA and containing Ciba-Geigy's insecticides may soon be on the market. Such a jug would be used like a traditional polyethylene jug. After being rinsed to eliminate all traces of the agrochemical it once contained, it could be left outside. It has been proven that within 6 to 8 weeks it biodegrates completely, leaving only carbon dioxide and water.

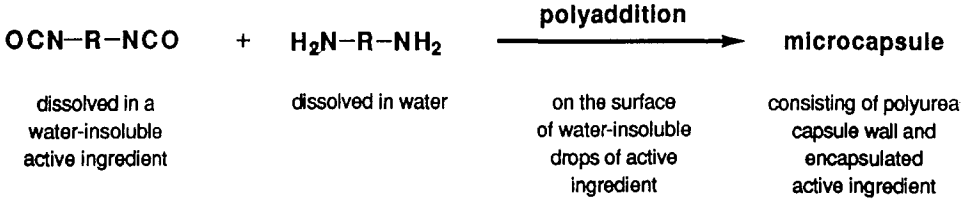
In general, if highly toxic or very volatile insecticides are involved, handling safety becomes a critical issue. In the last 5 years spectacular results have been achieved by *microencapsulation* [18] using simple polymers which either greatly improved the application safety or enabled the use of certain insecticides.

Technically, the process of microencapsulation is based on interface polyaddition of diamines to diisocyanates. Polyureas thus formed serve as a microcapsule wall (Scheme 11). The process seems to be extremely simple. All the know-how lies in the nature of surfactants and dispergents. However, the appropriate ones can only be found by a very careful trial-and-error type of experimentation. Namely, they must first enable creation of microscopic plastic capsules with an average diameter of less than 10 μm, i.e., not larger than red blood cells, and, second, the production of hundreds of tons/year of such microcapsules must be possible in an inexpensive, reliable, and reproducible manner.

The plastic polyurea wall prevents the active ingredient from direct contact with the skin and also from premature loss of activity in the household or in the field through degradation and evaporation. The uptake from the capsule through the skin is slow, and therefore the benefit for the user is a significantly increased safety margin while handling the product. For example, the excellent but rather toxic soil insecticide Isazofos was allowed for application only by professionals. The new capsule suspension formulation MIRAL 500 CS (Fig. 1), however, confers a greatly enhanced user safety while maintaining excellent insecticidal activity. The dramatic improvement of oral and dermal toxicity (Table 3) by encapsulation into a polyurea membrane resulted in the reduction of the WHO hazard classification from 1b to 3. Owing to the microscopic particle size, the product is as convenient to handle as an ordinary liquid concentrate.

The problem of the excellent insecticide Diazinon for the control of cockroaches, fleas, and other domestic pests was its high volatility, which posed considerable inhalation danger for users. By microencapsulation, the new formulation Diacap 300 CS exhibits a very spectacular prolongation of activity: one single spraying can give a season-long protection (Table 3)!

In this simple way, by means of ultrathin polyurea membranes, the application range of both these rather old insecticides from the class of organophosphates has been very considerably broadened. Now they much better fulfill—for the benefit



SCHEME 11. Microencapsulation process.

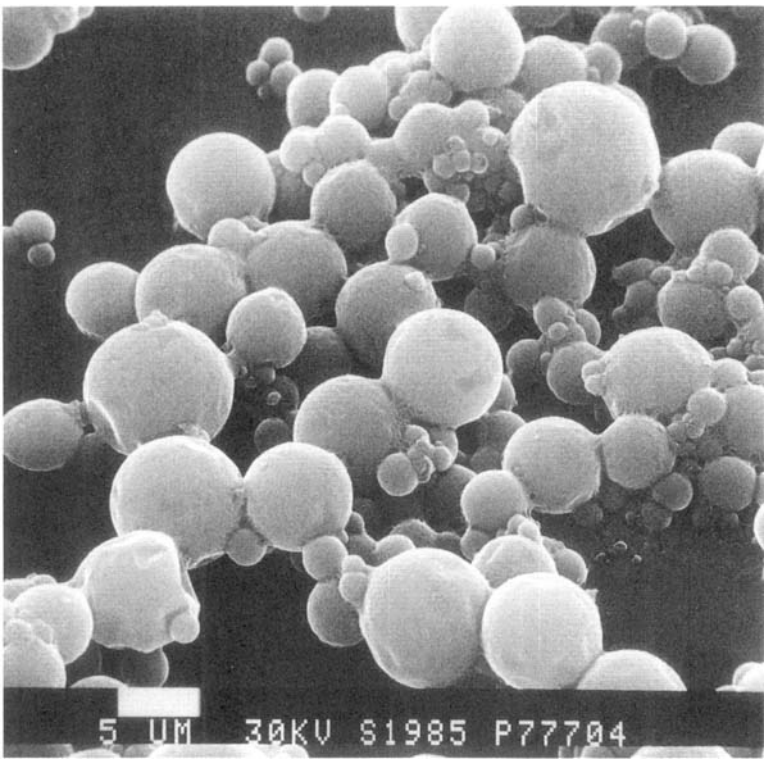
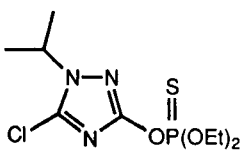
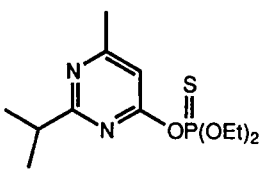


FIG. 1. Scanning electron photography of Miral CS 500, an insecticide microencapsulated in a polyurea membrane.

TABLE 3. Some Typical Benefits of Microencapsulated Insecticides

Insecticide (a.i.)	Problems of a.i.	Encapsulated a.i.
 Isazofos	High oral and dermal toxicity of emulsifiable concentrate	Very considerable reduction of toxicity of capsule suspension formulation
	Oral LD_{50}: 74 mg/kg vs >5000 mg/kg Dermal LD_{50}: 747 mg/kg vs >2000 mg/kg	
 Diazinon	High vapor pressure Phytotoxicity High oral toxicity	Duration of activity very substantially increased with a capsule suspension: 1 day → 8 months Reduced toxicity

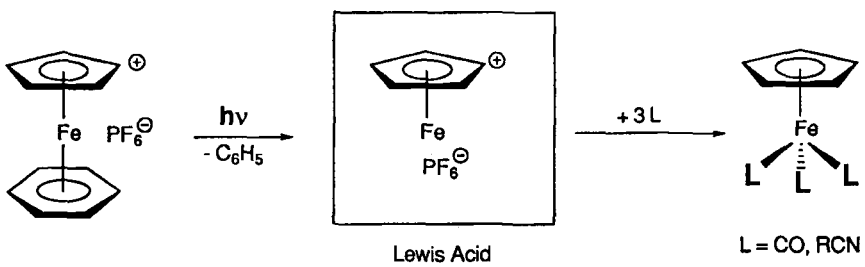
of users—the social expectations, the ecological demands, and also the economic necessities of the producer. One can paraphrase Churchill: "Never have so simple polymers done so much for so many users!"

PHOTOPOLYMERS

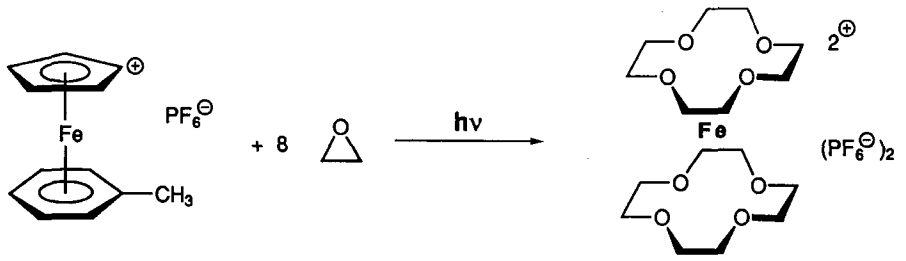
As mentioned in the Introduction, in a large research organization involved in synthetic activities, a great number of unexpected compounds, results, and observations frequently emerges. As a consequence, there exists an enhanced possibility of finding something useful by serendipity. Of course, an additional condition of success must be fulfilled at the same time, namely the mutual exchange of information between otherwise noncommunicating research groups.

The fruitful coincidence of serendipity and cross-information will be demonstrated by the example of discovery and development of excellent *iron arene photoinitiators*. The traditional stronghold of Ciba-Geiby in the polymer field is epoxy resins. About 10 years ago polymer researchers thought hard about the design of epoxy-based photosystems for the use in electronics and microelectronics. The then existing cationic initiators which were able to yield Brønsted acids under irradiation suffered from some serious undesired properties (subsequent degradation of networks, corrosion of metallic surfaces, low sensitivity, storage stability, etc.). At the same time, researchers pursuing some biooriented goals by means of organometallic synthesis came across the just reported [19] photochemical formation of Lewis acids by loss of an uncharged tridenate arene ligand (Scheme 12). The Lewis acids thus formed underwent complexation with new ligands. Knowing the needs of their polymer colleagues, they immediately tried to offer ethylene oxide as a ligand for the irradiated iron (II)–arene complex according to Scheme 13. As a result, not only an unprecedented template formation of crown-12-cyclic ether [20] but also the principle of photolytic activation of epoxies was discovered [21].

As a practical consequence, multifunctional novolac-epoxy compounds yield highly crosslinked polymers upon irradiation in the presence of less than 2% of an appropriate iron(II)–arene salt (Scheme 14). Such negative working photoresists retain the outstanding electrical, physical, and mechanical properties of epoxy resins. They are now marketed under the name Probimer 61 for use as high-resolution insulating and solder masks for printed wiring board manufacture.



SCHEME 12. Photolysis of a cationic iron(II)–arene complex according to Gill and Mann [19].



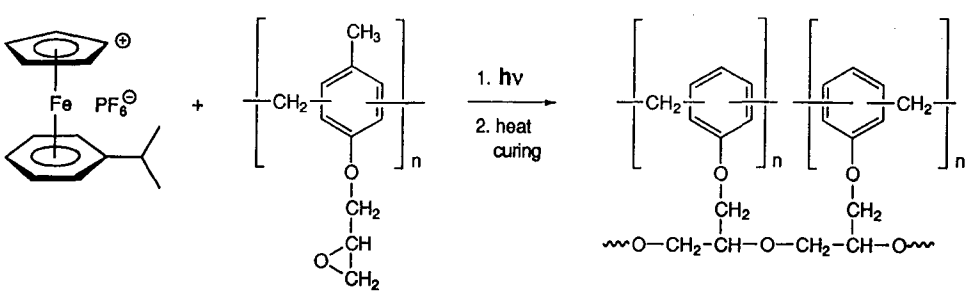
SCHEME 13. Formation of crown-12-cyclic ether by photolysis of a cationic iron-(II)-arene complex in the presence of ethylene oxide according to Meier and Rihs [20].

The equation according to Scheme 14 is not completely true, because after UV exposure the illuminated parts of the coating contain epoxy groups complexed to the central iron atom. In order to polymerize the irradiated areas of the epoxy matrix, a short heat treatment is necessary, e.g., 100°C for 5 minutes.

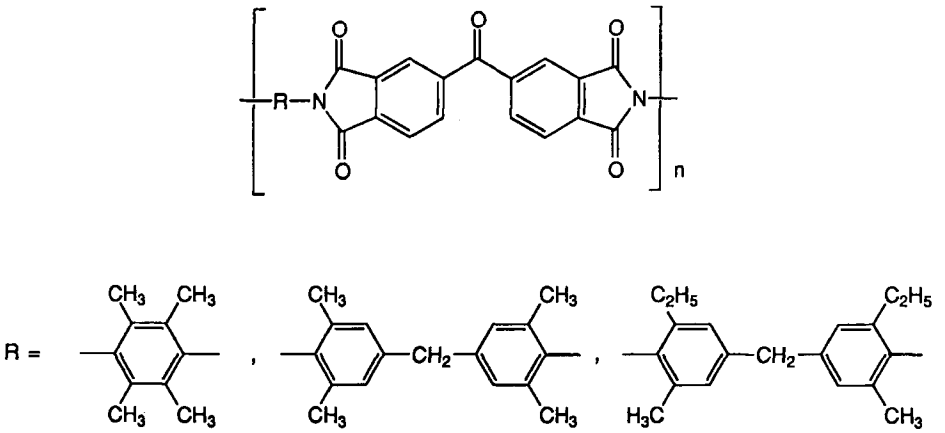
The iron(II)-arene complexes (sometimes called "ferrocenium salts," in error [22]) represent a real photochemical treasure for several reasons. Changes in the structure of arene ligands as well as in the counterions result in complexes with varying spectral sensitivities. The optical density in the UV and visible part of the spectrum decreases sharply during the irradiation. This photobleaching permits light penetration through thick layers, up to 100 μm, if required for application purposes [21a]. In addition, they can also be employed in the photocuring of polyurethanes [23].

The combination of iron(II)-arene salts and epoxies as shown in Scheme 14, however, cannot be used in the semiconductor industry, where exceptional ionic purity and high temperature resistance are essential [24]. Requirements for photostructurable coatings like

High solubility in common organic solvents
Storage stability of solutions
No volatiles released during processing
Low layer shrinkage
High thermal stability



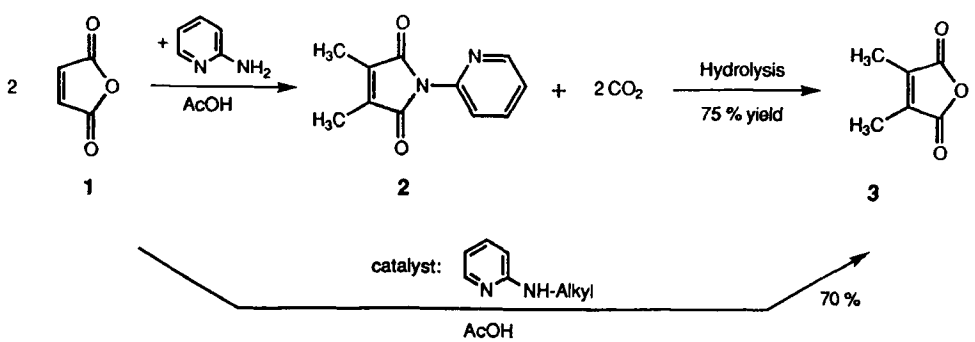
SCHEME 14. Schematic network structure formed by polymerization of a multifunctional epoxy-novolac with the iron(II)-arene salt Irgacure 261.



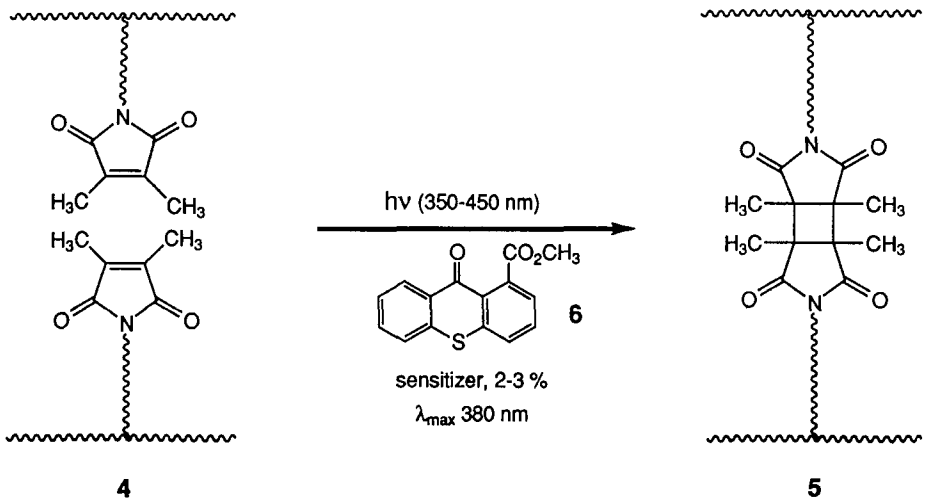
SCHEME 15. Autosensitive polyimides based on 3,3′,4,4′-benzophenone tetracarboxylic dianhydride.

are best met by *aromatic polymides*. When Pfeifer started in the early 1980s to do experiments with self-sensitizing and crosslinking polyimides based on benzophenone tetracarboxylic acid, he found in neighboring bioorganic laboratories plenty of polyalkyl-substituted dianilines as well as expertise for hydrogen abstraction reactions from suitable hydrogen donors by excited arylketone molecules [25]. Polyimides are particularly good examples of materials containing photosensitive carbonyl groups and an abundant amount of photoabstractable benzylic hydrogens (Scheme 15). T_g values could be tailored up to 440°C for the polyimide with tetramethyl-*p*-phenylenediamine. Upon UV-irradiation, photostructures of high resolution were obtained which did not suffer from thickness loss at high temperatures [26].

Insolubilization of the film is probably due to the molecular weight build up when the benzophenone-ketyl and alkyl radicals form bonds between adjacent polyimide macromolecules [27].



SCHEME 16. New decarboxylative dimerization of maleic anhydride (**1**) to dimethylmaleic anhydride (**3**).



SCHEME 17. Photocrosslinking of linear polymers bearing pendant side-chains with terminal dimethylmaleimidyl moieties.

Very recently Rohde and coworkers found [28] that copolymerization of just 10% of novel 2,3,6,7-thioxanthonetetracarboxylic dianhydride into a nonreactive polyimide based on inexpensive pyrromellitic dianhydride affords photosensitive polyimides with a high photospeed. The reason for this lies in the much better UV-absorption characteristics of the thioxanthone diimide structural units (λ_{max} 361 nm; ϵ 14,500) in comparison with the benzophenone ones.

Finally, a serendipitous discovery was made in our laboratories several years ago which led to the development of a superb *negative-working polymeric film for cartographic purposes.*

In a broader connection with the chemistry of imides for weed control, a reaction of maleic anhydride **1** with 2-aminopyridine in acetic acid was attempted. Instead of the expected imide of maleic acid, the imide of dimethylmaleic acid **2** was isolated (Scheme 16). Its hydrolysis afforded dimethylmaleic anhydride **3** in 75% yield [29]. The systematic study of the detailed mechanism of this originally mysterious decarboxylative dimerization **1**→**3** rendered the catalytic, one-pot preparation of **3** feasible [30]. Thus, the door was opened for industrial utilization of two already known properties of **3** and its imides: first, the pronounced ability to form [2+2]- cyclodimers under UV-irradiation [31], and, second, the reluctance to undergo radical polymerization due to steric hinderance. The latter property allows an easy radical homo- or copolymerization of dimethylmaleimidyl-functionalized acrylic monomers to afford linear, soluble polymers with pendant DMI groups (**4**). UV exposure of **4** in the presence of photosensitizer (preferably a thioxanthone derivative, e.g., **6**) yields crosslinked, insoluble polymers of type **5** (Scheme 17). A wide structural variety of tailor-made photopolymers are achievable using this approach. For example, a comonomer methacrylic acid provides acid groups for subsequent dyeing by basic dyes as well as for the development of thin layers by a low-alkaline water.

Applied on a polycarbonate film or an aluminum sheet, such 2–3 μm thin photocoatings exhibit excellent resolution, dimensional stability, and no oxygen inhibition of photocrosslinking. They find use in photolithographic applications and in photoresists [32].

CONCLUDING REMARKS

The commercial success of chemical and pharmaceutical companies in the 21st century will lie in the fast development of bioactive compounds for the marketplace. In order to facilitate the discovery and the progress of such lead compounds in the development pipeline, as illustrated by Scheme 1, there has recently been a sharp increase in interest in the possibilities offered by new specialty polymers or by sophisticated use of well-known polymers. Interest is mainly being shown in distinct categories of polymers, namely:

Biopolymers or biooligomers useful for the biorational design of low-molecular weight drugs and plant protection products
Support materials for the synthesis of biopolymers
Polymeric chiral stationary phases for the separation of racemates

While some synthetic activities in large research-based companies provide substantial excitement on the biological front, other experiments are rewarded by a number of worthwhile serendipitous discoveries. As a result, new compounds or materials with a more favorable combination of price, processability, and performance can be prepared which also satisfy users' needs outside the biomarket. In this paper, three of Ciba-Geigy's photopolymers originating from unexpected results or circumstances are described.

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The majority of examples presented here have been created by a number of excellent colleagues to whom I express my warmest appreciation, either for dedicated collaboration or exciting discussions or the friendly provision of very recent results. Their names are mentioned either in the text or in the references.

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