

## PDF hosted at the Radboud Repository of the Radboud University Nijmegen

This full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/16512>

Please be advised that this information was generated on 2014-11-14 and may be subject to change.

# Helical Poly(isocyanides)

Roeland J. M. Nolte

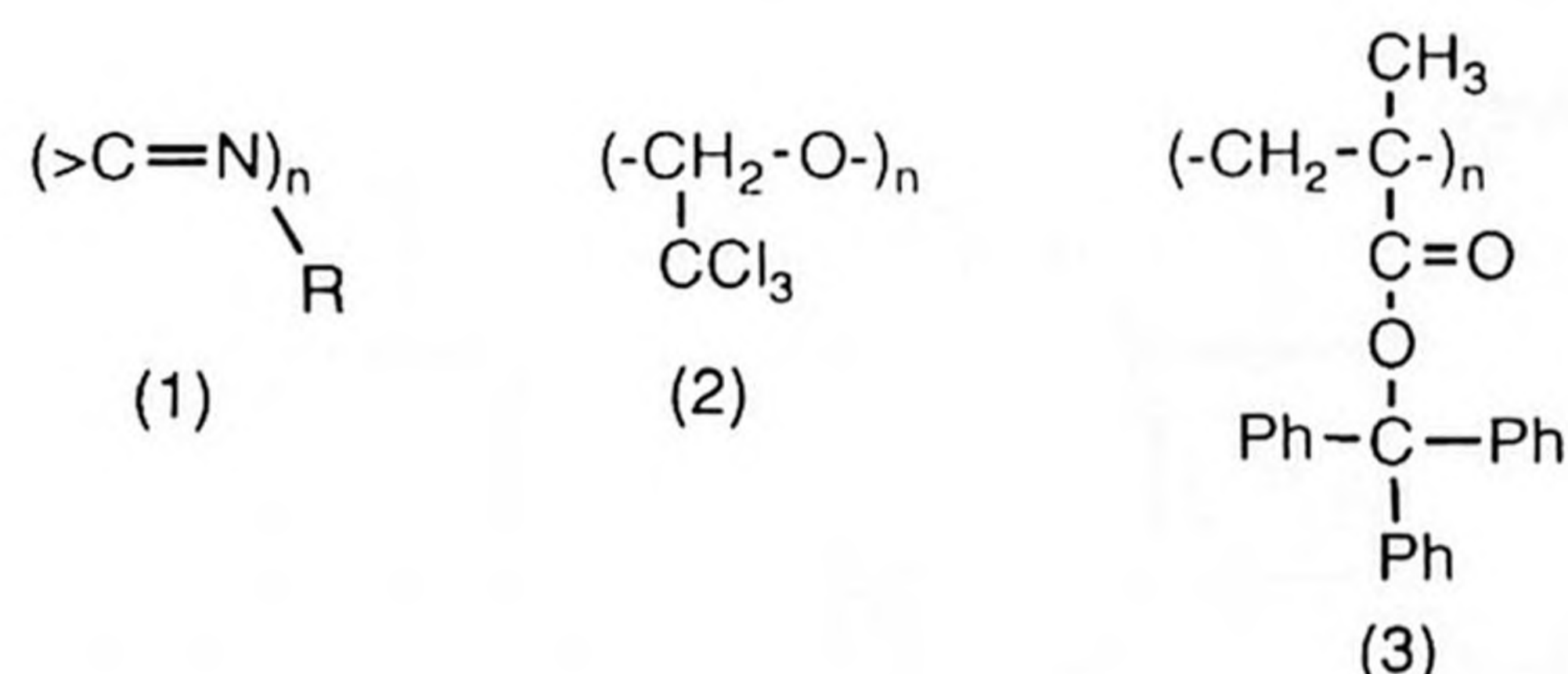
Department of Organic Chemistry, NSR-Centre, University of Nijmegen, 6525 ED Nijmegen, The Netherlands

## 1 Introduction

One of the most intriguing dissymmetric shapes is the helix. It was developed in natural systems in the early stages of evolution and used as the structural motif for the molecules of life (DNA and RNA) and as an important conformational element that enforces long range order in other biomacromolecules, *e.g.* enzymes. Helicity received attention in organic chemistry after the discovery of chirality at the end of the last century, but molecules with extended helical structures have been described only recently. Examples are the copper phenanthroline-based helices reported by Lehn and the self-organized quadruple helices from amphiphilic molecules synthesized by Fuhrhop.<sup>1</sup> In polymer chemistry helical architectures have been studied since the pioneering work of Natta, Pino, and others.<sup>2</sup> Most isotactic polymers exist as short range helices in solution. These are dynamic rather than static structures and the direction of the helical twist is very sensitive to small changes in polymer side-chain structure and the type of solvent.<sup>2</sup>

Polymers that maintain stable helical structures in solution, as do bio-macromolecules, are very rare, but are of great interest since they can display optical activity due solely to main-chain conformation. Furthermore, they may be used as versatile building blocks for the construction of novel chiral supramolecular architectures. To date, three examples of such helical polymers are known, *viz.* polymers of isocyanides (1),<sup>3</sup> poly(chloral) (2),<sup>4</sup> and poly(methacrylate esters) *e.g.* (3).<sup>5</sup>

Following suggestions by Millich<sup>6</sup> we were able to demonstrate in 1974 that poly(*t*-butylisocyanide) (1; R = *t*-C<sub>4</sub>H<sub>9</sub>) can be resolved into left-handed and right-handed helices which do not racemize even at elevated temperatures.<sup>3</sup> Subsequent studies have provided procedures for preparing helical poly(isocyanides) by helix-sense selective polymerization and have given

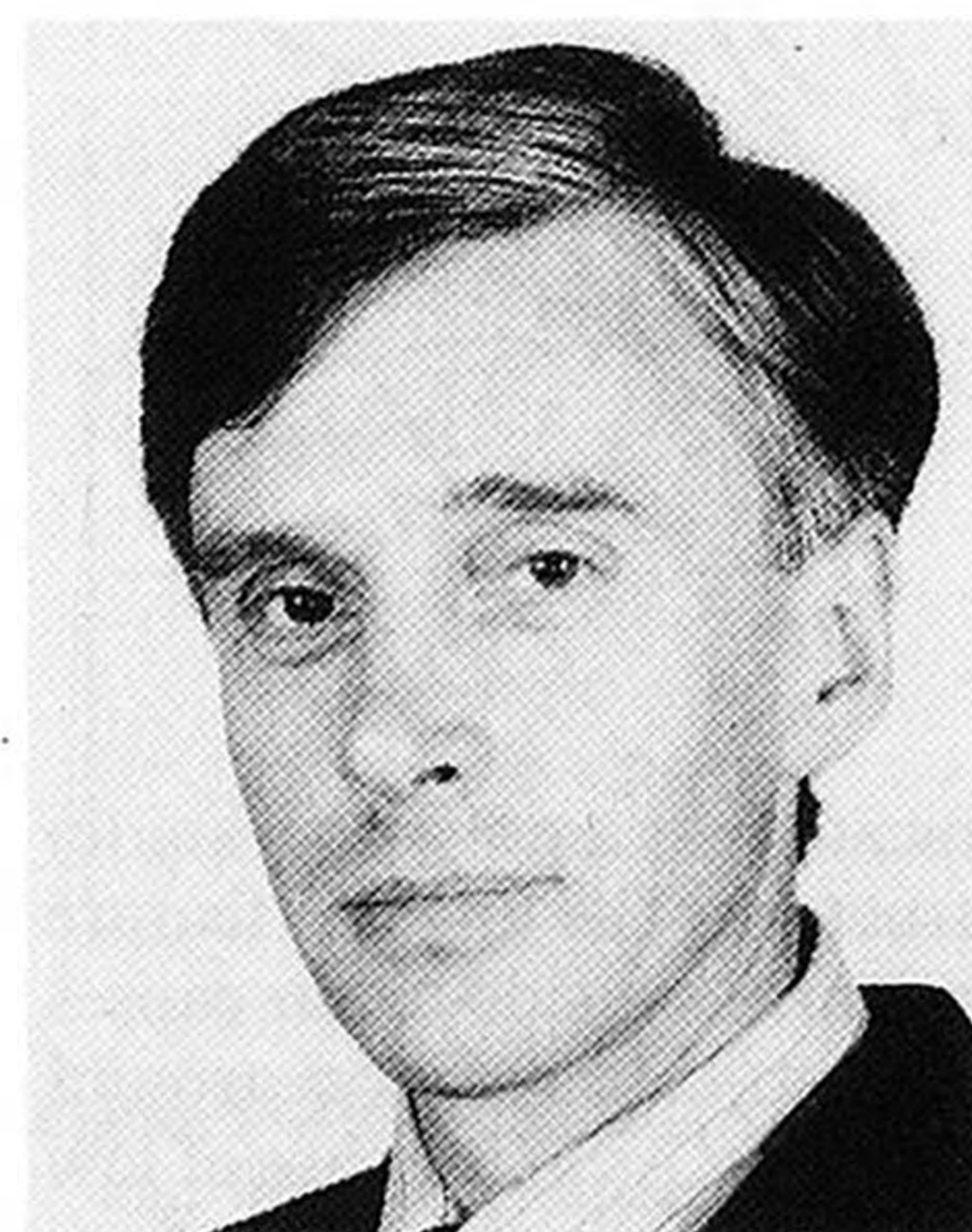


insight into the mechanism of the polymerization reaction.<sup>7</sup> The helical structure of a poly(isocyanide) is the result of restricted rotation around the single bonds connecting the main carbon atoms (atropisomerism). A similar hindered rotation is observed in poly(chloral) *viz.* around its carbon-oxygen bonds. This polymer can be prepared in a stable optically active form by anionic polymerization with *e.g.* Li- $\beta$ -cholestanoxide. Triphenylmethyl methacrylate and related bulky methacrylate esters yield optically active polymers when they are polymerized with initiators such as Li-(*R*)-(1-phenylethyl)anilide or (-)-sparteine-butyl lithium. The polymers are highly isotactic. The chiral carbon atoms in the polymer chains do not contribute to the optical activity as they are pseudo-chiral. The observed large optical rotations of the polymers are attributed to the presence of helical superstructures which again are the result of hindered rotation around single bonds.

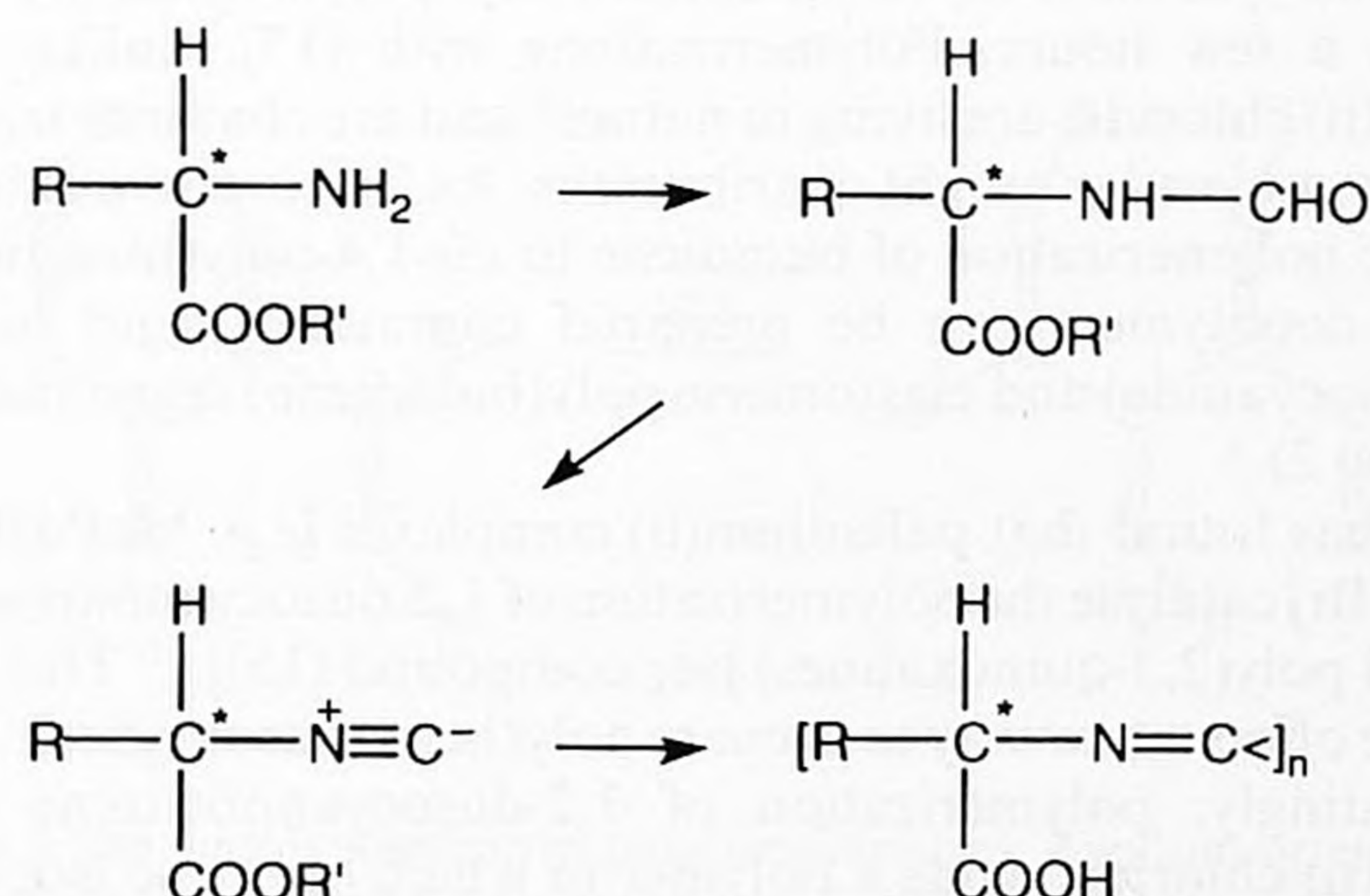
The purpose of the present review is to highlight the most interesting features of helical poly(isocyanides). It may hopefully serve as a starting point for further research in the field of atropisomeric polymers, in particular with regard to the use of these polymers as building blocks for the construction of novel dissymmetric architectures similar to those found in nature.

## 2 Synthesis

Millich was the first to develop a catalytic system for the polymerization of isocyanides.<sup>6</sup> He used an acid-coated glass system in combination with a radical initiator or air. We discovered that simple nickel(II) salts (NiCl<sub>2</sub>·6H<sub>2</sub>O; Ni(Acac)<sub>2</sub>, HAcac = acetylacetonate) are very efficient catalysts for polymerizing a wide variety of aliphatic and aromatic isocyanides, including monomers with additional double or triple bonds, with metal ligating functions, with crown ether rings, with donor-acceptor groups, and with stable radical substituents [see (4)–(16)].<sup>3,7</sup> The reactions should be carried out under aerobic conditions to prevent the formation of less reactive nickel(I) species, as was shown by Novak.<sup>8</sup> Yields are moderate to excellent depending on the type of isocyanide. Molecular weights vary between 5000 and 250000. Interesting starting materials for the preparation of the monomers are amino acids and peptides. Their amino functions can be easily converted into isocyanide functions as shown in Scheme 1. Polymerization with nickel chloride yields a new type of helical poly(amino acid) [*e.g.*

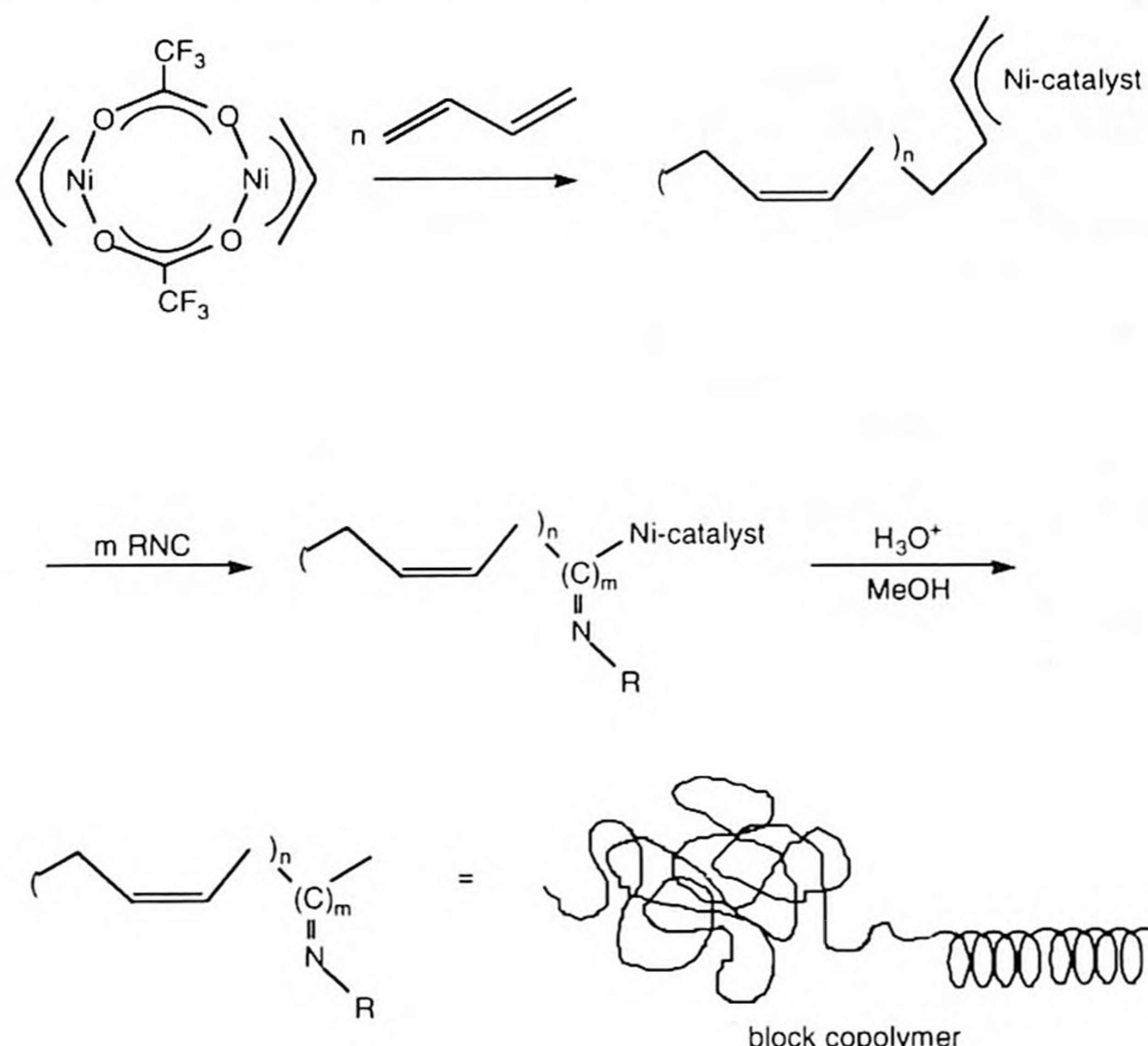


Roeland J. M. Nolte is Professor of Organic Chemistry at the University of Nijmegen, The Netherlands. He was educated at the University of Utrecht (Ph.D. in 1973) and did post-doctoral work with D. J. Cram at U.C.L.A. His research interests include molecular recognition, electron conducting molecular materials, chiral polymers, and metal-catalysed epoxidations.



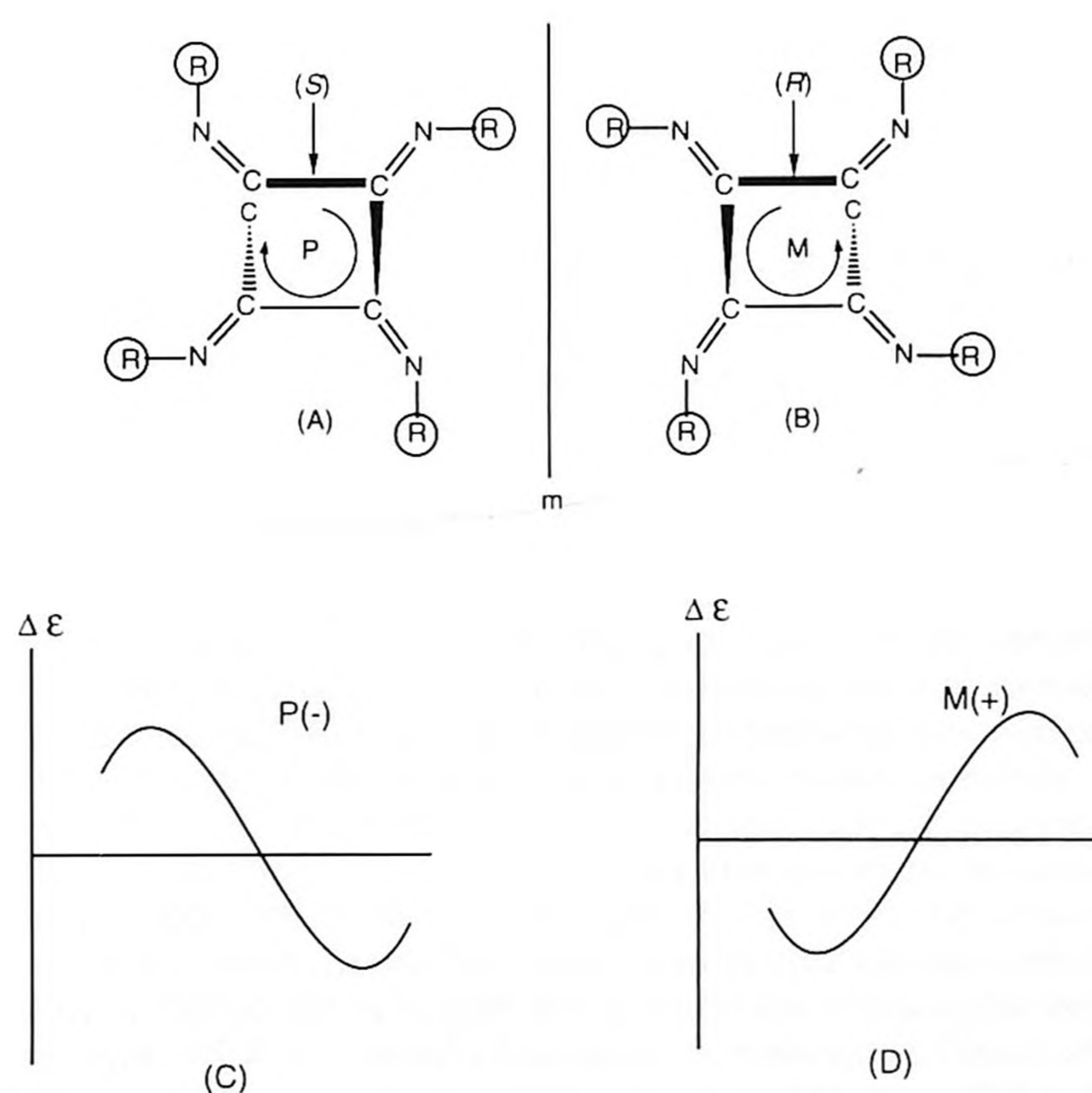
Scheme 1





Scheme 2

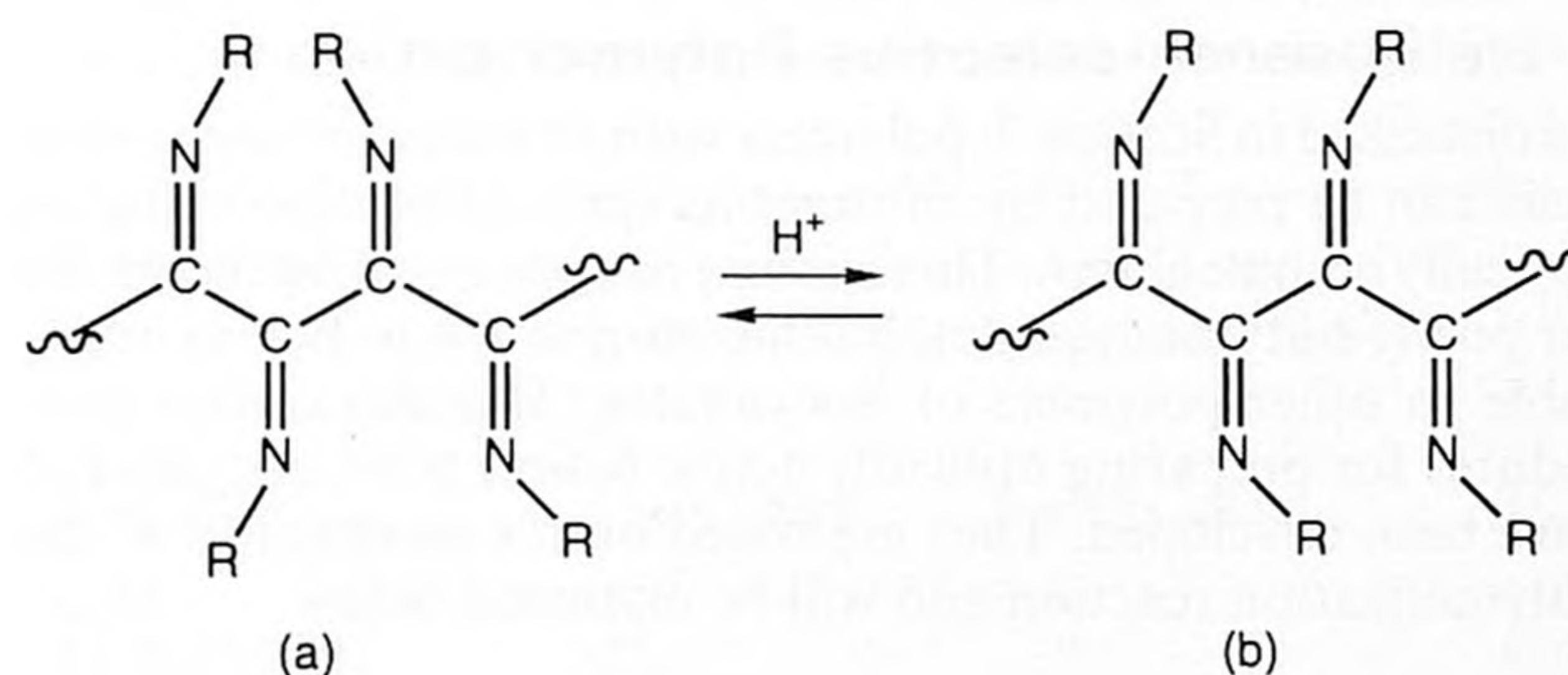
rations are possible around each of the main chain single bonds, *viz.* *R* or *S*. If these configurations are the same for all single bonds (meaning that the polymer is highly stereoregular or isotactic) a stable helix is formed. This helix is right-handed (*P*) if the above-mentioned configurations are all *S* and left-handed (*M*) if they are all *R* (see Figure 1). Alternating *R* and *S* absolute configurations would lead to a zig-zag (or syndiotactic) structure. However, for steric reasons such an arrangement is not feasible in practice. The following data support the helical structure of poly(isocyanides). Polymers of optically active isocyanides display optical rotations that are very different from those of the corresponding monomers or low-molecular weight model compounds. This feature, already observed by Millich<sup>6</sup> in poly(*α*-phenylethyl isocyanide) and later confirmed by us in extensive studies,<sup>13</sup> suggests that an additional chiral element is present in the polymers. In the circular dichroism spectra of these optically active polymers so-called exciton couplets – indicative of helices – are visible in the region from 240–400 nm.



**Figure 1** Right-handed (A) and left-handed (B) poly(isocyanide) helices and their corresponding circular dichroism spectra (C and D, respectively).

These couplets are due to the  $n-\pi^*$  transitions of the imino chromophores in the polymer main chains. In the UV-vis spectra these transitions are present as weak bands at approximately 300 nm. Circular dichroism calculations carried out by Huige<sup>14</sup> suggest that in the case of right-handed poly(isocyanide) helices the couplets are *Z*-shaped and in the case of the left-handed helices they are *S*-shaped (see Figure 1, C and D). Definitive proof that polymers of isocyanides can adopt helical structures comes from resolution experiments. Poly(*t*-butyl isocyanide), which has no chiral centres, could be completely resolved into (+)- and (-)-rotating polymer fractions with the help of a chiral column consisting of glass beads coated with an insoluble high molecular weight polymer of optically active (*S*)-*s*-butyl isocyanide.<sup>15</sup> The (+)- and (-)-rotating fractions were assigned to left- and right-handed helices, respectively, on the basis of a comparison between experimentally determined and calculated circular dichroism spectra. Further support for a helical structure is provided by molecular orbital and molecular mechanics calculations. Using the extended Hückel theory Kollmar and Hoffmann<sup>16</sup> showed that repulsion between the lone pairs of the imino groups in a poly(isocyanide) chain favours a departure from a planar structure. Similar repulsive effects are known to be operative in poly(ketones). Calculations on the series of polymers  $(\text{H}-\text{N}=\text{C}\langle)_n$ ,  $(\text{CH}_3-\text{N}=\text{C}\langle)_n$ , and  $(\text{CH}_3)_3\text{C}-\text{N}=\text{C}\langle)_n$  indicated that steric effects are more important than electronic effects in determining the polymer structure. For the hypothetical polymer  $(\text{H}-\text{N}=\text{C}\langle)_n$  a broad range of helical conformations are available in contrast to  $(\text{CH}_3)_3\text{C}-\text{N}=\text{C}\langle)_n$  for which the authors propose a quite stiff  $1_4$  helix. According to the theoretical analysis, the polymer with intermediate bulk,  $(\text{CH}_3-\text{N}=\text{C}\langle)_n$ , may adopt two helical structures with different degrees of helicity. Huige and Hezemans<sup>14,17</sup> have performed extensive molecular mechanics calculations using the consistent force-field method on various oligo- and poly(isocyanides). The hexadecamer of *t*-butyl isocyanide was calculated to have a helical middle section and disordered end sections. The dihedral angle  $\text{N}=\text{C}-\text{C}=\text{N}$  in this middle section was found to be  $78.6^\circ$  and the number of repeat units per helical turn was 3.75. The latter number is in agreement with circular dichroism calculations using Tinoco's exciton theory (3.6–4.6) and De Voe's polarizability theory (3.81).<sup>14</sup> The molecular mechanics calculations further revealed that the less bulky polymers  $(i\text{-C}_3\text{H}_7-\text{N}=\text{C}\langle)_n$  and  $(\text{C}_2\text{H}_5-\text{N}=\text{C}\langle)_n$  form helical structures as well. The polymer of methyl isocyanide was calculated to be disordered.

Another stereochemical feature of interest is *syn-anti* isomerism about the  $\text{C}=\text{N}$  double bonds of the monomeric units. Molecular mechanics calculations suggest that the occurrence of both *syn* and *anti* structures in one polymer chain is energetically unfavourable. However, <sup>1</sup>H- and <sup>13</sup>C-NMR experiments indicate that the polymers very often display more than one signal for certain H or C atoms. For instance, the polymer of 4-methoxyphenyl isocyanide has two methoxy signals in the <sup>1</sup>H-NMR spectrum at  $\delta$  3.25 and 3.75 ppm. Addition of acid results in a decrease of the former signal and an increase of the latter one, suggesting an equilibrium of the type shown in Figure 2.

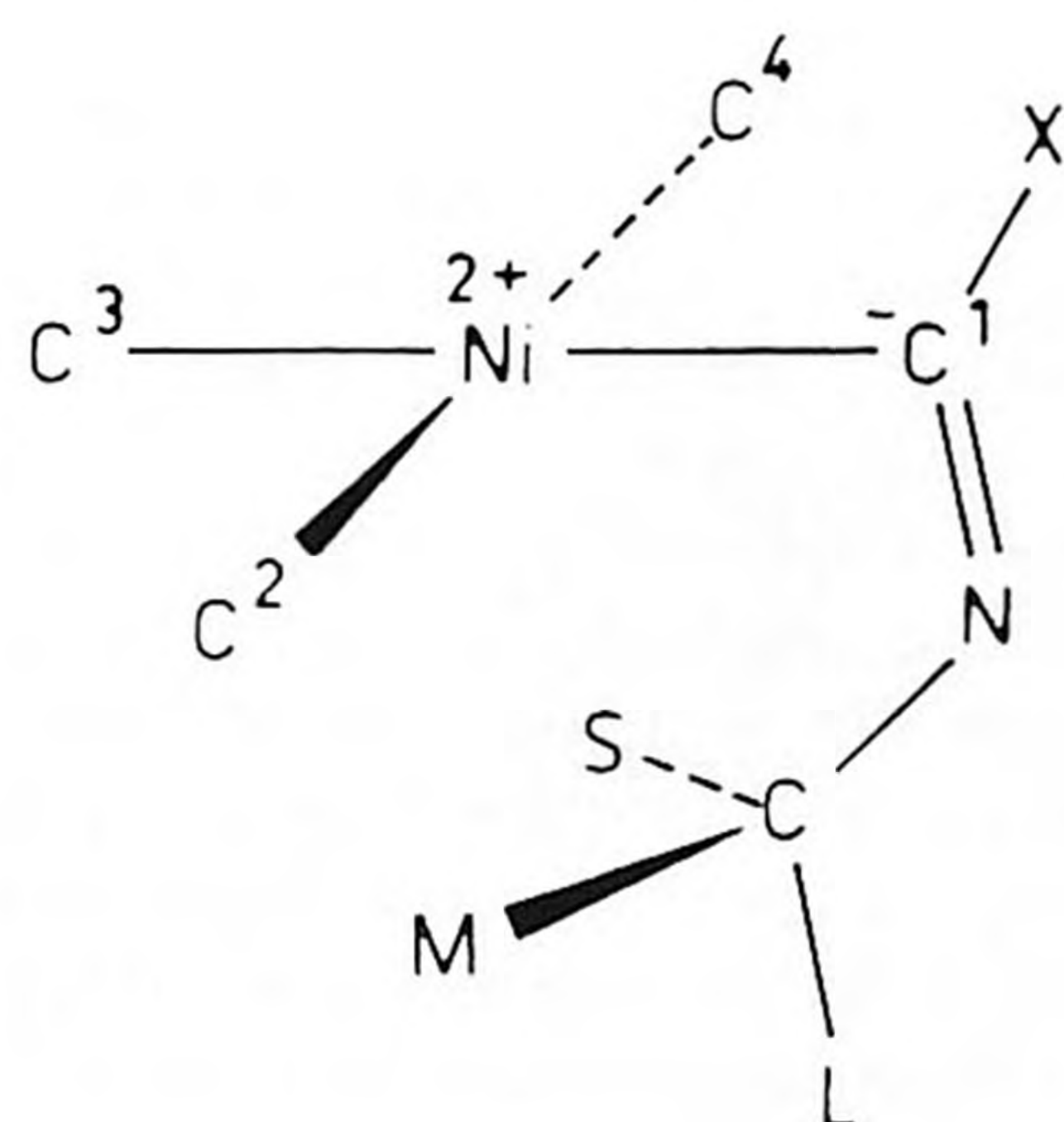


**Figure 2** *syn-anti* Isomerism in poly(isocyanides). Random orientation of side chains (a) and the thermodynamically more favourable all-*syn*- or all-*anti* configuration (which are identical), which is formed after the addition of acid (b).



butylisocyanide), *viz.* an *M*-helix gives rise to a (+)-sign of optical rotation and a *P*-helix to a (−)-sign, one can conclude that on polymerization (*S*)-PhCH(CH<sub>3</sub>)NC preferentially forms a right-handed helix, *i.e.* the polymerization reaction proceeds diastereoselectively. A similar analysis has been carried out with the help of circular dichroism spectra, in which case the shape of the exciton couplet of the optically active polymer is compared with the shapes of the couplet of (*P*)- and (*M*)-poly(*t*-butylisocyanide). In a few cases it has been possible to determine the degree of chiral induction, *viz.* in the case of isocyanides R(CH<sub>3</sub>)CHNC (R = ethyl, *n*-hexyl, *i*-propyl, *i*-butyl). The highest d.e. was measured for R = *i*-propyl and amounted to 62%.

Novak and an associate have investigated whether the polymerization of racemic mixtures of chiral isocyanides proceeds stereoselectivity, *i.e.* whether the racemic monomer mixture is resolved into all-*R* and all-*S* polymer molecules.<sup>19</sup> To this end enantiomerically pure (*R*)- or (*S*)-PhCH(CH<sub>3</sub>)NC was polymerized with catalyst (17). The polymer subsequently produced displayed a narrow polydispersity index (PDI =  $M_w/M_n = 1.1$ ). In contrast, when the racemic monomer mixture was polymerized the polymer molecular weight distribution was found to be quite broad (PDI = 1.6–1.8). This result, as well as the results from kinetic experiments and experiments with <sup>13</sup>C-enriched isocyanide monomers were taken as evidence that the polymerization of (*R*, *S*)-mixtures is only partly stereoselective.

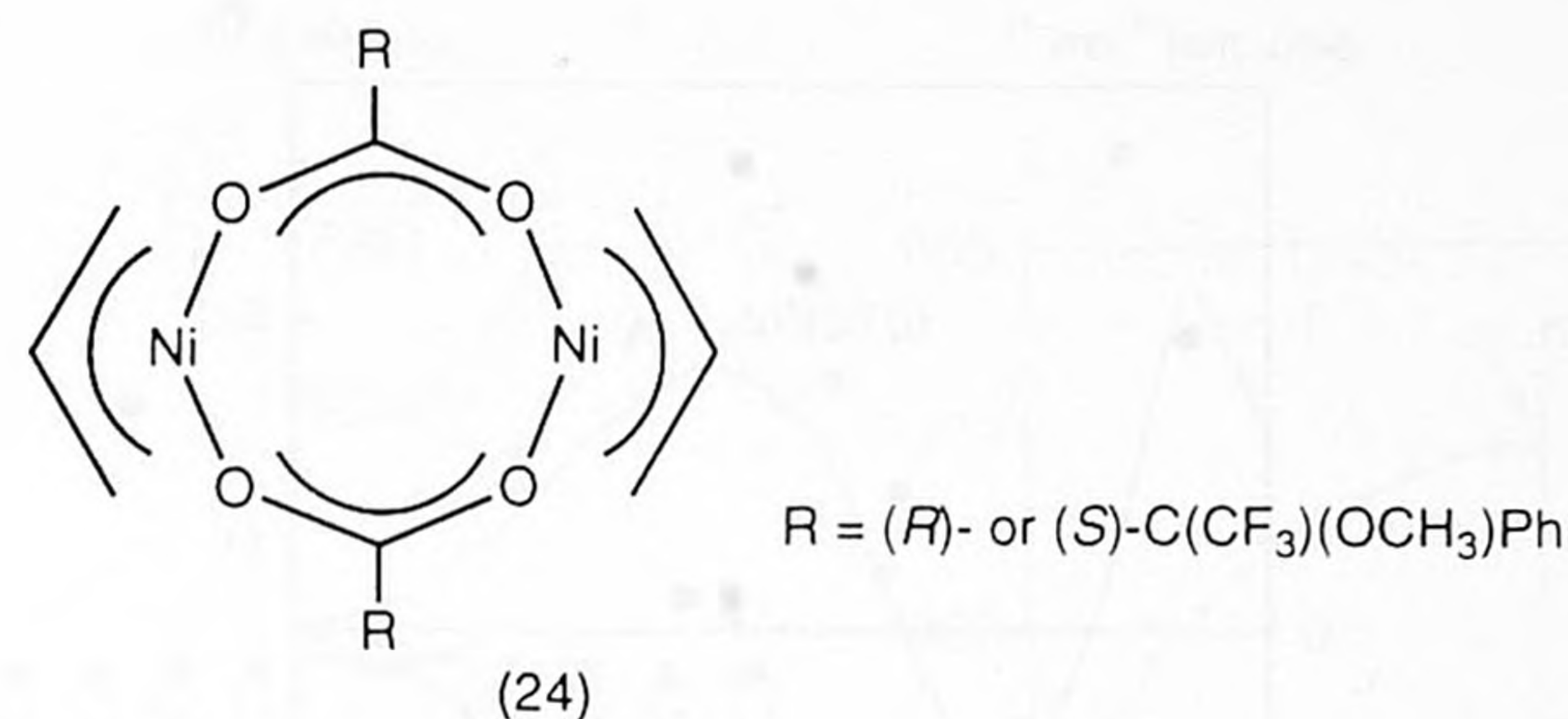


**Figure 3** Model for predicting the helix sense in the polymerization of chiral isocyanides.

The mechanism of the polymerization reaction allows one to predict which helix is generated from an optically active isocyanide. In Figure 3 one of the first intermediates in the polymerization reaction is shown. The nucleophile is denoted by X and the substituents on the chiral carbon atom are ranked according to their sizes, *viz.* S (small), M (medium), and L (large). As mentioned in Section 4, the plane of ligand C<sup>1</sup> is perpendicular to the nickel plane. The substituent L is placed in such a way that the least steric hindrance occurs in the transition state of the first carbon–carbon bond formation reaction, *i.e.* away from the nickel centre. As depicted in Figure 3, attack will occur on C<sup>4</sup> as this is the least sterically hindered side. In this way a right-handed helix is formed. This kind of reasoning has been applied to approximately 20 optically active monomers.<sup>13</sup> In most cases the predicted helix sense was found to be in agreement with the helix sense derived from optical rotation data and circular dichroism spectra. From this result one may conclude that the process of helix selection takes place at the catalytic centre.

## 5.2 Achiral Isocyanides

Helix-sense-selective polymerization of achiral isocyanides has been achieved with optically active catalysts of type (24). Polymerization of the sterically hindered *t*-butylisocyanide with (*R*)-(24) yielded a polymer with an excess of left-handed helices. Likewise (*S*)-(24) gave a polymer with an excess of right-handed helices. The e.e. values were estimated to be in the range of 45–70%. Less sterically encumbered monomers, *e.g.* *p*-methoxy-



phenyl isocyanide, were converted into optically inactive polymers by (*R*)- and (*S*)-(24).<sup>19</sup>

Addition of an optically active initiator to a nickel(II)-isocyanide complex generates a catalyst which can polymerize achiral isocyanides to optically active polymers. Some results obtained for the polymerization of *t*-butyl isocyanide using Ni(CNR)<sub>4</sub>(ClO<sub>4</sub>)<sub>2</sub> and different chiral amines are presented in Table 2.<sup>20</sup> Polymer samples displaying e.e. values up to 85% have been obtained by this procedure. The helix sense that is induced by the chiral initiator can be predicted from the polymerization mechanism by using similar reasoning as described for the polymerization of chiral isocyanides (see Section 5.1).

**Table 2** Enantioselective polymerization of *t*-butyl isocyanide with Ni(CNR)<sub>4</sub>(ClO<sub>4</sub>)<sub>2</sub> and chiral initiators<sup>a</sup>

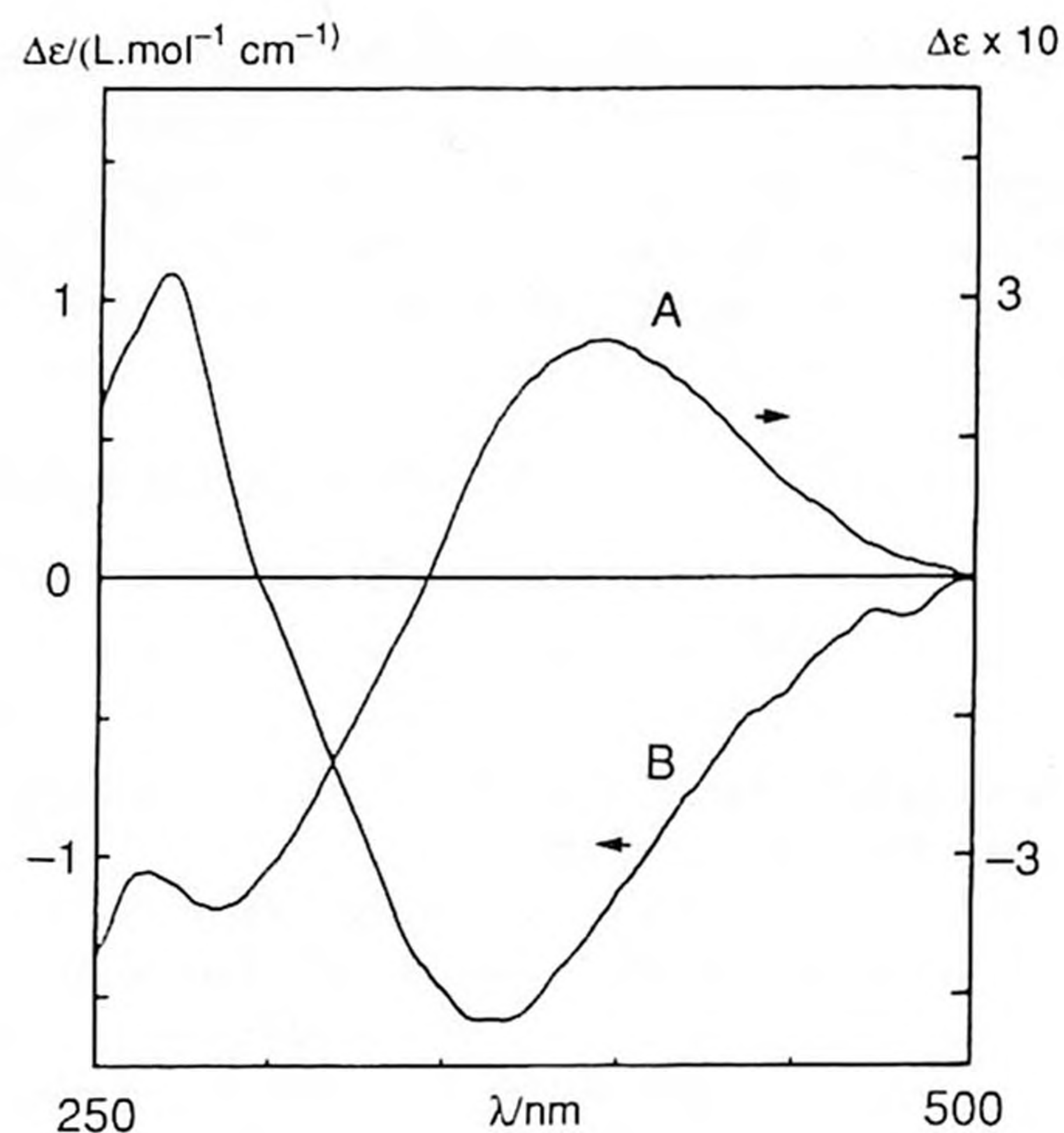
Initiator	e.e.(%)	Helix sense
( <i>S</i> )-C <sub>2</sub> H <sub>5</sub> CH(CH <sub>3</sub> )NH <sub>2</sub>	7	<i>P</i>
L-Prolinol	36	<i>M</i>
L-Alanine methyl ester	47	<i>P</i>
( <i>S</i> )-PhCH(CH <sub>3</sub> )NH <sub>2</sub>	61	<i>P</i>
( <i>S</i> )-PhCH(CH <sub>3</sub> )NH <sub>2</sub> <sup>b</sup>	83	<i>P</i>

<sup>a</sup> R = *t*-C<sub>4</sub>H<sub>9</sub>    <sup>b</sup> R = 2(*t*-C<sub>4</sub>H<sub>9</sub>)C<sub>6</sub>H<sub>4</sub>

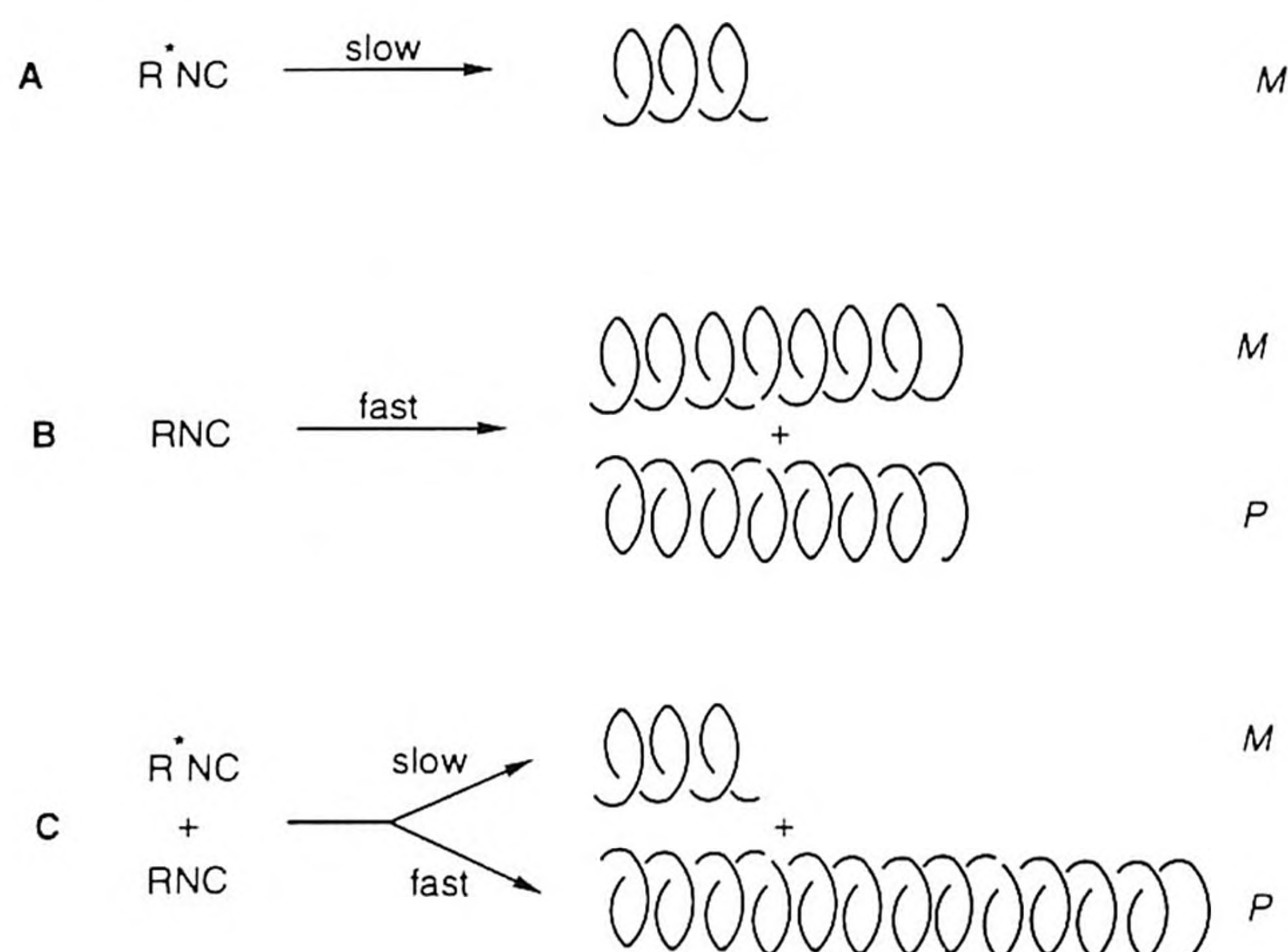
A third procedure for preparing optically active polymers from achiral isocyanides involves the use of bulky optically active co-monomers, *e.g.* esters of (*S*)-2-isocyanoisovaleric acid [(*S*)-*i*-C<sub>3</sub>H<sub>7</sub>CH(COOR)NC, (25)].<sup>21</sup> In the presence of nickel(II) salts these isocyanides slowly polymerize to give homopolymers with predominantly left-handed helices. When an isocyanide (25) is mixed with an achiral isocyanide (see Table 3) and subsequently polymerized with nickel chloride, polymer samples are obtained which consist mainly of the homopolymer of the achiral isocyanide. This homopolymer has a high optical rotation and a helix sense opposite to that of the chiral co-monomer (Table 3 and Figure 4). The mechanism of this unusual reaction is probably as follows. The bulky chiral isocyanide (25) is a slowly polymerizing monomer and forms an *M*-helix (Figure 5A). The achiral isocyanide is a fast-polymerizing monomer and yields a racemic mixture of *P* and *M* helices (Figure 5B). When the chiral isocyanide is co-polymerized with the achiral one, the former has a preference for inclusion into *M*-

**Table 3** Enantioselective polymerization of achiral isocyanides in the presence of optically active isocyanide(25)

R in (RNC) <sub>n</sub>	− [α] <sub>D</sub> <sup>20</sup> (deg)	Helix sense	$\bar{M}_w$
C <sub>6</sub> H <sub>5</sub>	610	<i>P</i>	44 000
4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	520	<i>P</i>	42 000
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	93	<i>P</i>	
<i>n</i> -C <sub>8</sub> H <sub>17</sub>	58	<i>P</i>	35 000
<i>i</i> -C <sub>3</sub> H <sub>7</sub>	105	<i>P</i>	45 000



**Figure 4** CD spectrum of the homopolymer from (25) (curve A) and the polymer obtained from 4-methoxyphenylisocyanide (curve B). Curve A reveals the presence of a left-handed helix, curve B the presence of a right-handed helix.



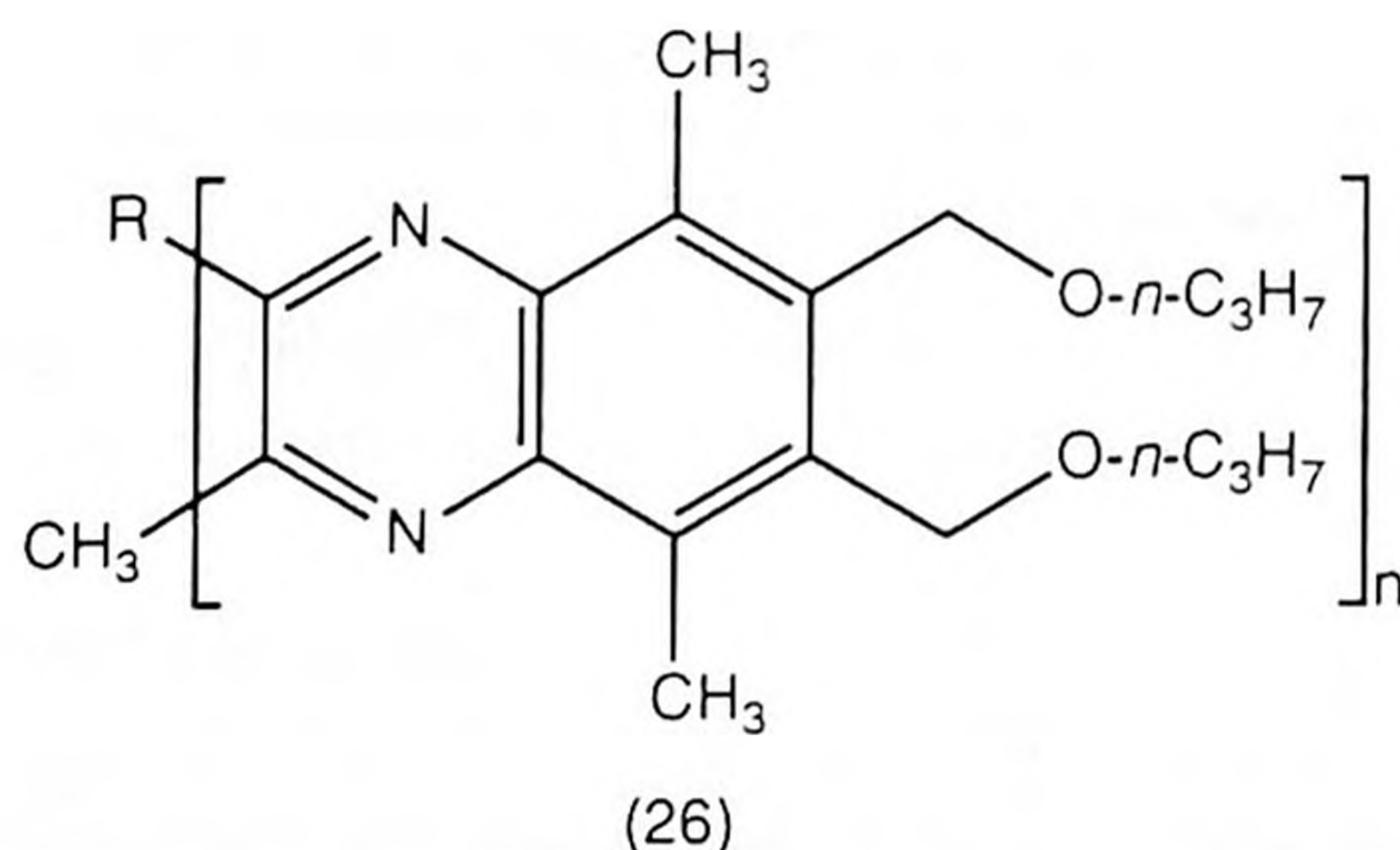
**Figure 5** Mechanism of the enantioselective polymerization of achiral isocyanides in the presence of an optically active co-monomer.

helices and retards the formation of these helices from the latter one. The *P*-helices continue to grow and eventually consume all the achiral monomer (Figure 5C).

Ito and co-workers have described the enantioselective polymerization of 1,2-diisocyanoarenes with optically active palladium(II) catalysts to give helical poly(2,3-quinoxalines), *e.g.* (26). These polymers displayed high optical rotations and large Cotton effects in their CD spectra, suggesting that they have helical conformations of one particular sense.<sup>22</sup>

## 6 Biomimetic Macromolecular Chemistry

For a long time scientists have been fascinated by enzymes and intrigued by the fact that these biopolymers can fulfil so many



functions and catalyse such a diversity of reactions. Unravelling the principles that underlie the action of enzymes continues to be a challenge for chemists and biochemists, and impressive progress towards this goal has been made in recent years. Much work is focused on the biopolymers themselves, but also on low molecular weight model compounds which can give insight into the details of the catalytic processes involved. Comparatively little attention has been given to synthetic polymers as biomodels which is surprising given the fact that many molecules and molecular systems in nature have macromolecular dimensions. In this section some applications of polymers of isocyanides in the field of biomimetic chemistry will be discussed. These polymers are versatile building blocks for the construction of biomodels because they (i) are helical, (ii) have a well-defined structure, and (iii) can be synthesized in great variety from easily accessible amines and amino acids.

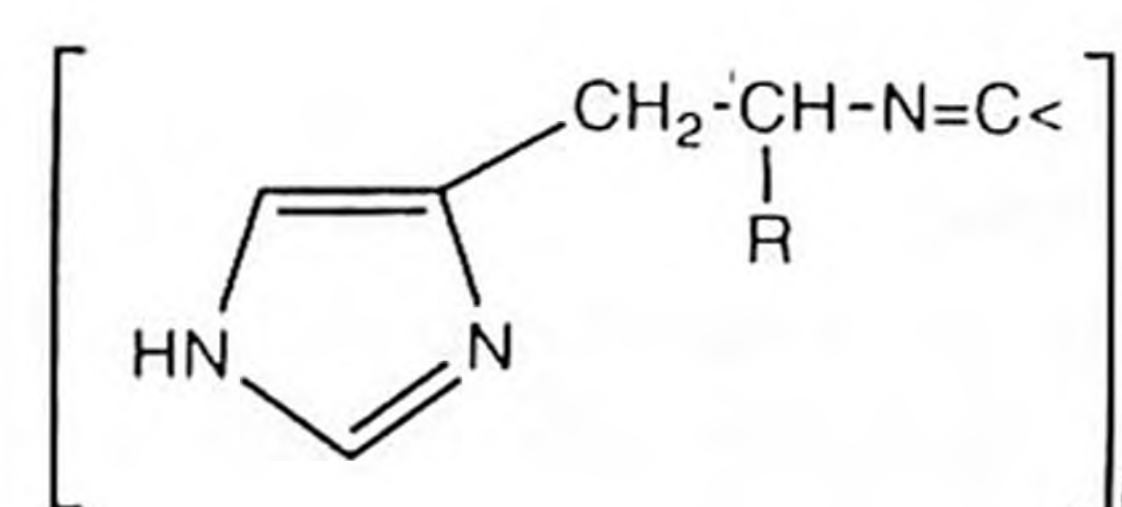
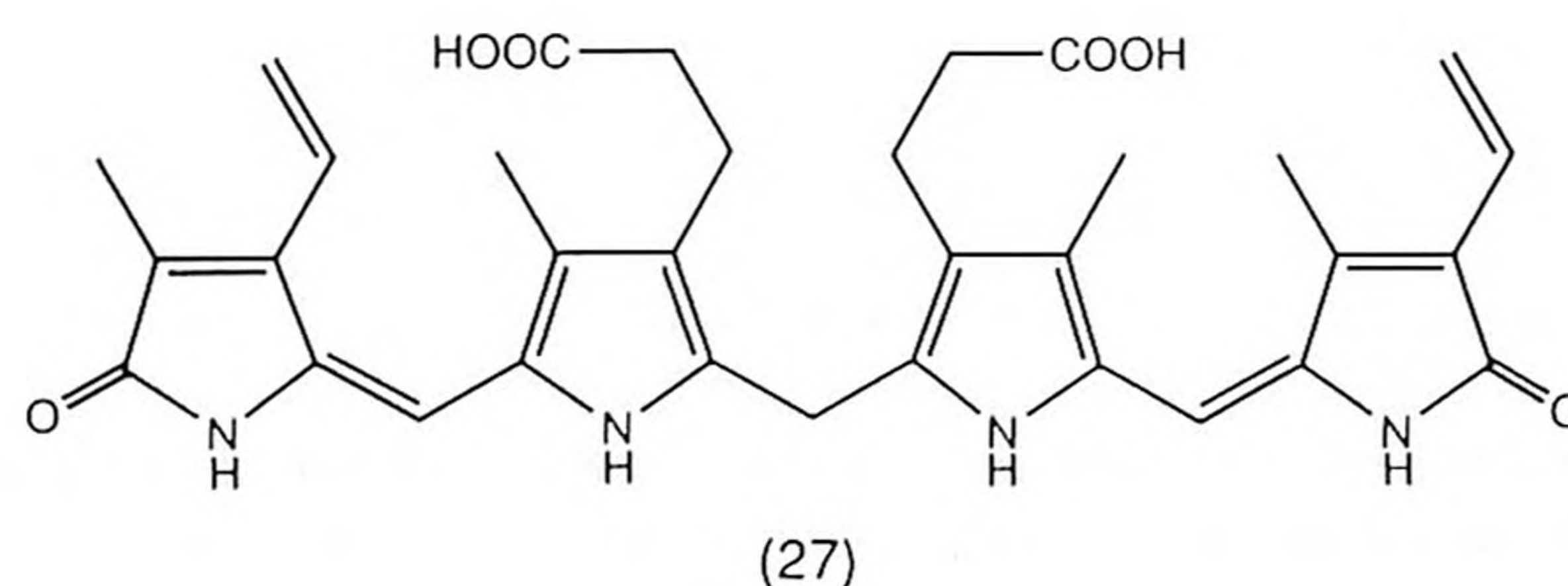
### 6.1 Bilirubin Binding

Bilirubin (27) is the end product of heme catabolism in man and most animals and is ultimately excreted in bile.<sup>23</sup> The compound has a low solubility in aqueous media. Almost all of the bilirubin transported in the blood is tightly bound to serum albumin. The nature of this binding is unknown. Salt bridges with charged residues of histidine and other amino acids as well as hydrogen bonds have been thought to be involved in the binding process.<sup>23</sup>

Two polymers of isocyanides poly(carbylhistidine) (28) and poly(carbylhistamine) (29) have been synthesized and used to study the type of binding interactions with bilirubin.<sup>24</sup> These poly(isocyanides) have appreciably different  $pK_a$  values:  $pK_a(28) = 9.4$  and  $pK_a(29) = 5.2$ . Addition of bilirubin at the pH of blood plasma (pH = 7.3) to poly(carbylhistidine) and poly(carbylhistamine) leads to complex formation with the latter polymer, but not with the former one. Bilirubin is an unstable compound, but complexed to (29) it can be kept for prolonged periods of time. Spectroscopic and other studies indicate that approximately one molecule of bilirubin is bound per helical turn of poly(carbylhistamine). At pH 7.3 bilirubin is a dianion and the observation that this dianion binds to the neutral (29) and not to the protonated (28) suggests that in the case of serum albumin, salt bridges to charged histidine residues do not play a major role. Instead, hydrogen bonding interactions are more likely to be operative, *viz.* between the neutral imidazole groups and the lactam rings of bilirubin.

### 6.2 Artificial Ion Channel

The unassisted transport of ions through cell membranes is very slow: the reported permeation coefficient for  $K^+$  is  $7 \times 10^{-13} \text{ cm s}^{-1}$ .<sup>25</sup> Generally, there are two ways by which nature facili-

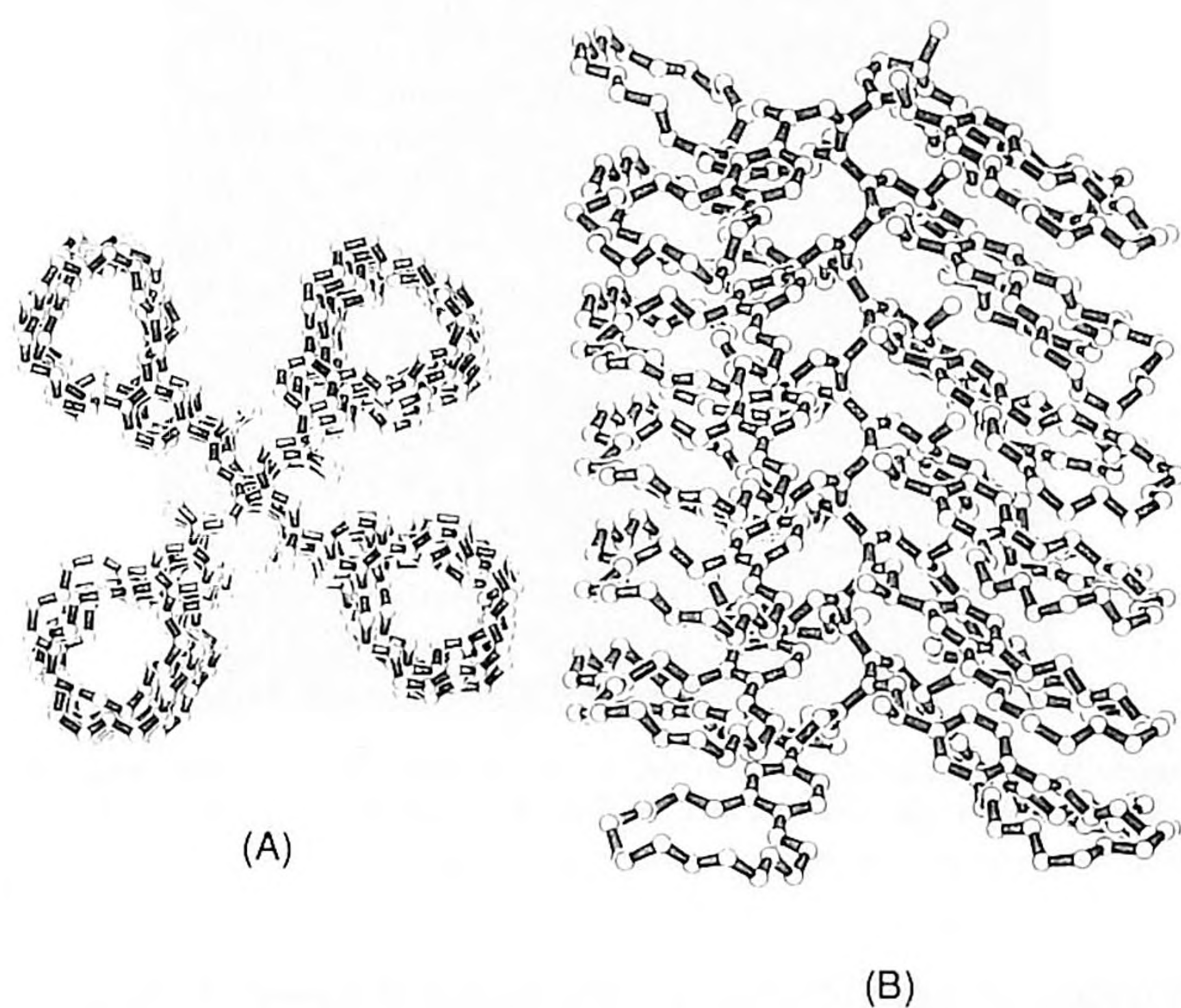


(28) R = COOH

(29) R = H

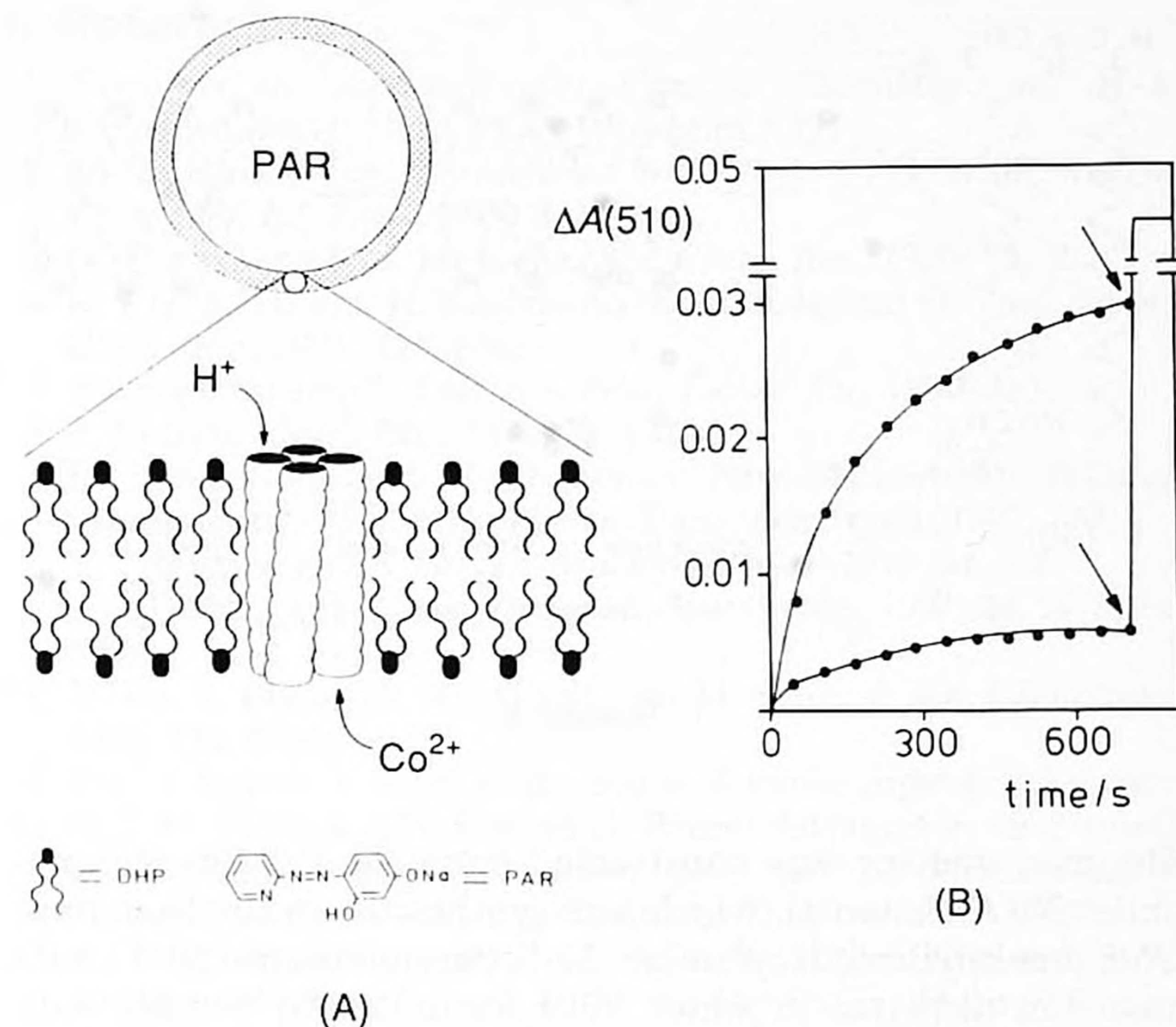
tates ion transport across a bilayer membrane.<sup>25</sup> One way is by carrier molecules, *e.g.* the antibiotics Valinomycin and Nonactin. A second, more frequently encountered mode is by proteins that form a transmembrane ion channel, the archetype being Gramicidin A. Several attempts have been made to design and synthesize artificial systems that mimic the latter mode of ion transport. Notable are the studies by Fuhrhop, Fyles, and Lehn.<sup>26</sup>

We have been interested in constructing artificial ion channels by stacking ring-like molecules, *e.g.* crown ether rings. The main problem is how to interconnect these macrocyclic rings. Piling them stepwise *via* lateral appendages is very difficult to achieve. We have solved this problem by anchoring the crown ether rings to a rigid poly(isocyanide) support.<sup>27</sup> Isocyanides containing crown ether rings of different sizes were synthesized and polymerized with nickel chloride to give polymers of type (11). As a result of the  $1_4$ -helical structure of the polymer backbone, the crown ether rings in (11) are positioned on top of each other and form 4 channels which run parallel to the polymer helix axis (see Figure 6). The molecular weight of the polymers amounted to 4000–20000 which corresponds to channel lengths of 10 to 50 Å. The metal ion binding properties of the channels were found to be greater than those of low-molecular-weight model compounds. This difference is explained by the fact that in the channels the metal ions can be sandwiched between consecutive crown ether rings, which favours binding. In the model compounds such sandwiching is not possible.



**Figure 6** Calculated structure of a poly(*a*-phenylethylisocyanide) with 18-crown-6 rings, top view (A) and side view (B). (Reproduced, with permission, from reference 27b.)

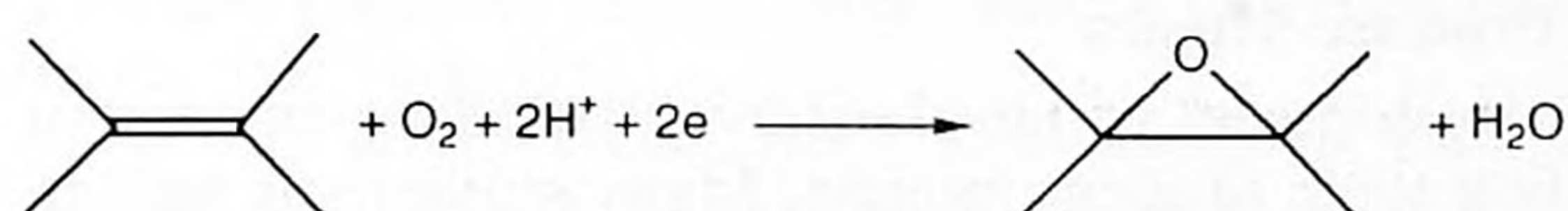
The ion channels were incorporated into bilayers of dihexadecyl phosphate (DHP) vesicles and ion transport across the vesicle bilayer was studied in the following way (Figure 7A). The dye 4-(2-pyridylazo)resorcinol mono sodium salt (PAR) was occluded in the inner aqueous compartment of the vesicles. This dye forms coloured complexes with cobalt(II) ions. These ions were added to the vesicle dispersions and the increase in the absorption of the cobalt–PAR complex in the UV–vis was recorded as a function of time. In the presence of channels, transport of cobalt ions was observed, without channels this transport was very small or absent (Figure 7B). Permeability coefficients were determined to be in the range of  $5 \times 10^{10} \text{ cm s}^{-1}$ . The activation energy for cobalt ion transport was calculated from experiments carried out at different temperatures, and amounted to  $E_a = 24 \text{ kJ mol}^{-1}$ . This number is consistent with a pore mechanism for the ion translocation process (Figure 7A). A very similar value of  $E_a$  has been found for Gramicidin A ( $E_a = 20.5\text{--}22.5 \text{ kJ mol}^{-1}$ ).



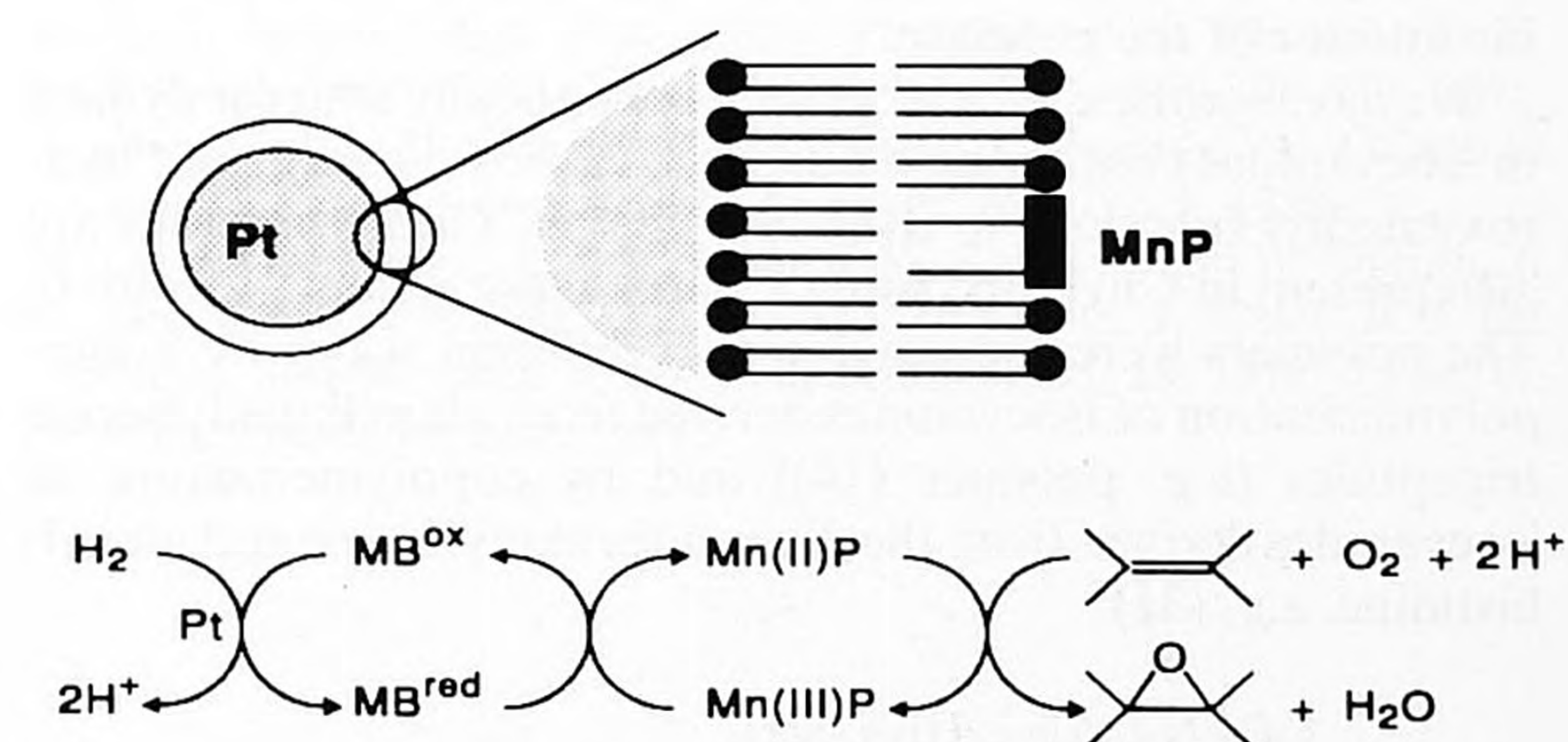
**Figure 7** Facilitated transport of cobalt ions across bilayers of dihexadecyl phosphate (DHP) vesicles by channel compound (11) (A). Plots of the change in absorbance of the cobalt (II)–PAR complex at 510 nm *versus* time for vesicles with (upper curve) and without (lower curve) channel compound (11). The arrows indicate the addition of a reagent (Triton X-100) which destroys the vesicles (B). (Reproduced, with permission, from references 27a and 27b.)

### 6.3 Cytochrome P-450 Mimic

The Cytochrome P-450-dependent mono-oxygenases are membrane-bound enzymes which catalyse a great variety of reactions, among which is the epoxidation of alkenes by molecular oxygen.<sup>28</sup> The active centre of the enzymes contains an iron(III) protoporphyrin IX and an axial ligand. After being reduced to iron(II) this centre binds and cleaves molecular oxygen, whereupon water and a high-valent iron–oxo complex are formed. The latter species transfers its oxygen to the substrate molecule. The electrons required in the process are provided by the cofactor NADPH *via* a coupled electron-transferring enzyme system.<sup>28</sup>

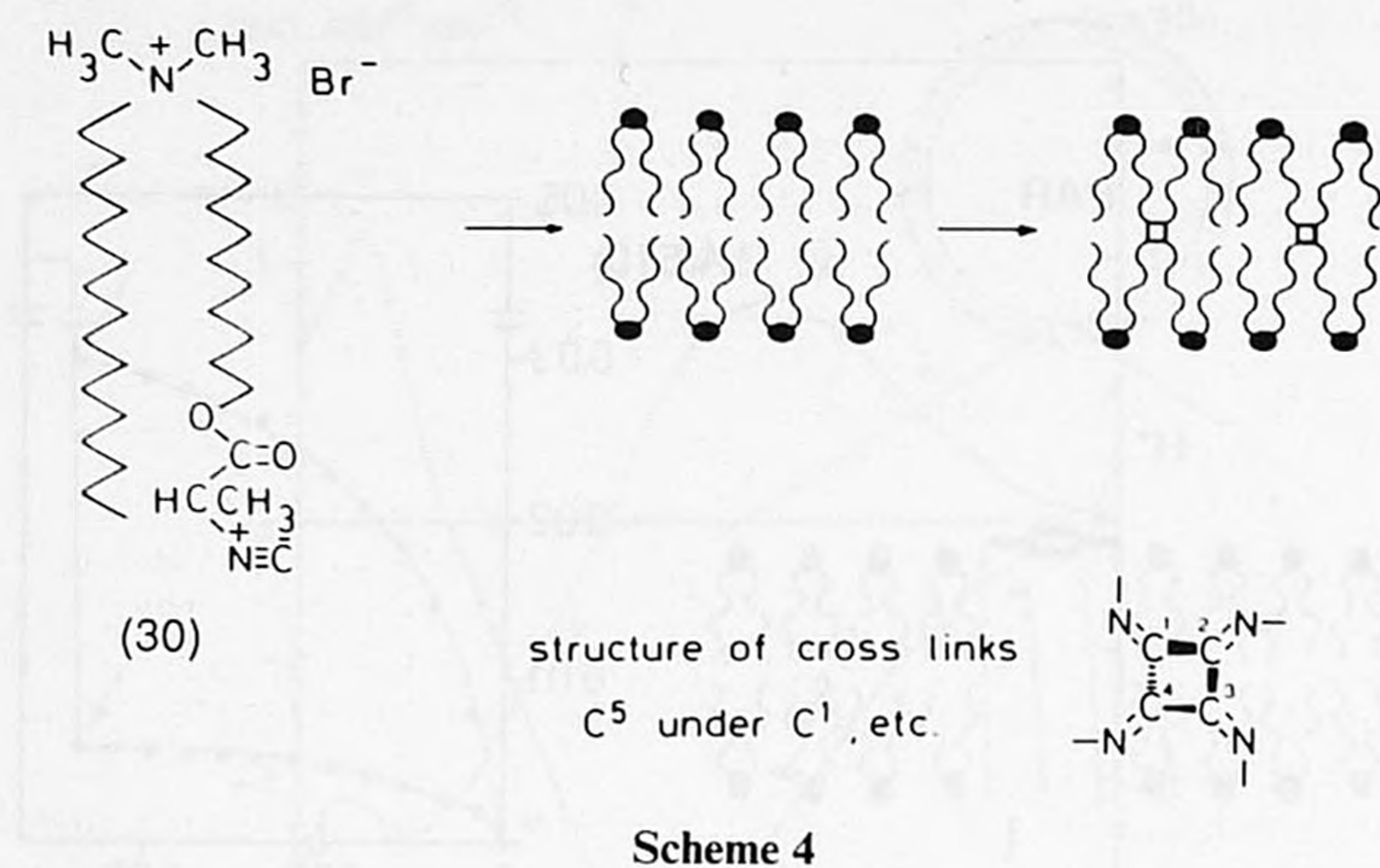


We have developed a synthetic model of Cytochrome P-450 which incorporates all the features of the natural system.<sup>29</sup> The most important part is a microreactor of stabilized vesicles which holds the components of the catalytic system, *viz.* a bilayer-bound manganese(III) porphyrin, an electron donor: colloidal Pt (incorporated in the interior of the vesicles) and  $\text{H}_2$ , and an electron carrier (methylene blue), which shuttles electrons from the colloidal Pt to the metalloporphyrin (Figure 8).



**Figure 8** A membrane-bound Cytochrome P-450 mimic based on polymerized vesicles from isocyanosurfactant (30). Pt is colloidal platinum,  $\text{MB}^{\text{ox}}$  and  $\text{MB}^{\text{red}}$  are the oxidized and reduced forms of the electron carrier methylene blue, and MnP is manganese(III) porphyrin.





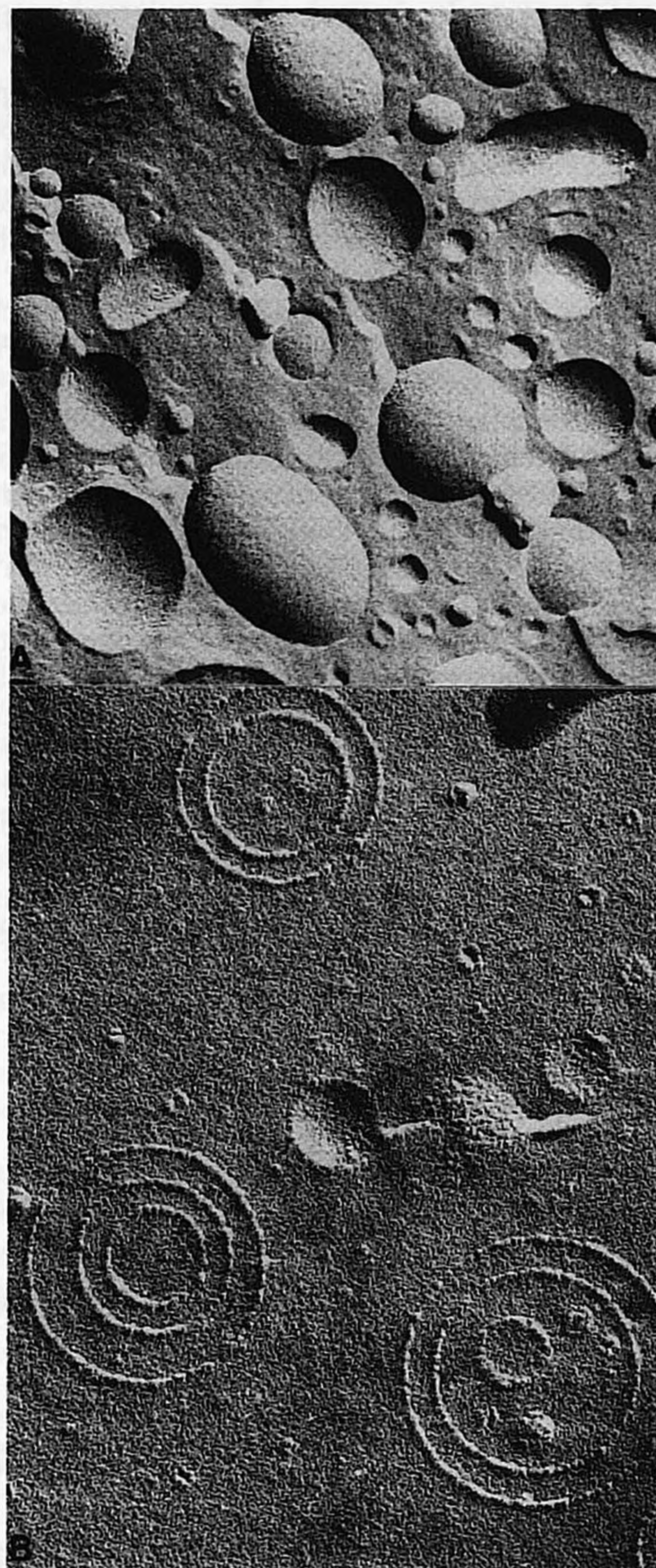
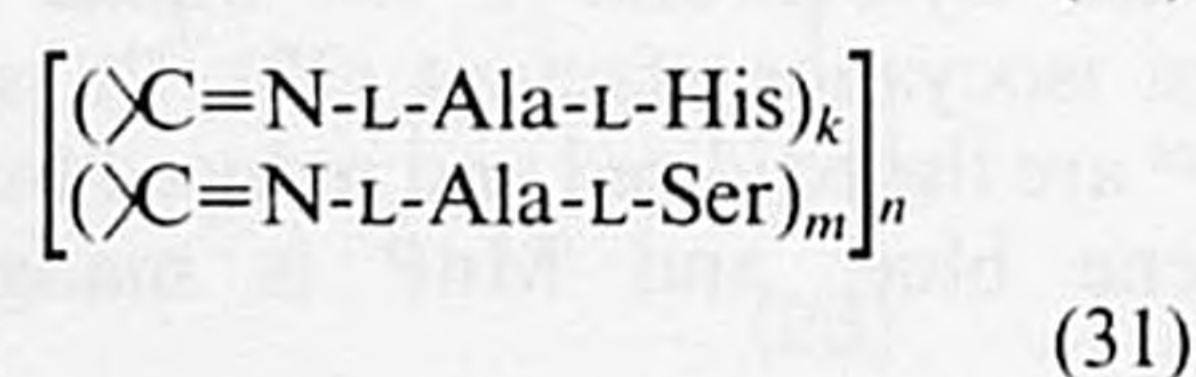
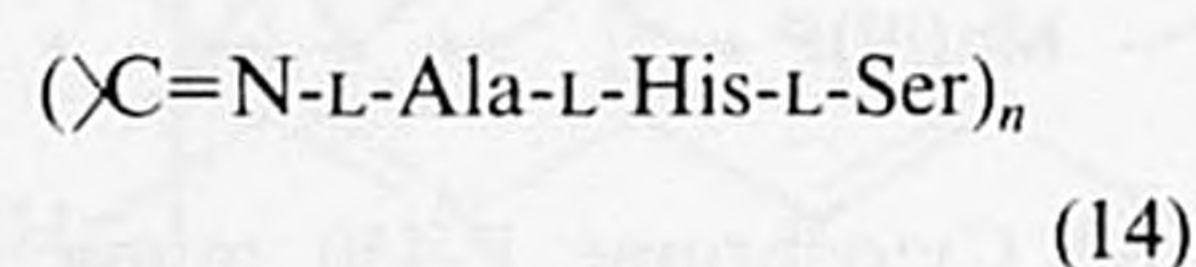
The microreactor was constructed from the isocyno-amphiphile (30) (Scheme 4), which was synthesized in the four steps from dimethylhexadecylamine, 11-bromoundecanol, and L-alanine. On dispersal in water, (30) forms closed vesicles with diameters of approximately 250 nm. These vesicles can be stabilized by polymerization of the isocyanate functions in the bilayers with nickel capronate.<sup>29</sup> The polymerized vesicles retain their structure – as was shown by electron microscopy, osmotic experiments, and fluorescent techniques. The degree of polymerization of the isocyanate surfactants within the bilayer was estimated to be approximately 75. Interestingly, freeze-fracture electron micrographs of the polymerized vesicles of (30) provided direct evidence that the bilayer halves were cross-linked: instead of the usual pattern of concave and convex half spheres observed for non-polymerized systems (Figure 9A), circles and ellipses were visible (Figure 9B). An explanation of the latter phenomenon is given in reference 29.

The membrane-bound Cytochrome P-450 mimic was shown to epoxidize water-soluble (2,5-dihydrofuran) as well as water-insoluble (styrene) alkenes at room temperature, with molecular oxygen as the oxidant. Turnover numbers are in the range of 1.5–8 mol alkene/mol catalyst.h, which is one hundredth of the activity of the natural enzyme system.

#### 6.4 Protease Mimics

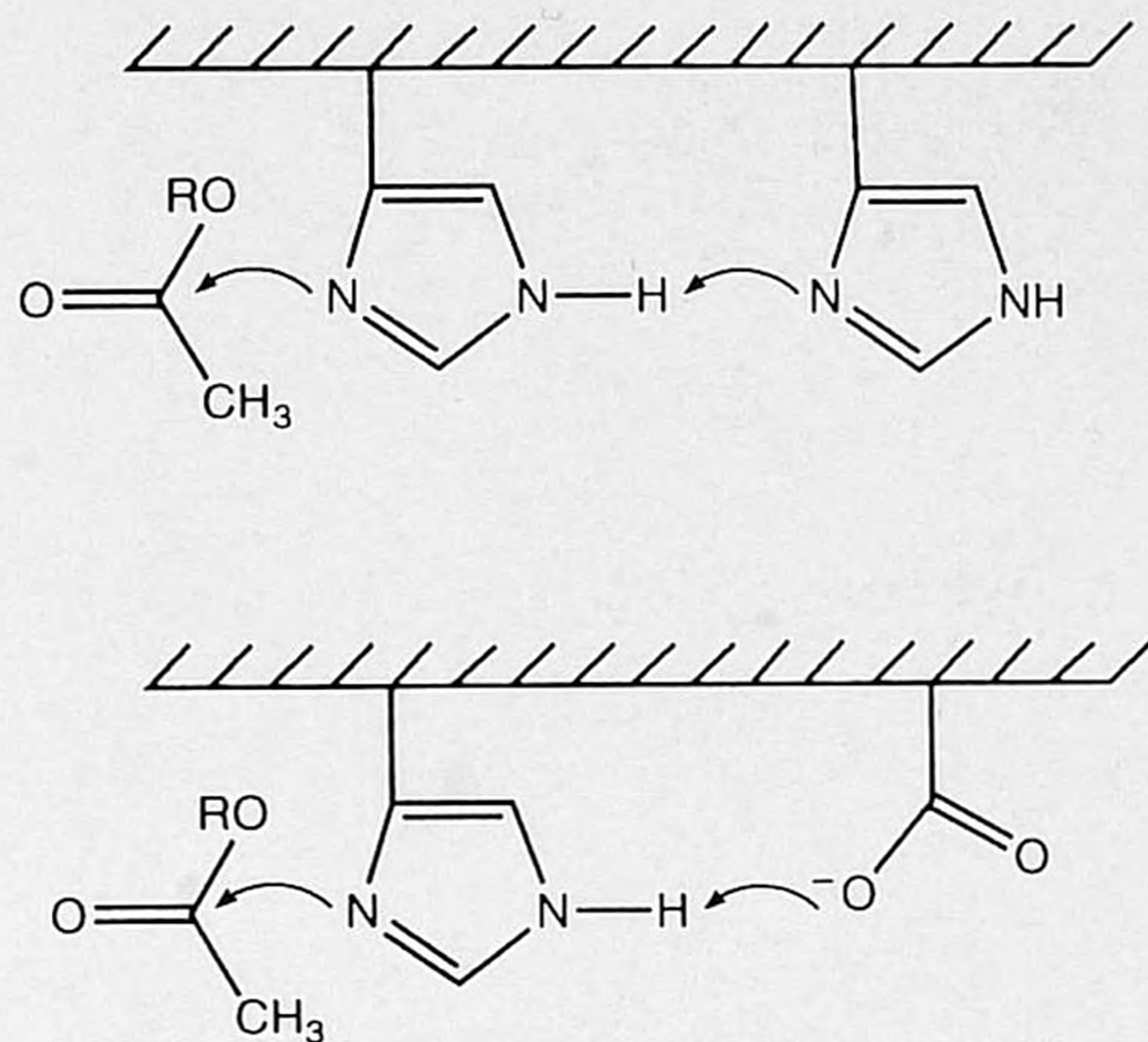
The development of novel catalysts based on enzymes is currently a topic of great interest. Many studies are dealing with catalytic systems mimicking proteases.<sup>30</sup> The reason for this choice is that the principles of protease action, exemplified by Chymotrypsin and Elastase, have been studied thoroughly and are now starting to be understood.<sup>30</sup> For the construction of an artificial proteolytic catalyst the following features are thought to be required: (i) a nucleophile and a proton-transfer system, organized in such a way to complement the structure of the substrate, (ii) a water-soluble chiral platform to anchor the catalytic functions and to provide a substrate binding site, and (iii) a hydrophobic microenvironment to mimic the hydrophobic interior of the protease.

We have synthesized a large series of optically active polymers of isocyanides containing imidazolyl, carboxylic acid, and hydroxymethyl functions in their side chains. These functions are also present in Chymotrypsin ('Charge relay system', feature i). The polymers were prepared in two different ways: by homopolymerization of isocyanides derived from alanylhistidylserine tripeptides (*e.g.* polymer (14)) and by copolymerization of isocyanides derived from the dipeptides alanylserine and alanylhistidine, *e.g.* (31).

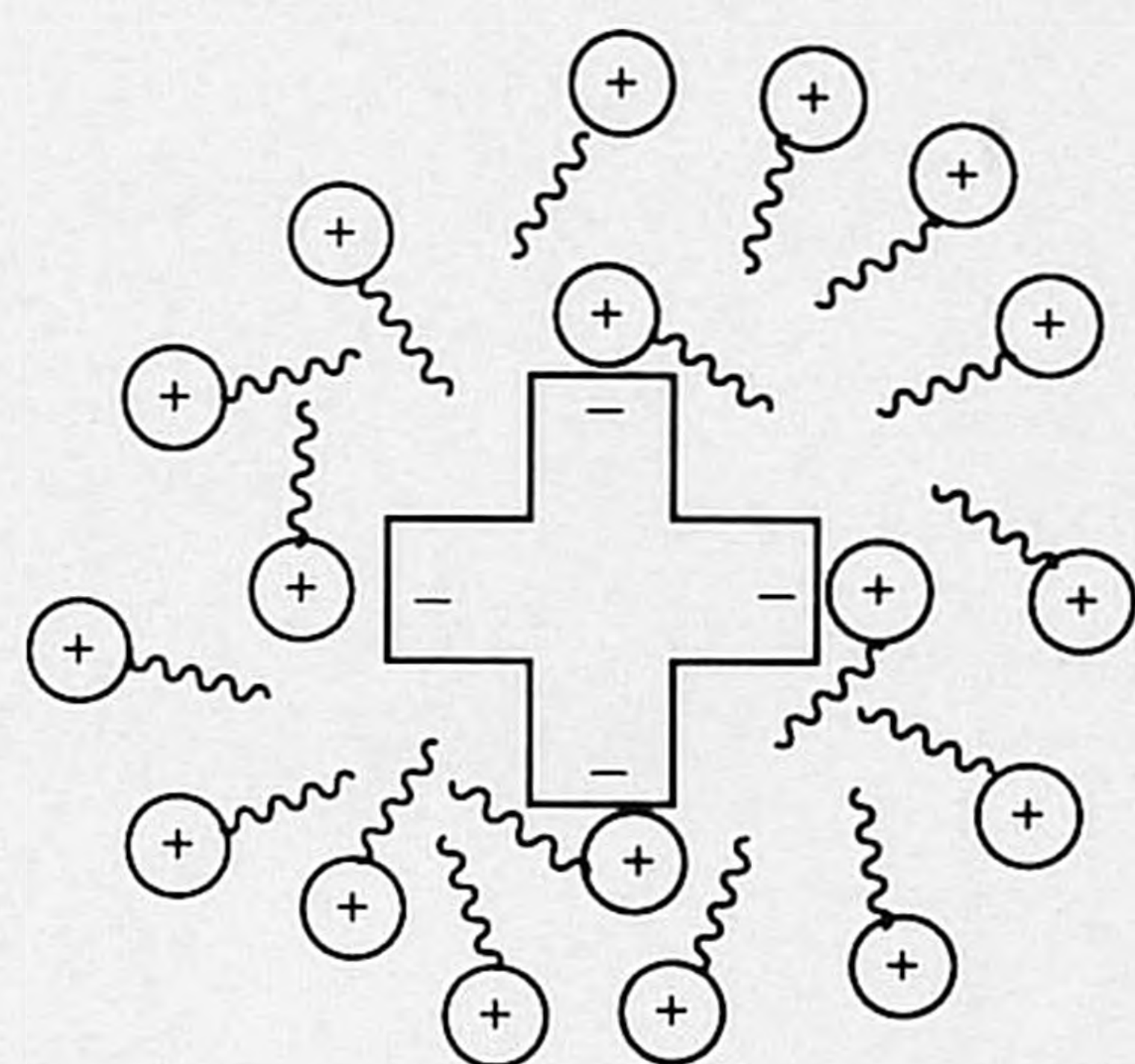


**Figure 9** Freeze-fracture electron micrographs of unpolymerized (A) and polymerized vesicles (B) from isocyanosurfactant (30). (Reproduced, with permission, from reference 29b).

Polymers of type (14) and (31) are soluble in water and have an excess of one helix sense (feature ii).<sup>31</sup> They were used as catalysts in the hydrolysis of achiral and chiral nitrophenyl esters. Extensive kinetic studies revealed that the hydroxymethyl functions had no appreciable effect on the catalysis. The homopolymers and copolymers showed markedly higher activities than the corresponding low-molecular weight compounds. This enhancement was ascribed to cooperative effects involving interactions between imidazolyl groups and neighbouring imidazolyl and carboxylate groups (Scheme 5). The activities could be further enhanced by adding positively charged surfactants, *e.g.* cetylpyridinium chloride or cetylundecyldimethylammonium bromide. Negatively charged surfactants did not show any effect. Positively charged surfactants arrange themselves around the negatively charged polymer molecules (Figure 10) and in this way create a hydrophobic pseudophase which is favourable for catalysis (feature iii), *viz.*, by changing the  $pK_a$  values of the imidazolyl groups and by increasing the concentration of substrate molecules in the vicinity of these groups.<sup>31</sup> The polymer-surfactant complexes displayed small enantioselectivities ( $k_L/k_D = 3$ ) in the hydrolysis of chiral amino acid esters. Higher enantioselectivity ratios were obtained when polymerized isocyanosurfactants of type (10) were combined with free (*i.e.* not polymer-bound) tripeptide catalysts. In this



Scheme 5



**Figure 10** Structure of the complex between a negatively charged poly(isocyanide) with tripeptide side chains and positively charged surfactant molecules.

case the enantioselectivity ratios amounted to  $k_L/k_D = 33$ .<sup>31</sup> Apparently, a polymer-anchored surfactant in combination with a free peptide catalyst is more effective in accomplishing enantioselectivity in the ester hydrolysis reaction than the combination of a polymer-anchored peptide catalyst and a free surfactant.

## 7 Concluding Remarks

Compared to other polymers, poly(isocyanides) have received little attention in the past, despite the fact that this class of polymers has been known since the 1970s. We hope to have shown in this article that poly(isocyanides) have a rich chemistry and deserve further study by organic chemists and polymer chemists. New and interesting applications can be foreseen for these compounds, in particular in the promising areas of biomimetic chemistry and supramolecular chemistry.

*Acknowledgment.* The author warmly thanks Dr. Wiendelt Drenth, Emeritus Professor of Organic Chemistry at the University of Utrecht, for his invaluable contributions to the field described in this article.

## 8 References

- 1 'Frontiers in Supramolecular Organic Chemistry', ed. H.-J. Schneider and H. Dürr, VCH, Weinheim, 1991.
- 2 (a) M. Farina, *Top. Stereochem.*, 1987, **17**, 1. (b) G. Wulff, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 21.
- 3 W. Drenth and R. J. M. Nolte, *Acc. Chem. Res.*, 1979, **12**, 30.
- 4 K. Ute, K. Hirose, H. Kashimoto, K. Hatada, and O. Vogl, *J. Am. Chem. Soc.*, 1991, **113**, 6305.
- 5 Y. Okamoto and E. Yashima, *Prog. Polym. Sci.*, 1990, 263.
- 6 F. Millich, *Chem. Rev.*, 1972, **72**, 101.
- 7 R. J. M. Nolte and W. Drenth in 'New Methods for Polymer Synthesis', ed. W. J. Mijs, Plenum Press, New York, 1992, 273.
- 8 T. J. Deming and B. Novak, *Macromolecules*, 1991, **24**, 326.
- 9 T. J. Deming and B. M. Novak, *Macromolecules*, 1991, **24**, 5478 and 6043.
- 10 Y. Ito, E. Ihara, M. Murakami, and M. Shiro, *J. Am. Chem. Soc.*, 1990, **112**, 6446.
- 11 P. C. J. Kamer, R. J. M. Nolte, and W. Drenth, unpublished results.
- 12 R. J. M. Nolte and W. Drenth in 'Recent Advances in Mechanistic and Synthetic Aspects of Polymerization', ed. M. Fontanille and A. Guyot, D. Reidel Publishing Company, Dordrecht, 1987, 451.
- 13 A. J. M. van Beijnen, R. J. M. Nolte, A. J. Naaktgeboren, J. W. Zwikker, W. Drenth, and A. M. F. Hezemans, *Macromolecules*, 1983, **16**, 1679.
- 14 C. J. M. Huige, Thesis, Utrecht, 1985.
- 15 (a) R. J. M. Nolte, A. J. M. van Beijnen, and W. Drenth *J. Am. Chem. Soc.*, 1974, **96**, 5932. (b) A. J. M. van Beijnen, R. J. M. Nolte, and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, 1980, **99**, 121.
- 16 C. Kollmar and R. Hoffmann, *J. Am. Chem. Soc.*, 1990, **112**, 8230.
- 17 C. J. M. Huige, A. M. F. Hezemans, R. J. M. Nolte, and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, 1992, **112**, 33.
- 18 (a) M. M. Green, R. A. Gross, F. C. Schilling, K. Zero, and Ch. Crosby III, *Macromolecules*, 1988, **21**, 1839. (b) P. C. J. Kamer, W. Drenth, and W. Drenth, *Polym. Prepr.*, 1989, **30**, 418.
- 19 T. J. Deming and B. M. Novak, *J. Am. Chem. Soc.*, 1992, **114**, 4400 and 7926.
- 20 P. C. J. Kamer, R. J. M. Nolte, and W. Drenth, *J. Am. Chem. Soc.*, 1988, **110**, 6818.
- 21 P. C. J. Kamer, M. C. Cleij, R. J. M. Nolte, T. Harada, A. M. F. Hezemans, and W. Drenth, *J. Am. Chem. Soc.*, 1988, **110**, 1581.
- 22 Y. Ito, E. Ihara, and M. Murakami, *Angew. Chem.*, 1992, **104**, 1508.
- 23 (a) R. Schmid in 'Jaundice', ed. C. A. Goresky and M. M. Fischer, Plenum, New York, 1975. (b) J. Jacobsen, *Int. J. Peptide Protein Res.*, 1977, **9**, 235.
- 24 J. M. van der Eijk, R. J. M. Nolte, V. E. M. Richters, and W. Drenth, *Biopolymers*, 1980, **19**, 445.
- 25 'Membrane Transport', ed. S. L. Bonting and J. J. H. M. de Pont, Elsevier, New York, 1981.
- 26 (a) J.-H. Fuhrhop, U. Liman, and V. Koesling, *J. Am. Chem. Soc.*, 1988, **110**, 6840. (b) V. E. Carmichael, P. J. Dutton, T. M. Fyles, T. D. James, J. A. Swan, and M. Zojaji, *J. Am. Chem. Soc.*, 1989, **111**, 767. (c) M. J. Pregel, L. Jullien, and J. M. Lehn, *Angew. Chem.*, 1992, **104**, 1695.
- 27 (a) U. F. Kragten, M. F. M. Roks, and R. J. M. Nolte, *J. Chem. Soc., Chem. Commun.*, 1985, 1275. (b) M. F. M. Roks and R. J. M. Nolte, *Macromolecules*, 1992, **25**, 5398.
- 28 R. E. White and H. J. Coon, *Annu. Rev. Biochem.*, 1980, **49**, 315.
- 29 (a) J. van Esch, M. F. M. Roks, and R. J. M. Nolte, *J. Am. Chem. Soc.*, 1986, **108**, 6093. (b) M. F. M. Roks, H. G. J. Visser, J. W. Zwikker, A. J. Verkleij, and R. J. M. Nolte, *J. Am. Chem. Soc.*, 1983, **105**, 4507.
- 30 (a) J. Drenth, *Recl. Trav. Chim. Pays-Bas*, 1980, **99**, 185. (b) T. Kunitake and Y. Okahata, *Adv. Polym. Sci.*, 1976, **20**, 159. (c) H. Dugas and C. Penney, 'Bio-organic Chemistry, A Chemical Approach to Enzyme Action', Springer, New York, 1989.
- 31 (a) H. G. J. Visser, R. J. M. Nolte, J. W. Zwikker, and W. Drenth, *J. Org. Chem.*, 1985, **50**, 3133 and 3138. (b) H. G. J. Visser, R. J. M. Nolte, and W. Drenth, *Macromolecules*, 1985, **18**, 1818. (c) M. C. Cleij, Thesis, Utrecht, 1989.