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Excursions of Synthetic Organic Chemists to the World of Oligomers and Polymers

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Abstract: The activities of a group devoted to organic synthesis in the field of polymer and oligomer chemistry have led to new types of dendritic cross-linking compounds for the polymerization of styrene to give high-quality materials. In addition the synthesis of uniform ('monodisperse'), high-molecular weight oligomers of 3-hydroxybutanoic acid provided samples for investigations to prove the hypothesis that polyhydroxybutyrates are natural ion-channel components in living organisms. Oligomers of β-amino acids were prepared and have been shown to form all the secondary structures known from natural peptides and proteins (composed of α-amino acids), *i.e.* helices, pleated sheets, turns, hair pins and stacks with properties differing fundamentally from those of the natural analogs.

Keywords: Dendritic cross-linkers · Oligo-(3-hydroxybutanoates) · β-Peptides · Polymer-bound chiral ligands · Secondary structures

Introduction

Originally, our group had been dedicated almost entirely to the development of synthetic methodology: umpolung of reactivity [1], chemistry of organo-sulfur and -selenium derivatives [2], of nitro-aliphatic compounds [3], of Li-enolates [4] and Li-carbenoids [5], and of titanium reagents [6], chiral building blocks for organic synthesis, self-regeneration of stereocenters [7], TADDOLs as chiral auxiliary system [8], as well as applications to natural product synthesis (macrolides and macrodiolides) [9]. Fifteen years ago, our work on the use of poly(hydroxybutanoate) (PHB) as a source of (*R*)-3-hydroxybutanoic acid (HB) for syntheses of enantiomerically pure compounds (EPC) led to the preparation of oligo(3-hydroxybutanoates) (OHB) and triggered our interest in the biology of the low-molecular-weight polymer cPHB [10]. This work, in turn, led us to investigate the NH-analogs of OHBs, the oligo-β-peptides [11] since 1995 and most recently also the γ-peptides [12]. Investigations of the reactivity of hydroxybutanoic acid also induced our entry into the field of chiral dendritic macromolecules [13] (we strictly distinguish between oligomers or macromolar compounds – consisting of uniform molecules – on the one hand, and polymers – consisting of an ensemble of particles with a Gaussian distribution of molecular weights, on the other hand). Finally, we started a program five years ago on self-made polymer-bound chiral catalysts [14].

In the following sections we will describe a few current results in the three areas of i) polymer-bound catalysts, ii) oligo(hydroxybutanoates), and iii) oligo-β-peptides.

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From TADDOL to a New Way of Cross-Linking Styrene Polymerization

TADDOL is an abbreviation of horrible systematic nomenclature for chiral diols accessible in as few as two steps from tartaric acid [15], and – more importantly – TADDOL stands for a chiral auxiliary system of incredibly broad applicability (an extensive review article on TADDOLs has just appeared [8]), see Fig. 1. In an effort to immobilize TADDOL for multiple use as a ligand for generating chiral Lewis acids [14] it occurred to us that we could attach to TADDOL so-called Fréchet branches [16] with peripheral styryl groups and use the corresponding dendrimer as cross-linker for styrene polymerization. The resulting polymer (Fig. 2a) formed in a suspension copolymerization with styrene consisted of beads with most unusual properties [17]: i) > 85% of the TADDOL moieties in the beads could be loaded with titanate, giving highly active catalysts for various enantioselective reactions; ii) the reactions of the Ti-TADDOLates inside the beads were diffusion-controlled; iii) the Et_2Zn addition to benzaldehyde gave 1-phenylpropanol with a higher rate when carried out with the polymerized TADDOLate than with its monomeric styryl substituted precursor; iv) the beads with dendritically incorporated TADDOLate could be used 20 and more times in the Et_2Zn-to-PhCHO addition with no detectable decrease of enantioselectivity or of swelling ability after the numerous operations involved in this multiple application [17][18]. The 'dendrimer effect' on performance of chiral catalysts has recently been confirmed with BINOL [19] and Salen derivatives [20] (Fig. 2b, c).

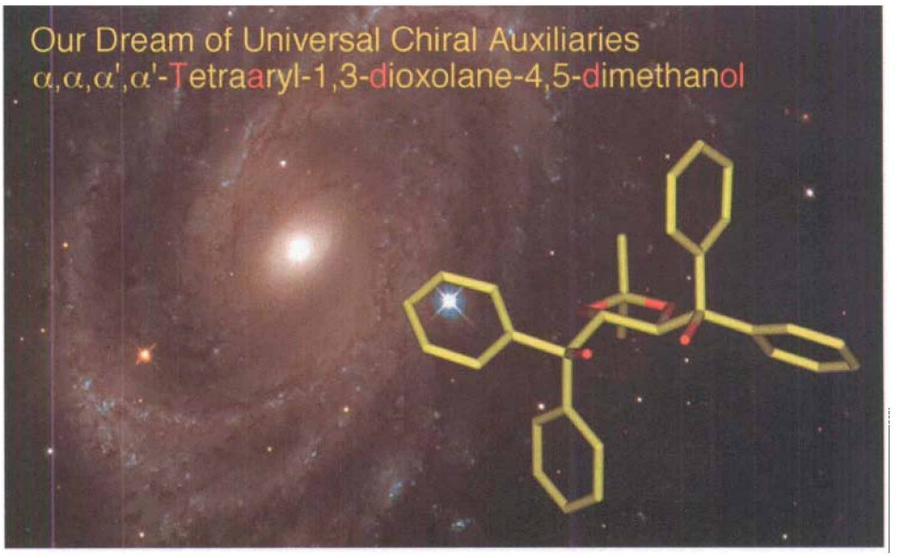

Fig. 1. TADDOL and its derivatives have evolved as one of the most widely applicable auxiliary systems for introducing chirality, for instance in reagents, in catalysts, in crystals, in NMR samples, or in liquid crystals [8].

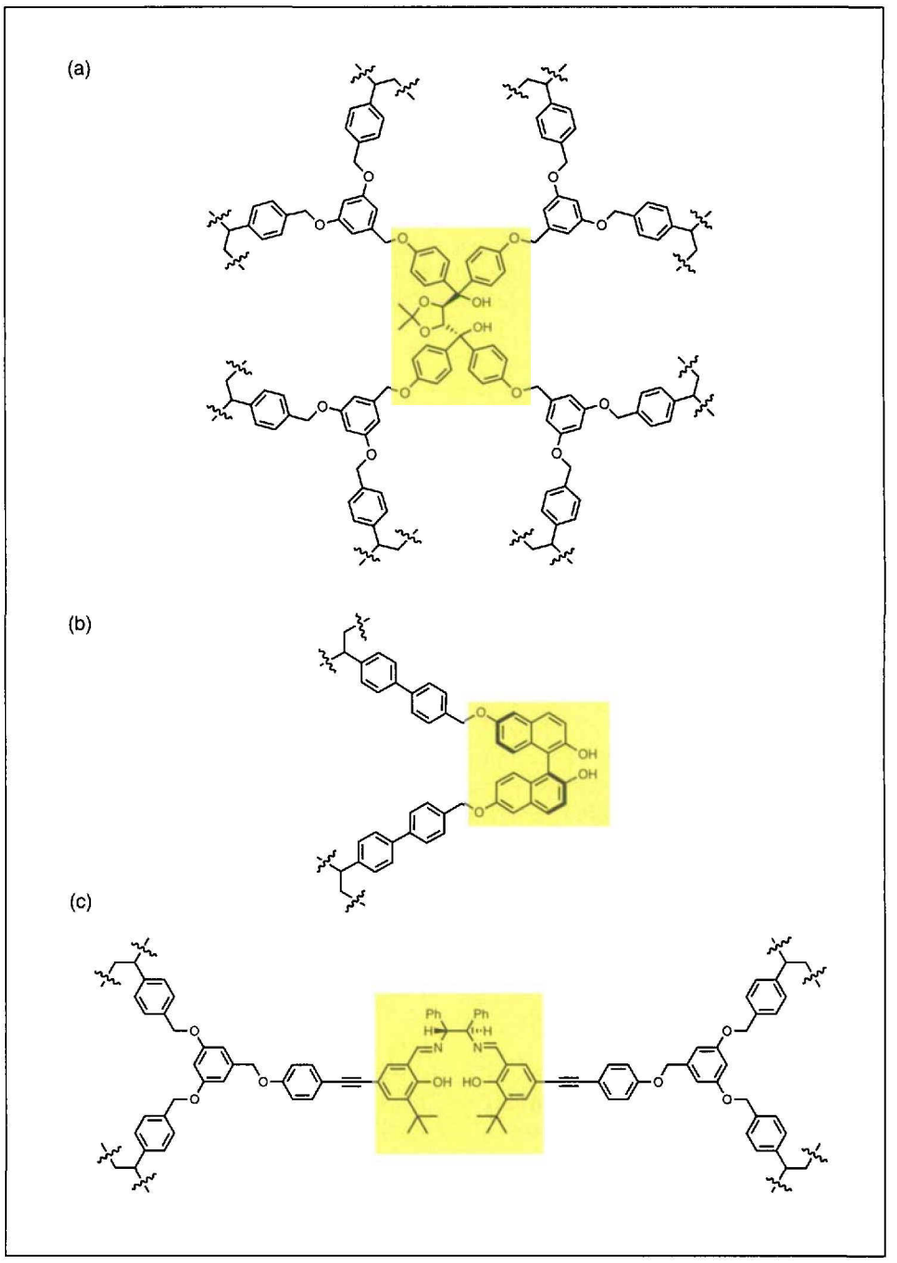

Fig. 2. Chiral ligands TADDOL (a), BINOL (b), and Salen (c) which have been dendritically incorporated into polystyrene. The corresponding styryl precursors are used as cross-linkers in suspension polymerization. The polymer beads thus obtained show outstanding performance in multiple applications [18–20].

From (*R*)-3-Hydroxybutanoic Acid (HB) to Biological Ion Channels

At the outset of our work on PHB and OHBs we were only interested in chemically degrading the – also biodegradable – biopolymer sPHB (microbial storage material, mol. weight *ca.* 10^6 Da; see *formula* in Fig. 3a, R = CH_3, n *ca.* 12000) to the monomeric acid, its esters or its reduction product 3-hydroxybutanol [21][22]. Over the years, our interest shifted entirely towards elucidation of the role which a short-chain, so-called complexing PHB (cPHB) of *ca.* 150 HB residues, plays in biology [23], and we were intrigued by the polymalate analogue (*formula* in Fig. 3a, R = CO_2H) which regulates DNA polymerase activity in certain fungi [24]. In order to prove the function of cPHB (present in small amounts in all living organisms, see review articles [10]) beyond doubt we have synthesized – from the monomer – oligomers of up to 128 HB units, also with fluorescence labels [25] (Fig. 3b), and used them for studying ion transport through phospholipid bilayers (Fig. 4). It turns out that 32mers of HB give rise to a non-ion-specific transport of alkali and alkaline earth ions through planar bilayers (single channel mechanism, voltage driven, patch-clamp experiments, see Fig. 4a) [26], while shorter oligomers (8mer, 16mer) are less or not 'active'. Also, Ca^{2+} transport through phospholipid vesicle walls was demonstrated in the experiment outlined in Fig. 4b (pore mechanism, concentration-driven influx [27]). Finally, the HB 128mer was used to prepare a complex with calcium polyphosphate (*ca.* 60 units) within a planar phospholipid bilayer and to demonstrate a Ca-specific transport (voltage-driven, patch-clamp experiment) with a current/potential slope identical to that measured with a cPHB•Ca•PP_i complex extracted from cell-wall fractions of genetically competent *E.coli* (Fig. 4c) [28].

All our investigations of structures, chemical properties, material properties, and activities in bilayers of the synthetic HB oligomers are compatible with the view that cPHB plays an important role in biology (as a fifth class of physiologically important biomacromolecules) [10][29].

From Oligo(3-hydroxybutanoates) to β-Peptides – a Step into the World of Hydrogen Bonding

The structure of OHB chains is entirely dependent upon the conformation of the building blocks in the backbone, with no intramolecular and weak intermolecular hydrogen bonding (OHBs are insoluble in H_2O or non-fluorinated alcohols, as well as in hydrocarbons). It occurred to us [11] that replacement of the chain-bound oxygen (weight 16) by NH (weight 15) should lead to backbone reinforcement by increased rotational barriers (RCO-OR *ca.* 13 kcal/mol, RCO-NHR *ca.* 20 kcal/mol), and also by intramolecular hydrogen bonding. Thus, we took the step from α- to β- and γ-peptides (in which each amino acid residue has in its backbone one or two more carbon atoms than natural systems, *i.e.* oligopeptides, proteins, enzymes).

The prediction of those knowledgeable in the field was that the new peptide analogs with their additional, 'freely rotating' single bond(s) would exist as a *chaotic* mixture of conformers (see the *formulae* in the top part of Fig. 5). Quite the contrary was the case: while α-peptides of less than 10 to 15 amino acids do not form stable 3.6_{13} helices in protic solvents such as MeOH [30], it takes only six β-amino acids to observe a 3_{14} helix [31], and four γ-amino acids to detect a 2.6_{14} helix [12][32] in the same solvent system (Fig. 5, bottom). Thus, homologation of the proteinaceous amino acids (without backbone rotational restriction! [33]) in a peptide leads to *more stable* secondary structures (formed by non-cooperative folding [34]). Furthermore, there is a switch in polarity and helicity of the resulting helices as we go from α- to β- to γ-peptides (see the presentation in Fig. 5).

As might have been expected, there is more variety of secondary structures in the world of β-peptides: when the proteinaceous side chains are put alternatively in the 2- (β^{2}-) and 3-position (β^{3}-) of the residues along a β-hexapeptide chain, a novel type of helix is formed in which there is no resulting dipole (the C=O groups point alternatively up and down along the helix axis) and in which two hydrogen-bonded rings of different ring sizes alternate (we call it a 12/10 helix) [31][35], see Fig. 6. Under certain conditions an interconversion of 3_{14}- and 12/10-helical structures may be observed, but it looks as if β-peptidic amide bonds flanked by two substituents (-CHR-NH-CO-CHR'-, as present in α-peptides) lead to stabilization of 10-membered hydrogen-bonded rings, as compared to the

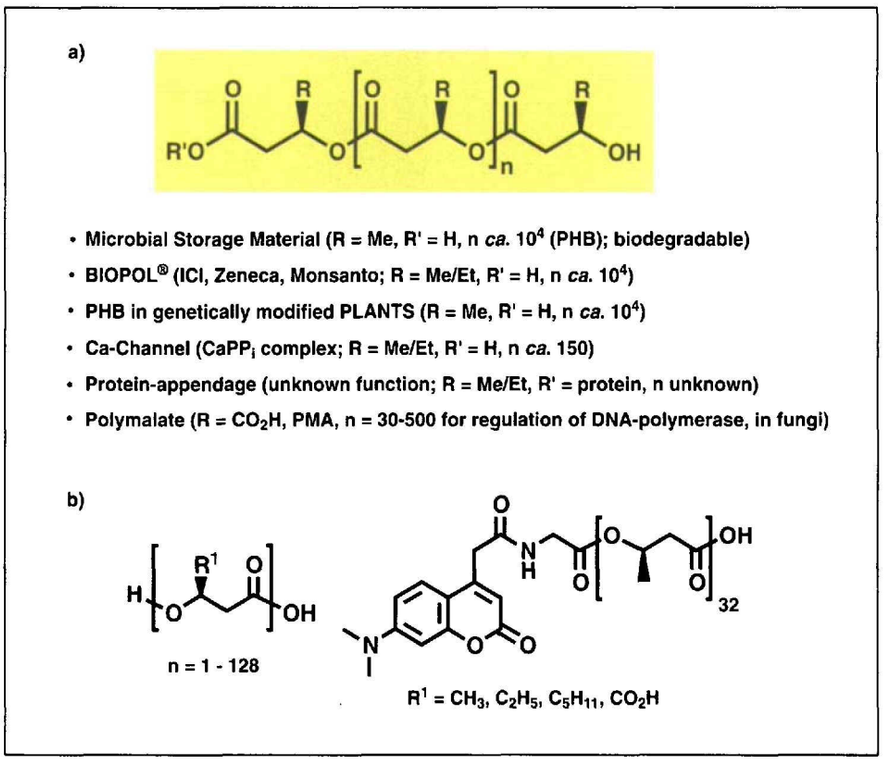

Fig. 3. PHB, cPHB and OHBs. (a) Poly-((*R*)-3-hydroxybutanoate) (storage material sPHB, R = Me) and the corresponding valerate (PHV, R = Et), the short-chain, complexing variety cPHB, and the polymalates (PMA, R = CO_2H) in biological systems. (b) Synthetic oligomers consisting of 2, 4, 8, 16, 24, 32, 64 or 128 HB units have been synthesized and are used for model studies of ion transport through phospholipid bilayers (see Fig. 4) [10].

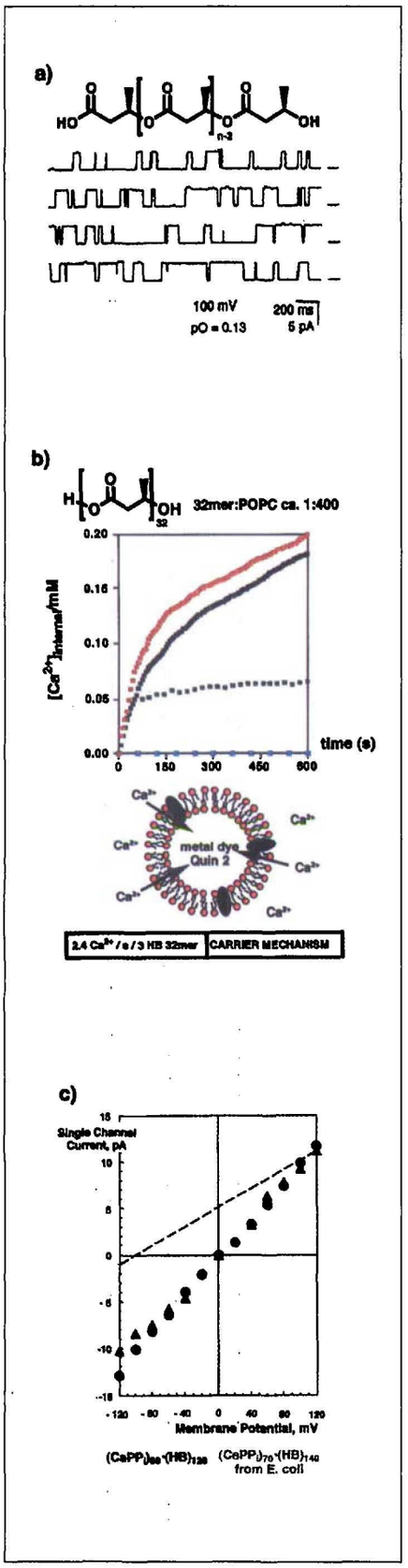

Fig. 4. Ion transport by oligo-((*R*)-3-hydroxybutanoates) in phospholipid bilayers may be voltage driven [26][28] (patch clamp experiments, single channel behavior (a),(c)) or concentration-driven [27] (*ion-pore effect, carrier* mechanism in vesicles (b)).

14-membered rings of the 3_{14} helices [35][36]. In fact, a single β^2/β^3-amino acid pair in the center of a β-hexapeptide, with a pair of $\beta^{2,3}$-disubstituted amino acids of *unlike* configuration (which cannot possibly form a 3_{14} helix and are forced to adopt linear structures, to assemble in sheets, Fig. 7), each in the N-terminal and C-terminal positions, leads to a hairpin structure in MeOH solution, with a 10-membered H-bonded ring forming a turn [37].

For β-peptidic 3_{14} helices fixed by disulfide clamps [38], stabilized by salt bridges [39], or garnished by functionalized side chains and by C=S bonds [40], for cyclo-β-peptides which stack to tube-like structures [41], for β-peptides of unknown structures, consisting of geminally disubstituted β-amino acids (unable to form a 3_{14} helix or a sheet) [42], for MD calculations of β-peptide structures [36][43] and for their physiological properties [44] we have to refer the reader to the literature.

After four years of research in this area it is evident that we have entered a whole new world of β-peptides, with many more exciting results to come.

Conclusions

Chemists engaged in organic synthesis, in development of new synthetic methodology, and in natural product synthesis are normally not fond of polymers (which may form in kind of accidents from their synthetic intermediates); they also do not like the prospect of preparing macromolecular compounds by repetitive techniques (creating nothing but ester or amide bonds). On the other hand, if synthetic organic chemists get involved in such activities, they are able to improve existing techniques by implementing new methodology, they are able to move very fast (using their experimental expertise and skill), they may make mistakes, but they have unbiased views of the field (such as polymer chemistry or repetitive, solid-phase synthesis). Thus, we have, for the first time, used dendritic cross-linkers in polymerizations to obtain materials of unusual properties; we have prepared and studied cyclic and open-chain oligomers of 3-hydroxybutanoic acid to learn about the properties and function of the ubiquitous but elusive biopolyester PHB; and we have found that there is a world of homologous un-

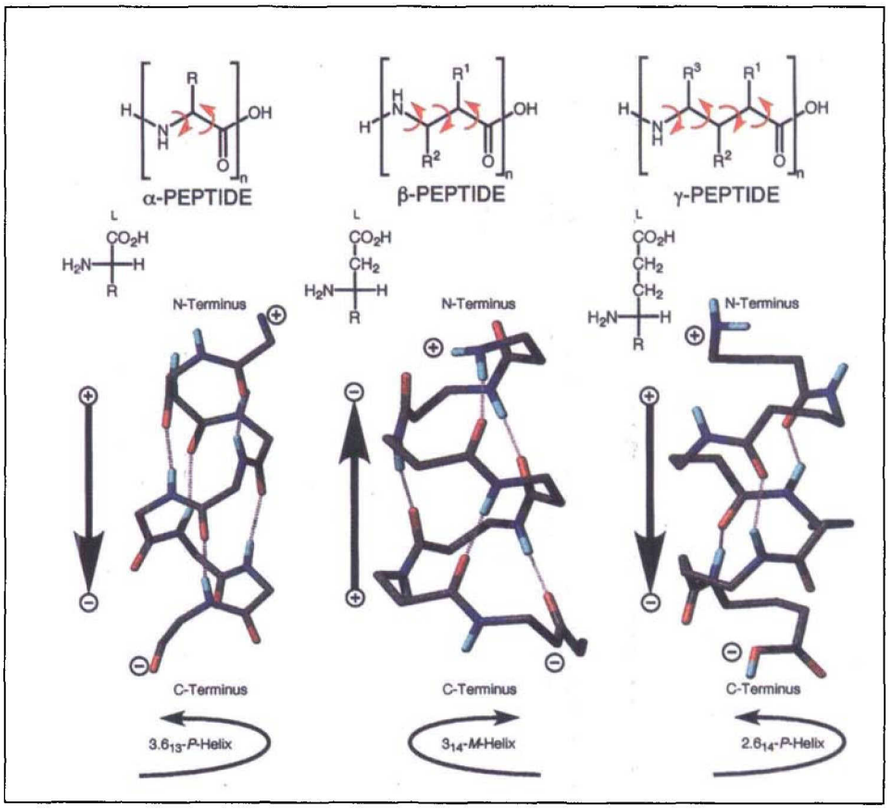

Fig. 5. Comparison of α-, β-, and γ-peptides and of the helices formed with *L*-amino acid building blocks. The dipole (N- to C-terminus) switches from ⟶ to ⟵ to ⟶, and so does the helicity from *P* to *M* to *P*. The α- and γ-peptidic helices are destabilized by charge (NH_3^+)/pole (+) interactions, the β-peptidic one is charge/pole stabilized. The stability in MeOH of the helical secondary structures increases from α- to β- to γ-peptide [32].

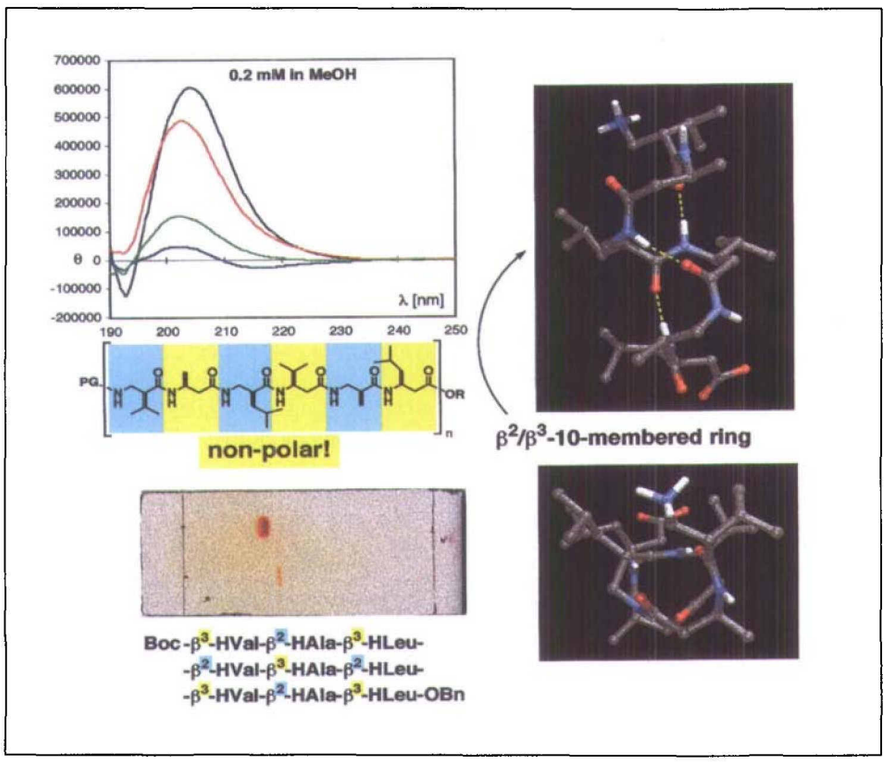

Fig. 6. β^2/β^3-Peptides consisting of alternating sequences of β^2- and β^3-amino acids fold to a 12/10 helical secondary structure having no resulting dipole moment and exhibiting a characteristic CD spectrum (single positive Cotton effect near 204 nm with (*S*)-building blocks). Deprotection destabilizes the 12/10 helix versus the 3_{14} helix (see Fig. 5). The polarity (R_f value on silica plates) of these oligopeptides does not increase with increasing chain length (comparison of a β-hexa- and a β-nonapeptide) [35][36].

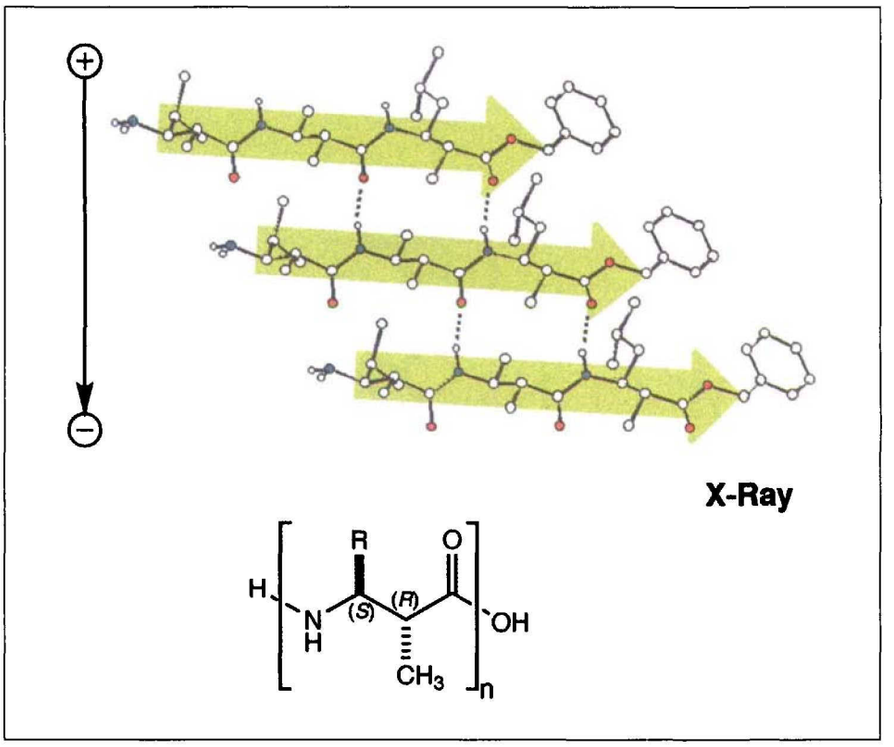

Fig. 7. β-Peptides of *unlike*-$\beta^{2,3}$-amino acids. They can fold neither to (*M*) nor to (*P*) 3_{14} helices (see Fig. 5). Rather, they have a linear conformation and form highly polar pleated sheets (all C=O dipols within a sheet are parallel and unidirectional); the compounds are insoluble as 'pieces of rock'.

natural peptides with properties which differ drastically from those of the natural α-peptides (...and proteins).

A more general conclusion: The work outlined here and the results are a demonstration of the fact that synthesis and analysis are the interdependent centerpieces of chemistry! Synthesis creates ever new compounds and materials, the structures and properties of which are studied by analytical methods of ever increasing sophistication (all the way down to single-molecule and atomic resolution!)

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