

Design and Synthesis of Functional Molecular Architecture

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Abstract: The central theme of the research conducted by the Diederich group is the creation of functional molecular architecture by design and advanced synthesis. Function is explored through interdisciplinary study, wherein national and international collaborations provide fertile grounds. Four areas of research are pursued: (i) In covalent fullerene chemistry, regio- and stereoselective templated synthesis protocols are developed to prepare three-dimensional building blocks for supramolecular construction and advanced materials such as electrochemical ion sensors. (ii) Advanced materials are also targeted by acetylenic scaffolding. Macrocyclic scaffolds of interest include perethynylated expanded radialenes featuring large π -conjugated all-carbon cores. Acyclic scaffolds such as monodisperse poly(triacetylene) (PTA) oligomers, with linear, π -conjugated all-carbon backbones expanding up to 18 nm length, are also actively investigated. Arylated tetraethynylethenes undergo photochemical *cis* \rightarrow *trans* and *trans* \rightarrow *cis* isomerization without competing thermal isomerization pathways – promising applications of these materials are foreseen in optical switching and memory storage devices. (iii) In supramolecular chemistry, dynamic receptors are developed with the potential to function as ‘molecular grippers’ on the single molecule level. Dendritic porphyrins are efficient models of hemoglobin and myoglobin and bind O₂ strongly and reversibly. They are also ideal model systems to explore the influence of the protein shell on the redox potential of the Fe^{III/II} couple in electron transfer proteins such as the cytochromes. (iv) Finally, the detailed understanding of molecular recognition principles generated in the studies with artificial receptors provides the basis for a modern medicinal chemistry program aimed at the structure-based *de novo* design of nonpeptidic enzyme inhibitors.

Keywords: Acetylenic scaffolding · Dendrimers · Fullerenes · Medicinal chemistry · Molecular recognition

1. Introduction

‘Targeted synthesis’ describes best the research pursued by the Diederich group at the interfaces between chemistry and materials science as well as biology. Molecules and supramolecules are designed and synthesized with the aim to express a desired function. This function can be the specific optoelectronic property of an advanced material or the ability of a small molecule to bind strongly and selectively to an enzyme active site. Many of the target compounds feature dimensions on the multianometer scale and could not have been prepared or

characterized only ten years ago. Rather, their successful development relies on recent advances in chemical synthesis, purification, and characterization. Key transformations in the preparation of these materials frequently involve metal-catalyzed cross-coupling reactions, many of which were only developed during the past decade [1]. The purification of monodisperse nanomaterials, such as higher-generation dendrimers with diameters exceeding 5 nm or π -conjugated molecular rods extending in length up to 18 nm, only became possible with the amazing recent advances in gel permeation chromatography (GPC). Rational design strategies greatly benefit from enhanced computing power and the increasing availability of user-friendly computer modeling software. Thus, it becomes increasingly possible to correctly predict the ‘active geometry’, *i.e.* the one required for expression of function, of a target molecule.

Functions of targeted molecular architecture are investigated and exploited

in national and international collaborations and interdisciplinary networks. Co-workers on the projects enjoy intensive interactions with physicists, materials scientists, and biologists from other laboratories. Thus, they become skillful in interdisciplinary teamwork, something essential for their future academic or industrial careers. Here we present selected recent investigations in the four areas of chemistry in which the Diederich group is active.

2. Covalent Fullerene Chemistry

During the past years, tether-directed remote functionalization has become the method of choice for the regioselective synthesis of higher adducts of buckminsterfullerene, C₆₀ [2][3]. A particularly attractive goal was the stereoselective formation of optically active *cis*-3 bis-adducts with an inherently chiral addition pattern, since these compounds had been shown to exhibit unusual chiroptical

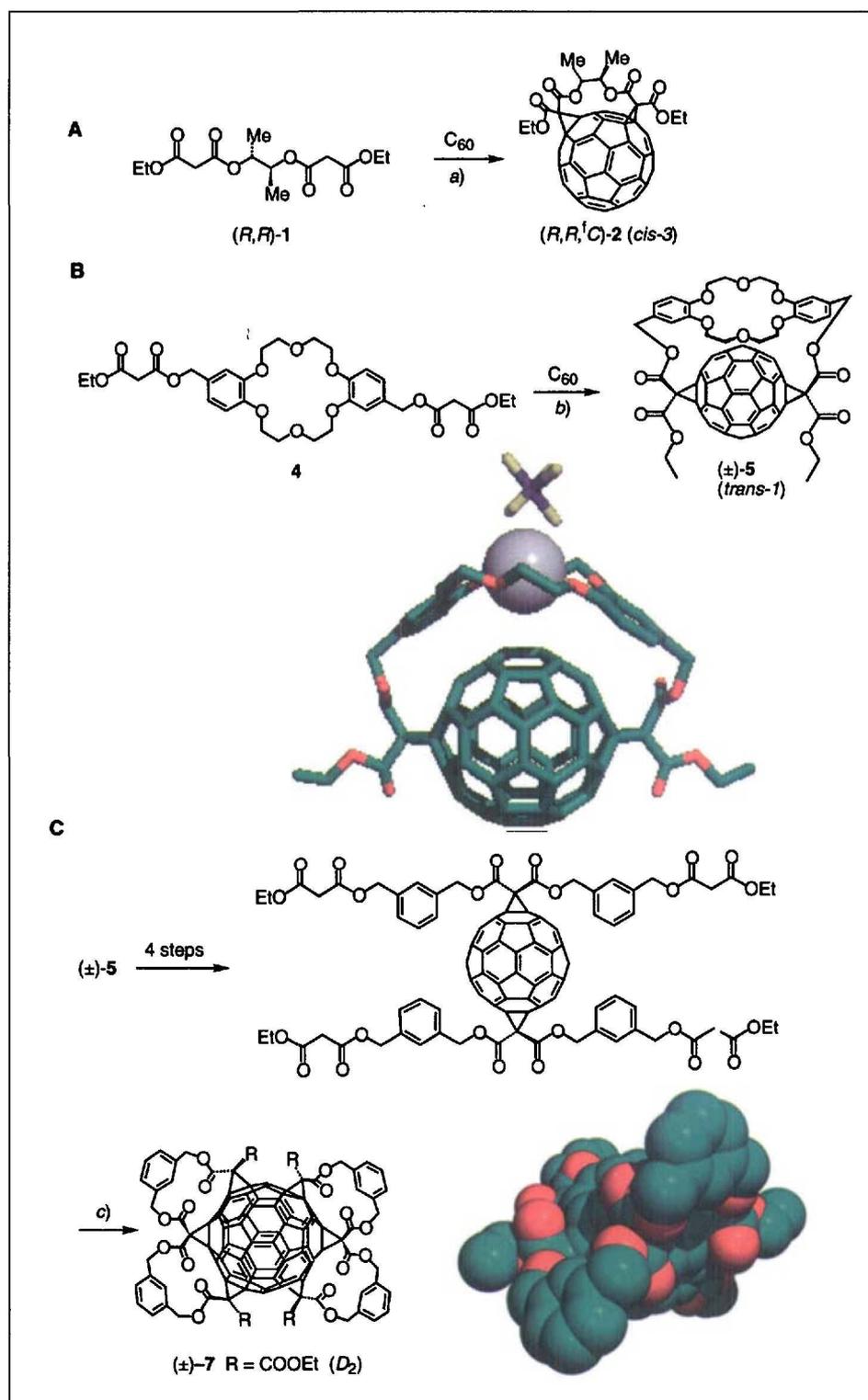
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properties with high-intensity Cotton effects expanding over the entire UV/VIS region of the circular dichroism (CD) spectra [4][5]. When bis-malonate (R,R)-**1**, with an optically active butane-2,3-diol tether, was reacted with C_{60} under the conditions of the Bingel cyclopropanation [6], macrocyclization occurred with complete regio- and diastereoselectivity (de >97%), yielding as the only isolable bis-adduct the enantiomeric cis -3 derivative (R,R ,^f C)-**2** (Scheme: A) [7]. To explain the remarkable stereoselectivity in this double addition to the fullerene sphere, computer-assisted calculations using semi-empirical methods (AM1 ('Austin Model 1') and OM2 ('Orthogonalization Method 2')), were undertaken. They revealed that formation of the observed diastereoisomer is likely to be preferred for conformational reasons. The substituents at the glycolic fragment are fully staggered, with *gauche* orientations of the two Me groups and the two ester linkages to the fullerene, and the two glycolic H-atoms adopt an *ap* (antiperiplanar) arrangement. In the calculated less favorable diastereoisomer (R,R ,^f A)-**3** (not shown), the Me groups adopt an *ap* and the two H-atoms a *gauche* orientation. The calculations also suggested that the conformational preference of the tether in the transition state of the macrocyclization step, which determines the regio- and diastereoselectivity. Evaluation of the vicinal coupling constants by 1H NMR spectroscopy clearly showed that the glycolic H-atoms in the experimentally formed cis -3 bis-adduct (R,R ,^f C)-**2** adopt an *ap* orientation ($^3J(H,H)=7.9$ Hz). This combined theoretical/spectroscopic analysis allowed assignment of the ^f C configuration to the inherently chiral addition pattern, in full agreement with configurational determinations based on the comparison of calculated and experimental CD spectra [8].

This stereochemical analysis has high predictive power. Bis-malonates with cyclic, glycol-derived tethers, in which the alkyl residues are forced to adopt the *gauche* and the H-atoms the *ap* conformation, produce stereoselectively one diastereoisomeric cis -3 bis-adduct. If, on the other hand, the geometry between the alkyl groups at the glycolic C-atoms deviates from a *gauche* relationship, as in the case of tethers derived from *exo*-*cis*- and *trans*-norbornane-2,3-diol or *trans*-cyclopentane-1,2-diol, the reaction not only lacks stereoselectivity, but hardly

any macrocyclic product is formed. In future work, optically active derivatives of the poorly explored higher fullerenes (C_{70} and beyond) [9] will be targeted by stereoselective tether-directed remote functionalization with the aim to produce an entire family of novel chiral objects with unusual chiroptical properties.

Tether-directed remote functionalizations yielding the *trans*-1 addition pattern, with the addends located in the centers of two opposite poles of C_{60} , had proven quite difficult for several years, mainly due to the challenge to design ex-



Scheme. A) Synthesis of (R,R ,^f C)-**2** by regio- and diastereoselective Bingel macrocyclization. B) Synthesis of the fullerene-crown ether conjugate (\pm) -**5** and X-ray crystal structure of the complex formed with KPF_6 . C) Synthesis of hexakis-adduct (\pm) -**7** with all addends aligned in a helical array along an equatorial belt. The X-ray crystal structure of (\pm) -**7** shows the helical nature of the addition pattern. Reagents and conditions: a) I_2 , 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), PhMe, 20 °C, 1.5 h, 24%. b) C_{60} , I_2 , DBU, KPF_6 , PhMe/MeCN, 20 °C, 6 h, 50%. c) I_2 , DBU, PhMe/Me₂SO, 20 °C, 12 h, 10%.

tended tethers with a suitable degree of conformational homogeneity that would span the entire fullerene sphere. An elegant solution was provided by using a dibenzo[18]crown-6 (DB18C6) derivative as the tether [10]. When bis-malonate **4**, rigidified by K⁺ ion complexation, was reacted with C₆₀ in the Bingel macrocyclization, the fullerene-crown ether conjugate (\pm)-**5** was obtained as the only regioisomer in 50% yield (Scheme: B). The ionophoric properties of (\pm)-**5** were investigated with an ion-selective electrode membrane in collaboration with E. Pretsch (ETH Zürich), and K⁺ ions were found to form the most stable complex among the alkali metal ions. The complex between (\pm)-**5** and KPF₆ was characterized by X-ray crystal structure analysis, which confirmed the close tangential orientation of the ionophore atop of the fullerene surface (Scheme: B). For the first time, effects of cation complexation on the redox properties of the carbon sphere in fullerene-crown ether conjugates were observed, as shown in collaboration with L. Echegoyen (Univ. Miami). Addition of KPF₆ to a solution of (\pm)-**5** resulted in a large anodic shift (90 mV) of the first fullerene-centered reduction process which was attributed to the electrostatic effect of the K⁺ ion bound in close proximity to the carbon sphere. Similar ion-complexation effects on redox properties were recently observed in crown ether conjugates of the higher fullerene C₇₀ [11]. In future work, we intend to attach more selective ionophores at van der Waals distance on top of fullerenes and explore the capacity of the resulting conjugates to serve as electrochemical ion sensors.

The DB18C6 tether in (\pm)-**5** is a true covalent template: it is readily removed by hydrolysis or transesterification, which unveils fascinating new perspectives for molecular scaffolding using *trans*-1 fullerene derivatives. Thus, the crown ether conjugate was transformed by a short route into the *trans*-1 derivative **6** with four tethered ethyl malonate arms (Scheme: C) [12]. Subsequent fourfold Bingel macrocyclization afforded the D₂-symmetrical hexakis-adduct (\pm)-**7** with the six addends in a distinct helical array along an equatorial belt, as was elegantly shown by X-ray crystallography (Scheme: C). π -Electron conjugation between the two unsubstituted polar regions in (\pm)-**7** is maintained *via trans*-stilbene-like bridges, and the compound retains – as had been projected based on prior results [13] – typical fullerene reactivity and physical properties. In future work,

we intend to use optically active tethers to prepare this unprecedented higher adduct in enantiomerically pure form in order to explore its chiroptical properties.

3. Carbon-rich Functional Materials by Acetylenic Scaffolding

Our program on acetylenic advanced materials has the following objectives in mind: (i) to expand the limits in size and complexity of stable monodisperse functional scaffolds accessible by organic synthesis and analytical characterization, (ii) to advance, in an interplay between experiment and theory, the fundamental knowledge of π -electron delocalization in acetylenic molecular architecture extending into one, two, and three dimensions, (iii) to provide new classes of chromophores with multianometer dimensions for optoelectronic devices and the development of molecular-scale electronics, and iv) to explore the existence of novel synthetic molecular allotropes of carbon.

Acetylenic functional materials are synthesized by taking advantage of a unique molecular construction kit consisting of substituted 1,2-diethynylethenes (DEEs) and tetraethynylethenes (TEEs) for one- and two-dimensional scaffolding [14] and of 1,1,2,2-tetraethynylethanes and 1,3-diethynylallenes [15] for three-dimensional scaffolding. One part of our program deals with the preparation and study of monodisperse oligomers with novel linear π -conjugated backbones. Examples are the stable monodisperse poly(triacetylene) (PTA) oligomers **8a–k**, which extend up to 17.8 nm (24-mer **8k**) in length (Fig. 1A) [16]. They are the longest known molecular rods featuring a fully conjugated non-aromatic all-carbon backbone. This series of compounds enabled for the first time the investigation of physicochemical properties in PTAs into the higher oligomeric regime, where saturation of the properties becomes apparent (at about $n=10$ monomeric units). This interdisciplinary study included evaluation of linear (UV/VIS) and nonlinear (third-harmonic generation (THG) and degenerate four-wave mixing (DFWM)) optical properties (in collaboration with P. Günter, ETH Zürich), Raman scattering, electrochemistry (in collaboration with M. Gross, Univ. Strasbourg) and theory (in collaboration with J.-L. Brédas, Univ. Arizona) [17]. Despite their many acetylenic subunits, these oligomers are high-melting and remarkably stable; the proposed favorable

linear *s-trans* conformation of the planar π -conjugated backbone was confirmed for 4-mer **8d** by X-ray crystallography [16b]. In future work, we intend to attach anchor groups to the oligomeric termini, allowing their oriented binding between metal surfaces to span and bridge photolithographic gaps in optical and electronic nanoscale devices and circuitry.

Oxidative acetylenic coupling of suitable TEE precursors provided perethynylated expanded radialenes such as **9a–c**, new chromophores containing large all-carbon cores (Fig. 1B) [18]. Macrocyclic cross-conjugation is effective in these stable, high melting, and readily soluble compounds which feature the following salient properties: (i) facile electrochemical reduction in multiple one-electron transfer steps, (ii) very strong electronic absorptions extending over the entire UV/VIS spectral region, and (iii) high third-order nonlinear optical coefficients. The X-ray crystal structure of expanded [6]radialene **9b** was solved by P. Seiler (ETH Zürich) and its all-carbon core, which is isomeric with fullerene C₆₀, was shown to adopt a nonplanar, 'chair-like' conformation (Fig. 1B). In future work, we are aiming for even larger two-dimensional carbon sheets bearing solubilizing and stabilizing peripheral groups.

A third avenue in acetylenic scaffolding is the formation of DEE- and TEE-based achiral and chiral molecular switches for applications in photoaddressable memory storage and readout devices and waveguides [19] or as optically active dopants for the induction of switchable cholesteric phases. These targets have come into reach since arylated TEEs and DEEs have been shown to undergo reversible, photochemically-induced *cis*→*trans* and *trans*→*cis* isomerization without competing, undesirable thermal isomerization pathways. Compound (*R,R*)-**10** provides an example for an optically active TEE-based molecular switch, which can be reversibly isomerized for prolonged periods of time without photobleaching (Fig. 1C) [20].

4. Supramolecular Chemistry

Macrocyclic and cleft-type receptors for small biomolecules (sugars, steroids, amino acids, small peptides, nucleotides) are designed and prepared, and the driving forces for complexation in the liquid phase are investigated [21]. The group is particularly interested in molecular association processes in aqueous solution in view of the biorelevance of the data col-

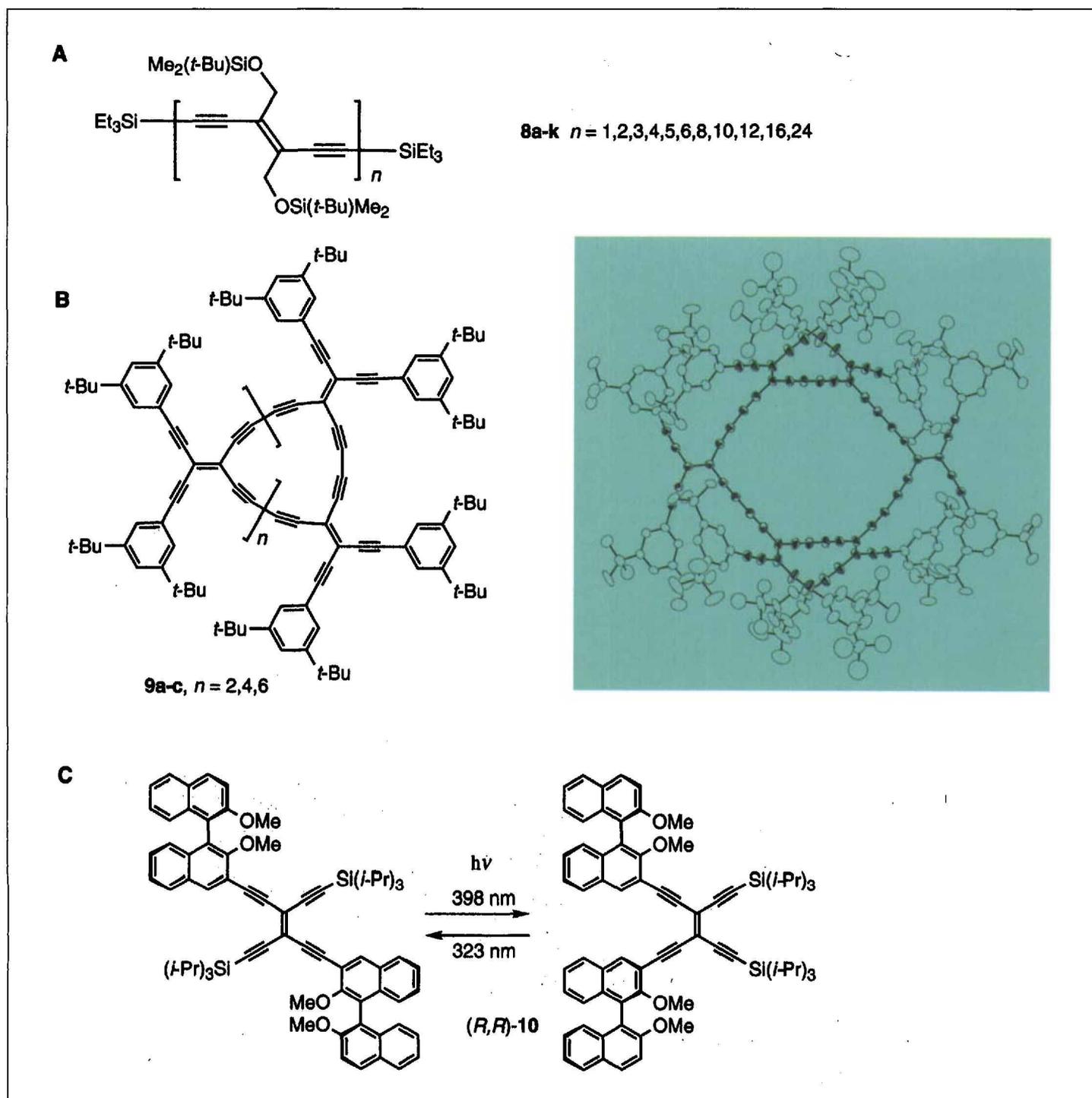


Fig. 1. A) Monodisperse poly(triacetylene) (PTA) oligomers **8a-k** expanding in length to 18 nm (**8k**). B) Perethynylated expanded radialenes **9a-c** and X-ray crystal structure of **9b** with an all-carbon core isomeric to [60]fullerene. C) The TEE-based molecular switch **(R,R)-10** undergoes photochemical *cis-trans* isomerization without competition from thermal pathways.

lected in this medium. At the center of our current molecular recognition work with synthetic receptors is the understanding of sulfur-aromatic interactions. Many protein X-ray crystal structures show close contacts between methionine S-atoms and the side chains of aromatic amino acids. Also, we attempt to identify and quantify the preference of nucleobases to undergo stacking interactions with other neighboring nucleobases and base analogs.

In other developments, we have become interested in preparing dynamic receptors that function as 'molecular grippers'. These compounds are investigated on surfaces at the single molecule level using STM (scanning tunneling microscopy) and AFM (atomic force microscopy; collaboration with IBM Rueschlikon) and could become future tools in the construction of molecular electronics circuitry. Among the most fascinating systems, featuring two dramatically different, reversibly switchable geometries, are a family of cavitands, consisting of a resorcin[4]arene bowl bridged by four quinoxaline moieties, which had been introduced by Cram and Cram [22]. These molecules were found to exist in an open 'kite' conformation at low temperature (<213 K) but to adopt a 'vase' conformation, capable of guest inclusion, at elevat-

ed temperatures (>318 K) (Fig. 2A). We recently discovered that protonation with common acids promotes, at room temperature, the reversible conformational change from 'vase' to 'kite', and that this change can be conveniently followed by optical spectroscopy [23]. These findings greatly expand the utility of the Cram cavitand system in molecular and supramolecular switching processes.

Much of our dendrimer research focuses on the binding and catalytic properties of iron porphyrin cores encapsulated within dense dendritic branching that mimics the role of the peptidic shell in globular heme proteins. We showed (in collaboration with J.P. Collman, Stanford University) that dendrimers with a five-coordinated iron(II) heme core are excellent models for hemoglobin and myoglobin, displaying high O₂ and reduced CO binding affinity [24]. In ongoing work, we explore the influence of H-bonding on gas binding selectivity; also, in collaboration with W.H. Koppenol (ETH Zürich), NO complexation by dendritic iron(II) porphyrins is investigated.

In other work, the dendritic iron(III) porphyrin **11**, with two built-in axial imidazole ligands, was found to function as a perfect model system for electron transfer proteins such as the cytochromes [25]. The dendritic shell has a very large influ-

ence on the redox potential of the Fe^{II}/Fe^{III} couple by creating a unique microenvironment around the porphyrin core. Upon changing from a simple iron(III) heme with two axial imidazole ligands to **11** in aqueous or organic solutions, the redox potential becomes more positive by as much as 400 mV, thereby making the system a much better oxidizing agent. Future work will focus on supramolecular dendrimer assembly and the study of electron transfer processes between dendrimers incorporating at their cores cofactors and other chromophores with different redox potentials.

5. Structure-based *De Novo* Design of Nonpeptidic Enzyme Inhibitors

The detailed understanding of molecular recognition principles generated in our continuing studies with artificial receptors provides the basis for a modern medicinal chemistry program aimed at the structure-based *de novo* design of nonpeptidic enzyme inhibitors as potential lead compounds for drug discovery research. In this interdisciplinary program, design and synthesis are done in the Diederich group, whereas the biological testing occurs in the laboratories of collaborators, mainly at Roche, Basel,

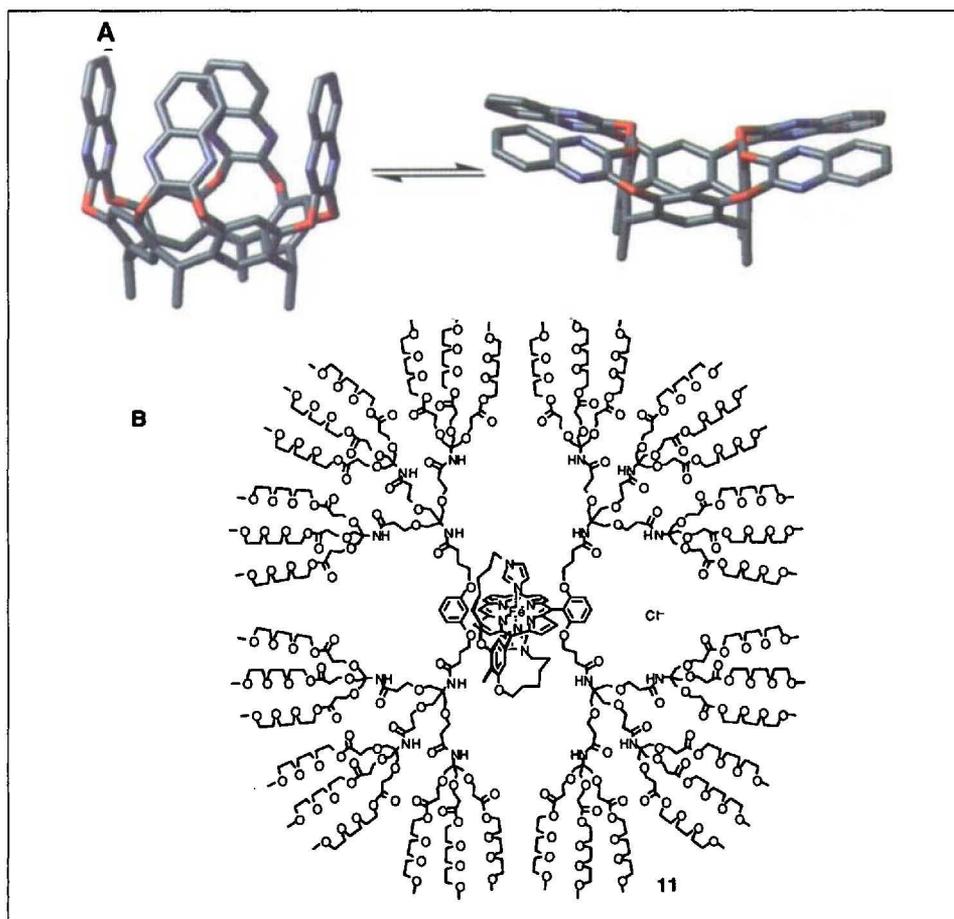


Fig. 2. A) Molecular model of the 'vase' and 'kite' conformers of a quinoxaline-bridged resorcin[4]arene cavitand derived from acetaldehyde. H-atoms are omitted for clarity. B) The water-soluble dendritic iron porphyrin **11** with two tethered imidazoles as axial ligands is a valid model for globular electron transfer proteins such as the cytochromes.

but also at academic institutions. To participate in all aspects of the entire program, graduate students frequently spend time in the laboratories of the collaborators on the biology side to perform the assays and run enzyme kinetics. One of the early targets was the serine protease thrombin, a key enzyme in the blood coagulation cascade [26]. With the help of computer modeling, the active site of this enzyme, as revealed by X-ray crystallography, could be visualized in three dimensions, and the available free space filled with a designed organic molecule that is complementary in size and shape as well as in its intermolecular interaction potential. The first active compound synthesized showed binding affinity in the low micromolar range, and after two optimization cycles, the tight binding inhibitor (+)-12 with a K_i of 7 nM and high selectivity against other serine proteases (Fig. 3A) was obtained.

The enzyme catechol-O-methyltransferase represents another target, whose inhibition is relevant for patients with *Parkinson* disease. L-Dopa administered to these patients is readily methylated by this *S*-adenosylmethionine (SAM) and

Mg^{++} ion dependent enzyme, thereby reducing the amount of dopamine that is eventually delivered to the brain. We decided to design bisubstrate inhibitors which bind to both the SAM and catechol binding sites of COMT. The challenge to keep such inhibitors in a low molecular weight range, which is relevant for bio-availability, was successfully met, and the first generation inhibitor (-)-13 showed a binding affinity in the single-digit micromolar range [27]. Its computed docking into the active site of COMT is shown in Fig. 3B. Bisubstrate inhibition is a promising although rather poorly exploited concept in medicinal chemistry, and we are interested in applying this strategy in future work also to kinases, targeting the

inhibition of both the substrate and ATP binding sites. Examples of other targets in ongoing research are the aspartyl proteases plasmepsin I and II, which are used by the malaria pathogen *plasmodium falciparum* to degrade human hemoglobin, and neprilysin, a zinc metalloprotease which cleaves diverse peptides such as substance P and enkephalins. In the latter project, we aim to develop a highly selective inhibitor which does not coordinate to the zinc(II) ion.

6. Summary and Perspectives

The development of functional molecular architectures at the interfaces between chemistry and materials science as

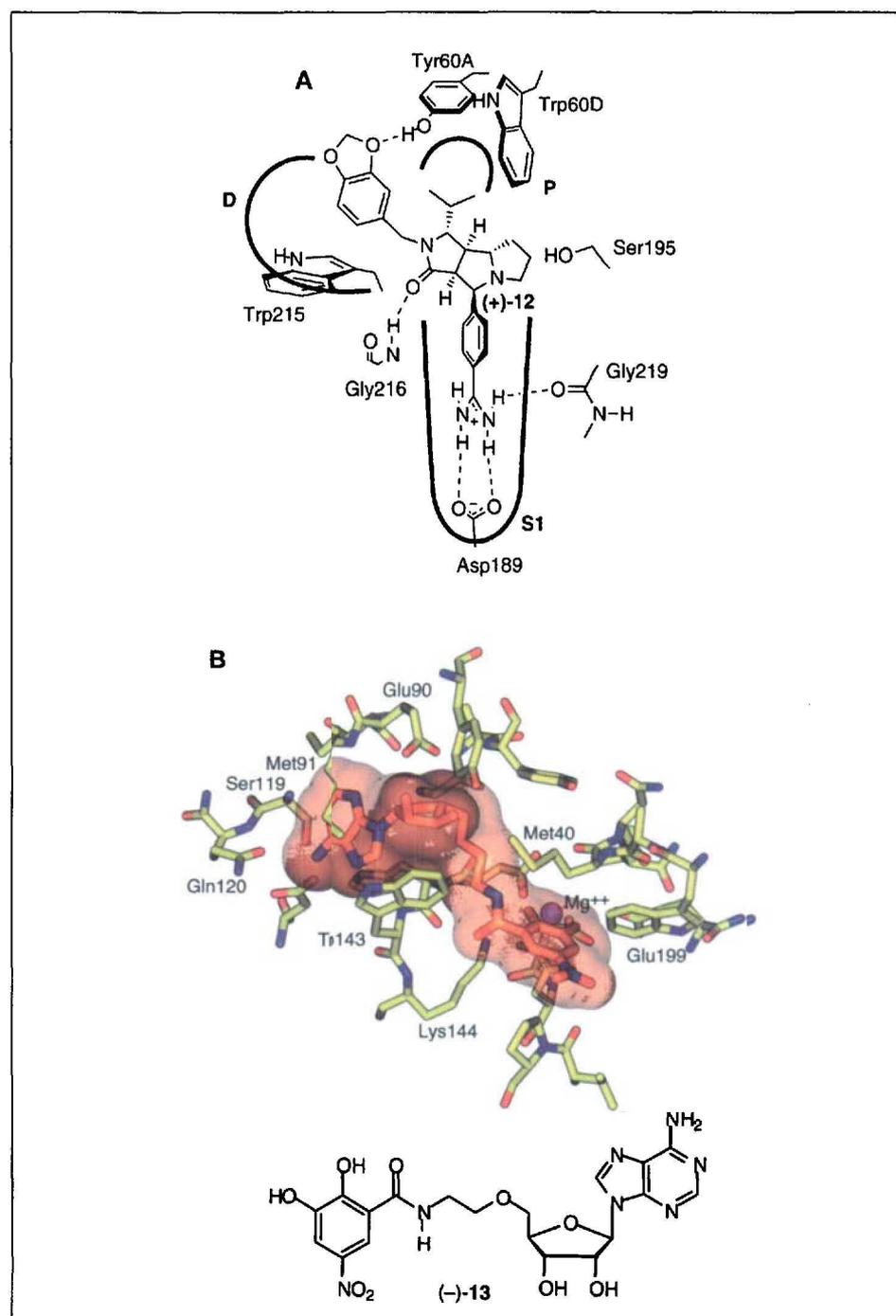


Fig. 3. A) Schematic representation of the bonding interactions in the complex between (+)-12 and thrombin as revealed by X-ray crystal structure analysis. S1 = specificity pocket; D = hydrophobic distal pocket; P = hydrophobic proximal pocket. B) Computer-modeled ternary complex between COMT, Mg^{++} , and bisubstrate inhibitor (-)-13. The Connolly surface of the inhibitor is shown.

well as biology has now been successfully pursued in the Diederich group for more than 15 years. The research program ensures in-depth learning in the areas of core-competence of the group, namely design, synthesis, and physical-organic evaluation. While pursuing their projects in a specific research area, members of the group are continuously exposed to the wide range of other active developments. This generates substantial cross-fertilization and provides great benefits to individual projects. We are looking forward to continuing our exploratory journey into functional molecular architecture in the new chemistry building at ETH Hönggerberg.

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