Focal Point: Chemical Research

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Supramolecular Chemistry and Molecular Recognition*

Supramolecular chemistry involves the study of molecular assemblies in which noncovalent interactions such as Coulomb forces, hydrophobic interactions, and hydrogen bonding are the principle binding forces. As such it has become an established research area encompassing all disciplines of chemistry which have been traditionally separated in the past.

Nowadays it is understood that noncovalent interactions are extremely important in many biological processes such as receptor–ligand binding, enzyme–substrate complex formation, antibody–hapten binding, and cell surface recognition, to name but a few. Accordingly, supramolecular chemistry is likely to provide insight into these phenomena by the investigation of artificial synthesizable molecular assemblies. Besides this, it can be predicted that applications in nanotechnology will use supramolecular devices as sensors and as modules for storing and processing information.

To capture the recent development in this fast growing area the Section Chemical Research of the New Swiss Chemical Society invited some protagonists of the field for a state-of-the-art report on the occasion of its annual autumn meeting in Basel. The following account reviews some aspects of the presentations. Selected references are provided for further information.

Keywords: ILMAC · Molecular recognition · Supramolecular chemistry

The Nature of the Mechanical Bond

J.F. Stoddart

In his lecture *Fraser Stoddart* (UCLA, USA) focused on rotaxanes [1], a new class of interlocked compounds consisting of two components: a macrocycle **M**, a cyclophane or a polyether, and a dumbbell-shaped component **S-T-S** containing terminal, bulky stopper units **S** which prevent dissociation of the components; **S-**

T-S and **M** are said to be bound mechanically due to the absence of any covalent linkage between them. In contrast pseudorotaxanes contain **S-T-s** with at least one stopper **s**, which is small enough to allow sliding of **S-T-s** through the lumen of **M**. Hence for pseudorotaxanes, no mechanical bond exists and the self-assembling individual components are in equilibrium with the inclusion complex (Scheme 1).

Stoddart outlined different ways of synthesizing the components and explained the various conditions and substructures required for self-assembly (see, for example, Scheme 2). Accordingly molecular switches can be constructed which respond to a change in potential [2] or a change in pH of the solvent [3]. As shown in Scheme 2, the rotaxane is colorless in the protonated form when the ammonium group is hydrogen-bonded to the crown-ether substructure of **M**, but becomes red in color when deprotonated because **M** slips over to the *bis*-pyridinium unit of **S-T-S**, binding in a dissymmetrical fashion. These results are very promising with regard to future applications of molecular devices as sensors in nanotechnology.

Scheme 1
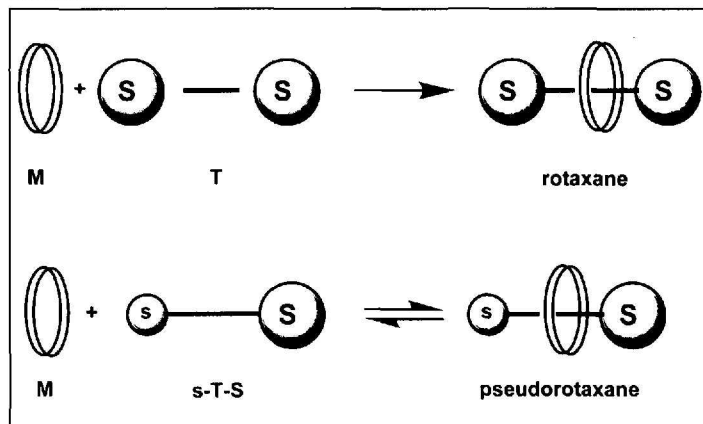
Scheme 2

Scheme 3

2 $\rightleftharpoons$ = complementary
peptide strands

S. Matile
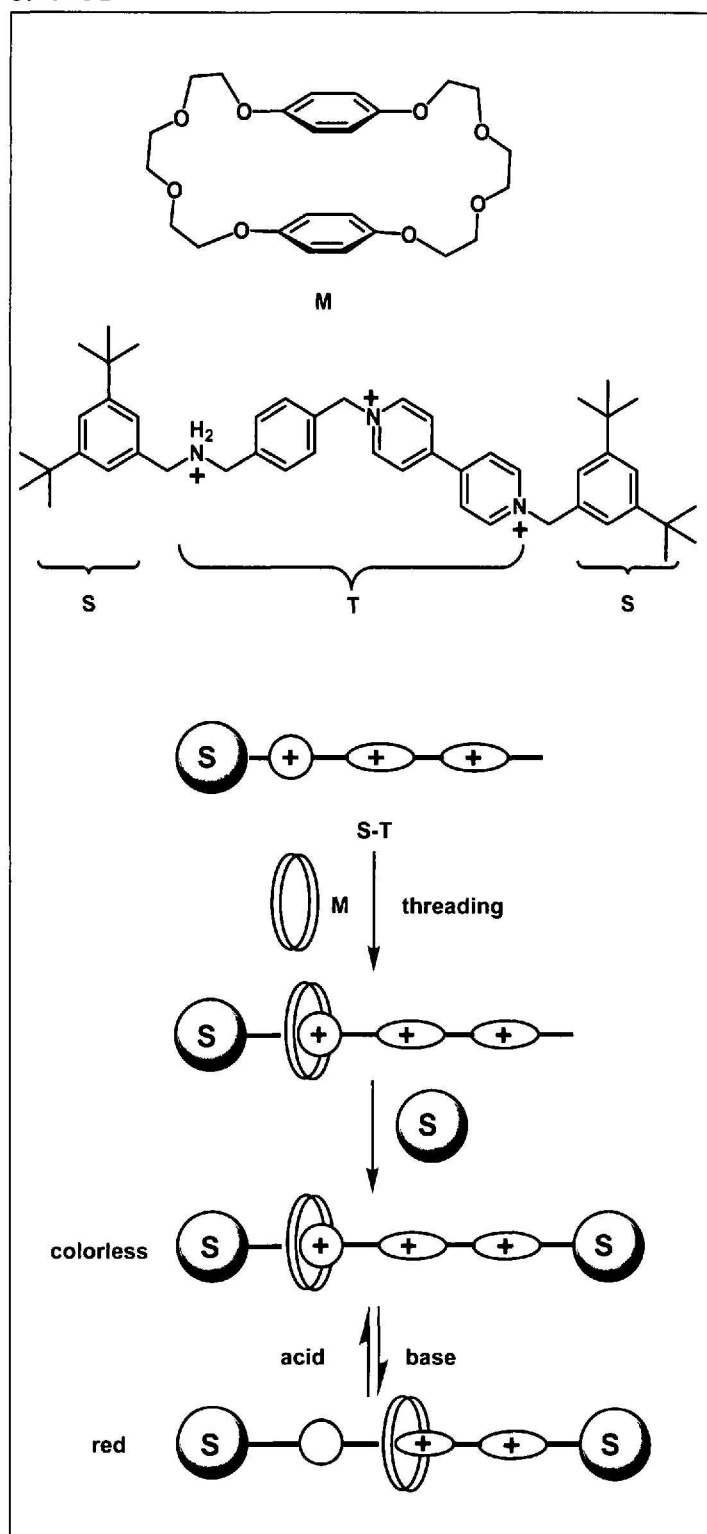
Rigid-Rod Molecules – Versatile Synthetic Models for Challenging Biological Processes

Recent results of a research program on the significance of rigid-rod molecules as supramolecular ion channel models were discussed in the lecture of *Stefan Matile* (Université de Genève, Switzerland). Oligo(*p*-phenylene) molecules carrying short peptide strands (**1**, Scheme 3) have been found to be suitable building blocks which are easily prepared and which self-assemble by intermolecular β-sheet formation to yield rigid-rod β-barrels like **2** [4].
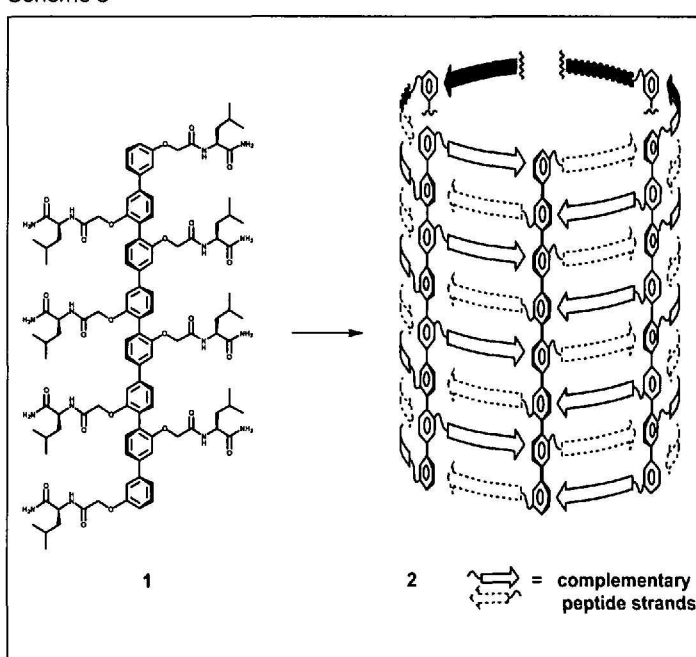
Design strategies to elucidate the formation mechanism of these artificial β-barrels and to control diameter and chemical nature of their interior by the use of various residues at the oligo(*p*-phenylene) rods were reported. Applications such as encapsulation and planarization of hydrophobically matching carotenoids or transport of ions across biomembranes [5] were illustrated with reference to pertinent biological questions – for example: 'Why do lobsters turn from blue to red during cooking?' – or 'How can ion channels be both selective and efficient?'
Additional supramolecular motifs containing rigid-rod molecules have been constructed, from barrels to more complex bicycle tires, pinwheels, herringbones, reversed micelles, mixed bilayer membranes, and last but not least giant vesicles. Although this presentation emphasized the structural features of the rigid-rod supramolecule, some of their intriguing, sometimes puzzling activities did not pass unrecognized. Finally Matile pointed out that the possibility of investigating the mode of action of endogenous antibiotics with rigid push-pull rods is of high medical importance with regard to antibiotic resistance.
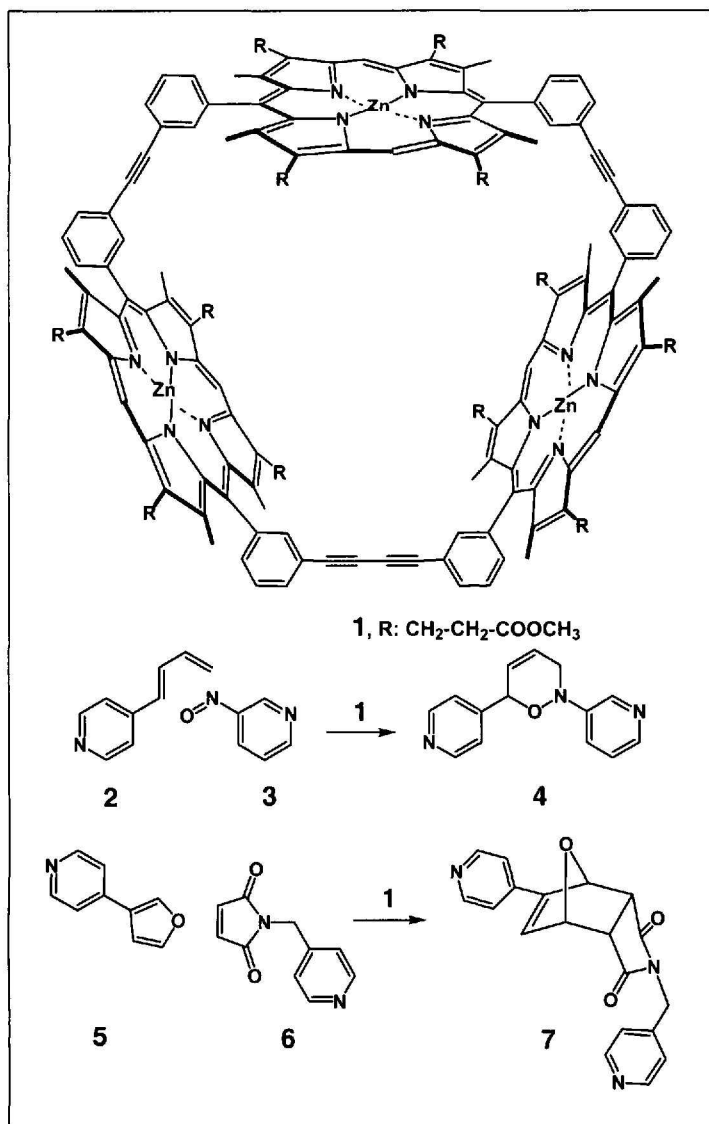
J. Sanders

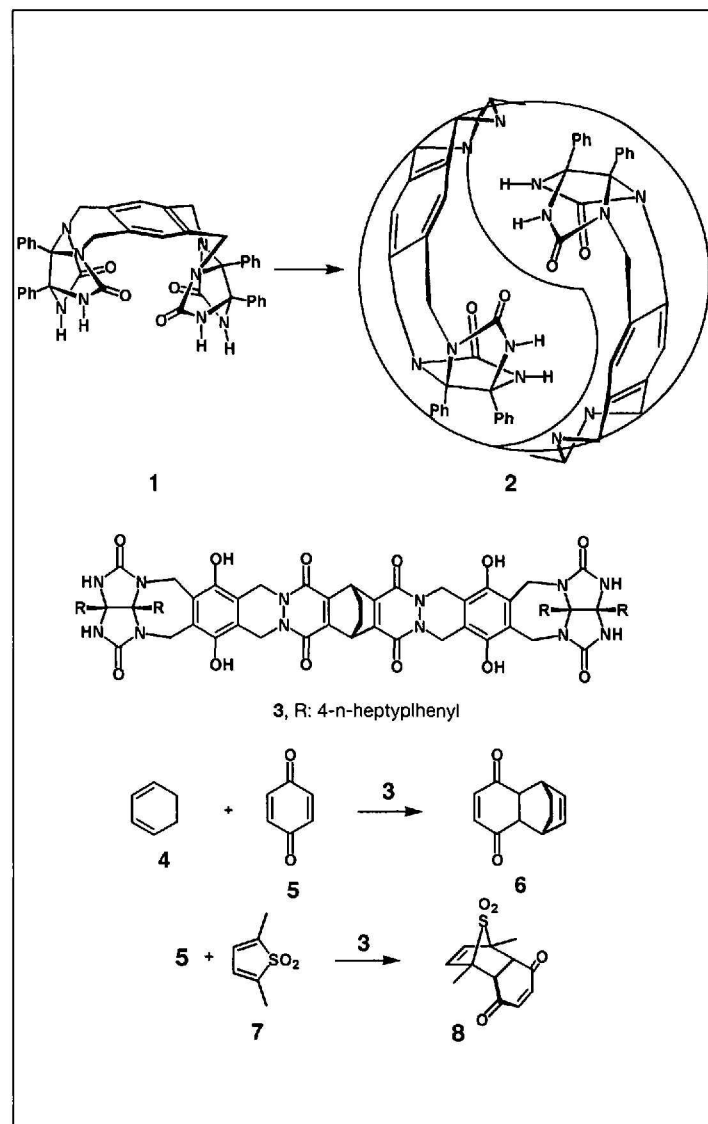## Adventures in Molecular Recognition

Due to their almost planar shape, metalloporphyrins are ideal subunits to construct fairly rigid supramolecules which are useful as templates for catalysis [6].
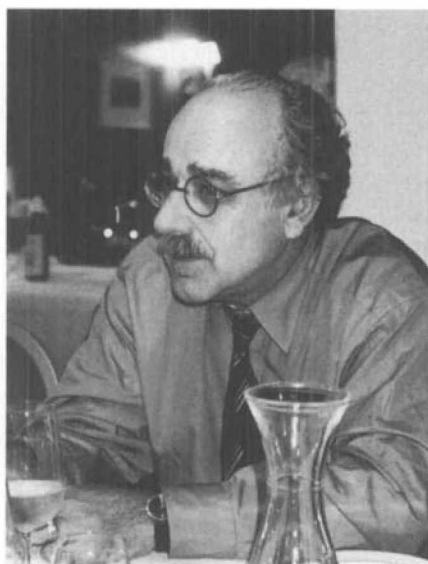
Jeremy Sanders (University of Cambridge, UK) reported the template-supported synthesis of various oligomeric zinc porphyrins of which, for example, the trimer **1** catalyzes the essentially irreversible, regiospecific hetero Diels-Alder reaction of **2** and **3** → **4** at 25 °C with rate accelerations up to 1030fold, relative to the control reaction [7] (Scheme 4). A product-like transition state is suggested because the oxazine **4** displays a particularly high binding affinity to **1**, and the addition of **4** to the reaction mixture reduces the rate considerably. The observed rate acceleration was dependent on the solvent, on the core-size of the porphyrin trimer, and on the individual porphyrin distances. Trimer **1** and the corresponding more flexible trimer expanded by one acetylene unit, were also used to probe the stereoselectivity of a Diels-Alder reaction. In the presence of **1** the reactants **5** and **6** gave only the *endo*-adduct **7** whereas the homologue produced exclusively the *exo*-adduct. Obviously the larger trimer is more flexible and is able to accommodate the geometric demands of the *exo*-pathway [8]. Hence **1** is ideally suited to act as a template for a Diels-Alder reaction that somewhat mimics an enzyme-substrate complex which lacks intrinsic chemical reactivity. Further aspects of Sander's lecture described the synthesis of a new trinuclear, heterometallic oligoporphyrin assembly which may provide a new approach to catenanes and rotaxanes based on porphynoid subunits [9].

Scheme 4

1, R: CH₂-CH₂-COOCH₃

2 **3** **4**

5 **6** **7**

Scheme 5

1 **2**

3, R: 4-n-heptyplhenyl

4 **5** **6**

5 + **3** **7** **8**

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J. Rebek, Jr.

Molecular Assembly and Encapsulation

A different supramolecular motif for encapsulation and catalysis was employed by *Julius Rebek* (TSRI, La Jolla, USA). Some years ago his group discovered a method to prepare the *bis*-glycoluril building block **1** [10], which was shown to dimerize to a tennis-ball like structure **2** by means of eight intermolecular hydrogen bonds, and which contained an internal volume for encapsulation of 60 Å^3, suitable for the binding of methane, (Scheme 5). A *bis*-glycoluril with an extended spacer, **3**, self-assembles to a softball-supramolecule with an internal volume that binds two benzene molecules face to face. Thus the cavity was considered to be large enough to encapsulate the two components **4** and **5** of a Diels-Alder reaction.

Since the encapsulation constant of **5** is 8.6×10^3 greater than for **4** and the *endo*-product **6** was shown to be an excellent guest with estimated $K_a \sim 10^4$ M^{-1}, the reactive inclusion complex could not be observed, the reaction displays product inhibition, and the rate acceleration is quite moderate (170fold) [11]. Under the same reaction conditions, when **4** was replaced by the thiophene dioxide **7**, true catalysis was observed with turnover of **7** as a result of the absence of product inhibition by **8** [12]. Rebek pointed out that his supramolecular systems present opportunities for studying aspects of recognition phenomena related to volume, *i.e.* the selection of guests by self-assembled capsules is governed by an optimal match of the size of the substrate and the cavity of the receptor, similar to the problem in drug design.

In fact, the best binding of a guest in the internal cavity of a molecular capsule was found to have a packing coefficient of ~0.55 (~55% space filled), which is also the ratio estimated for most organic liquids [13]. It can be argued, however, that deviations from this figure may lead to productive binding if additional host–guest interactions are operative such as hydrogen-bonding and Coulomb forces.

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