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Review Commentary

Elements for the construction of molecular devices: template effects and self-assembly[†]

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ABSTRACT: Four elements which may prove useful for the construction of molecular shuttles and other devices at the molecular level are discussed. (i) A novel anion-mediated template effect allows functionality to be introduced into the axle center pieces of rotaxanes so that molecular motions of the axle and wheel can be controlled by external stimuli. (ii) The deslipping kinetics of rotaxanes provide valuable insight into large changes of the deslipping rate caused by minimal structural changes. These effects, once understood, could be exploited for an optimization of the functionality of molecular devices. (iii) A wheel with an exocyclic metal coordination site provides access to self-assembled species that combine more than one macrocycle or rotaxane. This is a step towards a controlled growth of more complex species and in future may help to reduce the synthetic efforts needed for the generation of large and complex systems through self-assembly rather than covalent synthesis. (iv) In particular, for self-assembled systems with their often high degree of symmetry, mass spectrometry provides a valuable tool for the determination of their sizes. Beyond characterization, mass spectrometry provides an insight into structural details and the intrinsic reactivity of supramolecular species and thus can be expected to play an increasingly important role in the examination of molecular devices. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: supramolecular chemistry; molecular machines; mechanical bond; rotaxanes; templates; deslipping kinetics; self-assembly; mass spectrometry

INTRODUCTION

Supramolecular chemistry is currently experiencing a shift of focus from structure to function.[1] While the aesthetics of beautiful molecules and the invention of ever-new topologies of mechanically interlocked compounds has motivated earlier research, many groups today are working on the implementation and development of devices[2] at the nanometer scale for molecular electronics,[3] artificial photosynthesis,[4] construction of ion channels,[5] or the control of molecular motions,[6] just to mention a few. The promises and visions of this endeavor are multifaceted and range from the construction of computer chips of the smallest possible size to the self-fabrication of new materials with as yet unforeseen properties.[7] However, before these goals can be achieved, a large amount of additional work has to be dedicated to this field, which could be considered to be still at the very beginning.

For example, the control of molecular motions in mechanically bound species such as rotaxanes and catenanes has been achieved and molecular shuttles have been synthesized whose states can be addressed by light,[8] electrons[9] or chemical signals.[10] However, the problem of unidirectional motion[11] in what could be called a molecular rotational motor has only recently been addressed[12] and it is still not at all clear which machine could be driven by such a motor and how the mechanical energy could be converted to drive that machine. Often, even the synthesis of mechanically bound molecules is a veritable challenge, although the literature provides a huge body of studies on template effects for efficient rotaxane and catenane syntheses.[13] Nevertheless, whether it is easy to realize depends a great deal on the particular details of the desired structure.[14] Other problems remain to be solved, among them the question of how to optimize a molecular motor with respect to its efficiency once it has been successfully realized. Beyond a single molecular machine, order is needed for joint action of a large number of such machines if macroscopic

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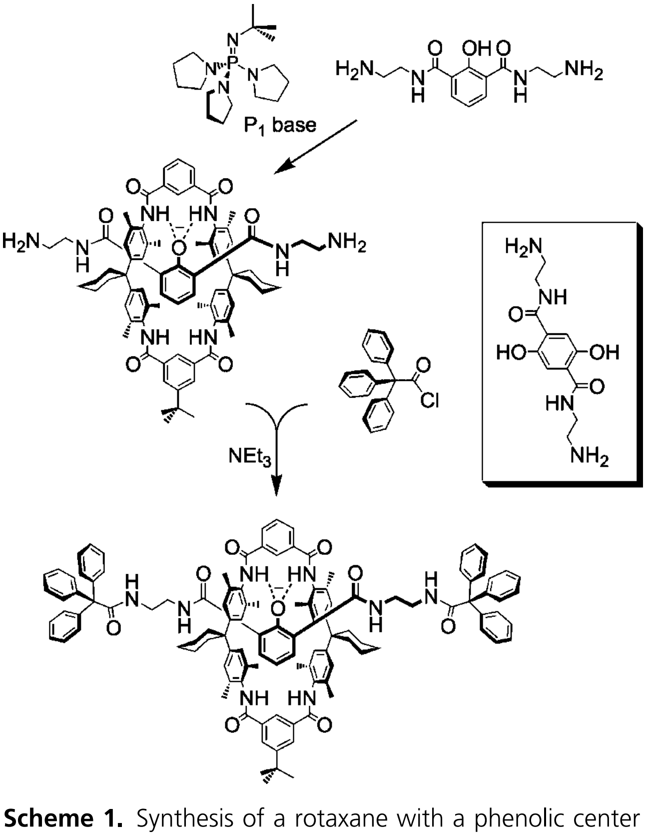
effects are to be generated. Such order can be realized in membranes, as nature does frequently,[15] on surfaces,[16] or by self-assembly[17] of small and easy to synthesize building blocks into larger and more complex species. Finally, the problem of a sufficiently precise characterization of such complex and weakly bound entities must be solved. These ideas, which have been addressed only very briefly here, are the outline of the scope of the present paper. Some of our recent results on each of these topics will be presented.

RESULTS AND DISCUSSION

Novel anion-mediated template effect for the synthesis of rotaxanes with functionalized axle center pieces

Let us begin with the synthesis of rotaxanes with functional groups, i.e. phenolic OH groups, incorporated in their axle center pieces (Scheme 1). These phenols can be expected to permit controlled structural changes mediated by external stimuli, e.g. deprotonation should greatly enhance their hydrogen bonding abilities and thus should affect the motion of the tetralactam macrocyclic wheel around the axle significantly. For their synthesis,[18] the same phenolic OH group can be elegantly exploited (for other anion template effects for the synthesis of rotaxanes, see Ref. 18).[19] The center piece is deprotonated and threaded into the macrocycle by formation of strong hydrogen bonds between the two components. The P1 phosphazene base is excellent for deprotonation, because it increases solubility in non-competitive solvents such as methylene chloride even beyond that of the neutral phenol itself. Once threaded, two stoppers can be attached to the amino groups at the two ends of the axle center piece, thus trapping the wheel on the axle by a mechanical bond. Evidence for the formation of the rotaxane comes from NMR studies and mass spectrometry. Owing to the anisotropy of the aromatic rings of the macrocycle, characteristic shifts of the signals for the axle protons can be observed relative to the free axle. In the MALDI mass spectra, intense signals for the protonated, sodiated and potassiated rotaxane are observed compared with only very minor signals for the two components. This indicates a fairly stable structure and thus excludes the formation of proton or sodium bridged dimers, which lack the mechanical bond. Interestingly, methylation of the phenolic OH group with methyl iodide after deprotonation could not be achieved. This points to the strongly hydrogen-bonded phenolate ion, which bears the wheel positioned exactly around the nucleophile as a non-covalent protecting group.[20]

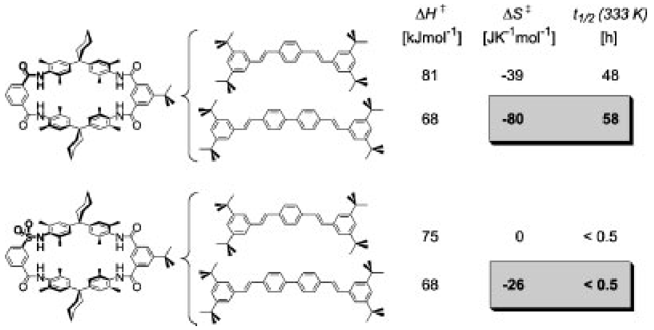


Scheme 1. Synthesis of a rotaxane with a phenolic center piece through a novel anion template effect

Deslipping kinetics of rotaxanes: large effects from small structural changes

Besides making rotaxanes, their destruction through deslippage of the wheel over one stopper can be informative.[21] A detailed analysis of the deslipping kinetics provides insight into the complementary size of the stopper boundaries and the inner diameter of the wheel cavity and thus allows steric demand to be measured experimentally through a supramolecular approach. Beyond the measurement of steric size, the deslipping kinetics also provide access to features connected to the dynamic behavior of the rotaxane, such as internal hydrogen bonding, flexibility and others.[22]

Differences in flexibility lead to changes in the entropy of activation. For example, the sulfonamide wheel shown in Scheme 2 deslips more quickly than the corresponding tetralactam macrocycle due to the lower rotational barrier of the S—N bond as compared with the C—N bond in carboxamides.[23] This is reflected in the change of the activation entropy, while the activation enthalpy remains almost the same for both rotaxanes. Conversely, a change in the size requirements leads to differences in the enthalpic contributions to the barrier. The pyridine building block in the tetralactam macrocycle in Scheme 3 is capable of forming rather strong intramolecular hydrogen bonds with the adjacent amide NH protons. This reduces significantly the size of the wheel and deslipping is only possible after breaking the hydrogen bonds. Thus, their binding energy contributes to the activation enthalpy, increasing the half-life by a factor of more than 10 000.[23]



Scheme 2. Activation parameters for the deslipping reaction of rotaxanes bearing tetralactam and sulfonamide wheels. The different deslipping rates are mostly due to changes in activation entropy, which reflect the higher flexibility of the sulfonamide group

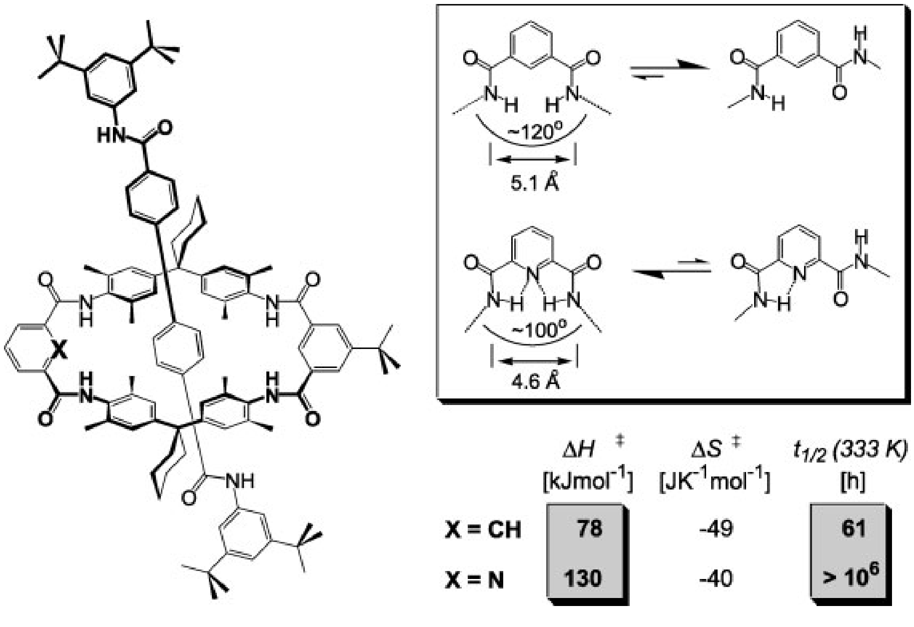
These results suggest that the deslipping reaction is a highly sensitive tool to detect small changes in the structure of these rotaxanes and their consequences for the dynamic behavior. Probably, one of the smallest possible structural changes is isotopic substitution and it is an interesting question whether the deslipping reaction would give different results for rotaxanes with deuterated stoppers as compared with their unlabeled analogues.[24] This is indeed the case: owing to the smaller vibrational amplitude of the C—D bond, the deuterated rotaxanes depicted in Fig. 1 deslip at a ca 10% higher rate yielding a secondary, steric kinetic isotope effect of ca 0.9.

Finally, the mere orientation of an ester group in the axle is significant (Fig. 2).[25] The rotaxane with the benzoic acid stopper (Fig. 2, top) does not show any deslipping in tetrachloroethane even after prolonged heating for 200 h. In marked contrast, the rotaxane with the phenol stopper (Fig. 2, bottom), which differs only by the orientation of the ester groups, deslips with a half-life of ca 2 h. Since this effect is much reduced in a competitive solvent such as DMSO, we interpret these results as being a cooperative interplay of hydrogen bonding between axle and wheel and the reduced flexibility of the benzoic acid stopper, which bears a carbonyl group conjugated to the stopper phenyl ring. The conjugation increases rigidity due to a higher rotational barrier.

These findings, which can only be summarized briefly here, demonstrate that small structural changes can cause unexpectedly large effects in the deslipping kinetics. Once understood, such effects can consequently be utilized to optimize the function of molecular machines without completely changing their structure, thus avoiding unwanted side effects.

Building larger architectures: macrocycles and rotaxanes with exocyclic metal coordination sites

On working towards molecular machinery, one encounters the problem of putting together large and complicated species in order to generate a complex function. Covalent synthesis has disadvantages here, because it would require a considerable effort, comparable to the total synthesis of complex natural products. Self-assembly strategies allow the chemist to use much simpler building blocks, which are suitably ‘programmed’ to organize themselves into the desired complex architecture.[17] In order to proceed in this direction, we synthesized a new tetralactam wheel bearing an exocyclic metal coordination site (Scheme 4).[26] In the preparation, an



Scheme 3. Activation parameters for the deslipping of rotaxanes bearing isophthalic acid amide or pyridine dicarboxamide subunits in their wheels. Intramolecular hydrogen bonding, as shown in the inset, fixes the wheel conformation and reduces the inner diameter. For deslipping, the hydrogen bonds must be broken

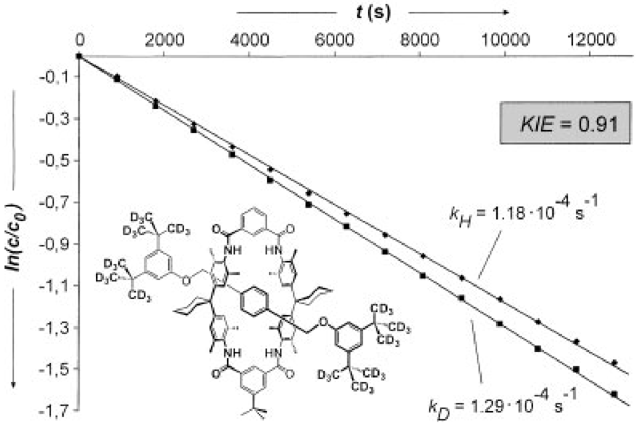


Figure 1. The deslipping reaction of rotaxanes follows a unimolecular rate law as indicated by a linear plot of ln(c/c_0) versus time t. Rotaxanes with deuterated stoppers deslip at a higher rate than their unlabeled isotopologues with an inverse kinetic isotope effect of 0.9. This KIE reflects the lower vibrational amplitude of the C—D bond

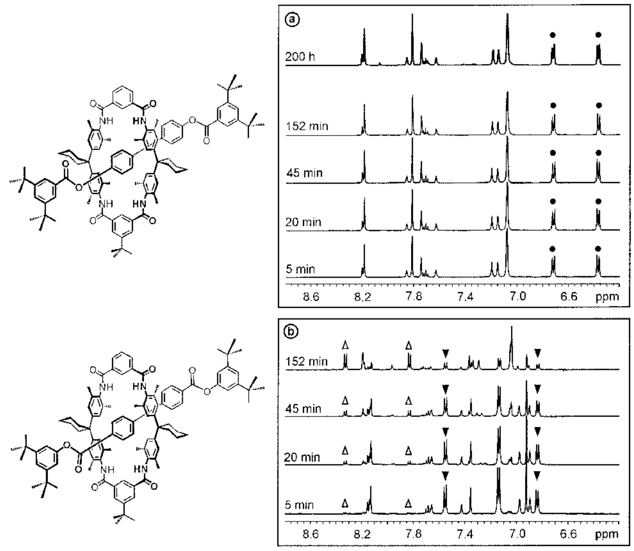
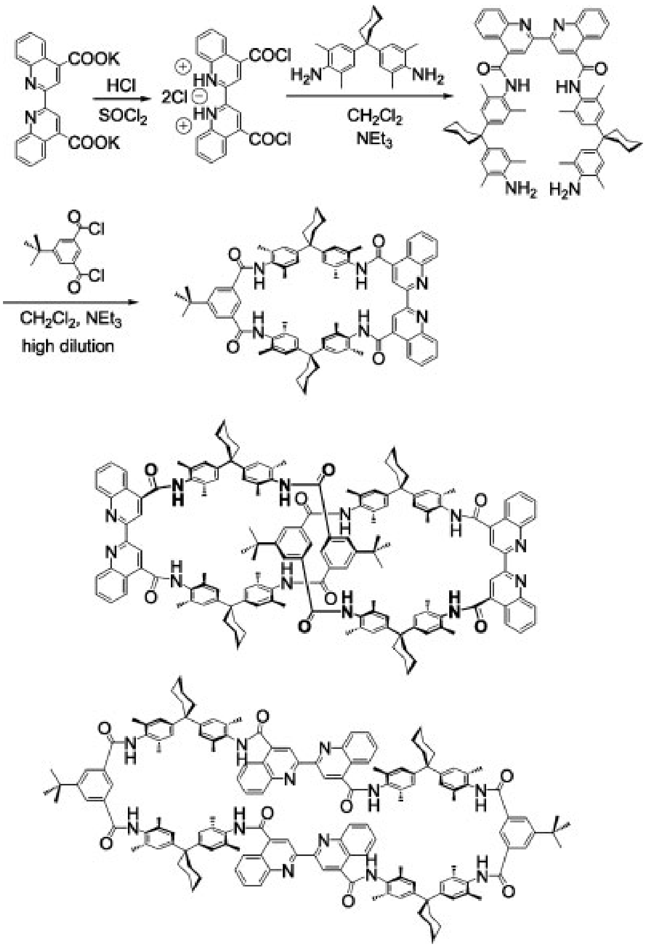


Figure 2. ^{1}H NMR spectra (tetrachloroethane-d_2, 120 °C) obtained after different time intervals for two rotaxanes that differ merely with respect to the orientation of the ester groups in the axle. While the rotaxane on top does not deslip even after prolonged heating, the half-life of the second rotaxane is ca 2 h at 120 °C

octalactam macrocycle that is twice as big and a catenane with the same elemental composition are formed, which can easily be characterized by mass spectrometry (see below). It is possible to prepare rotaxanes from the tetralactam macrocycle, if a larger tris-(t-butylphenyl)-methyl phenol stopper is used to prevent deslippage. All species have been examined with respect to their ability to form complexes with Cu(I) and it turned out that the tetralactam macrocycle and the catenane dimerize through one or two copper ions, respectively, while the large macrocycle forms a figure-eight shaped monomer with the copper ion at the center (Plate 1). Interestingly, a bpy$_2$Ru(II) complex of the tetralactam macrocycle showed excellent anion binding behavior. While dihydrogen phosphate binds in DMSO to the macrocycle alone with a binding constant of ca 1000 M^{-1}, the ruthenium complex exhibits much stronger binding ($K = 25\,000\ \text{M}^{-1}$).



Scheme 4. Synthesis of a tetralactam macrocycle bearing an exocyclic metal coordination site and the octalactam and catenane side products

It should be possible to extend the principle illustrated for these macrocycles, catenanes and rotaxanes to even larger self-assembled species and thus provide access to complex systems with complex functions. However, one problem remains: it is necessary to connect identical units to each other so that a fruitful combination of the principles of self-assembly and some other type of 'sequence' information are required. So far, this problem seems to remain largely unresolved.[1b]

Mass spectrometry as a tool for the investigation of supramolecular species

The fourth aspect of this paper is the characterization of supramolecular species. In particular, the analysis of

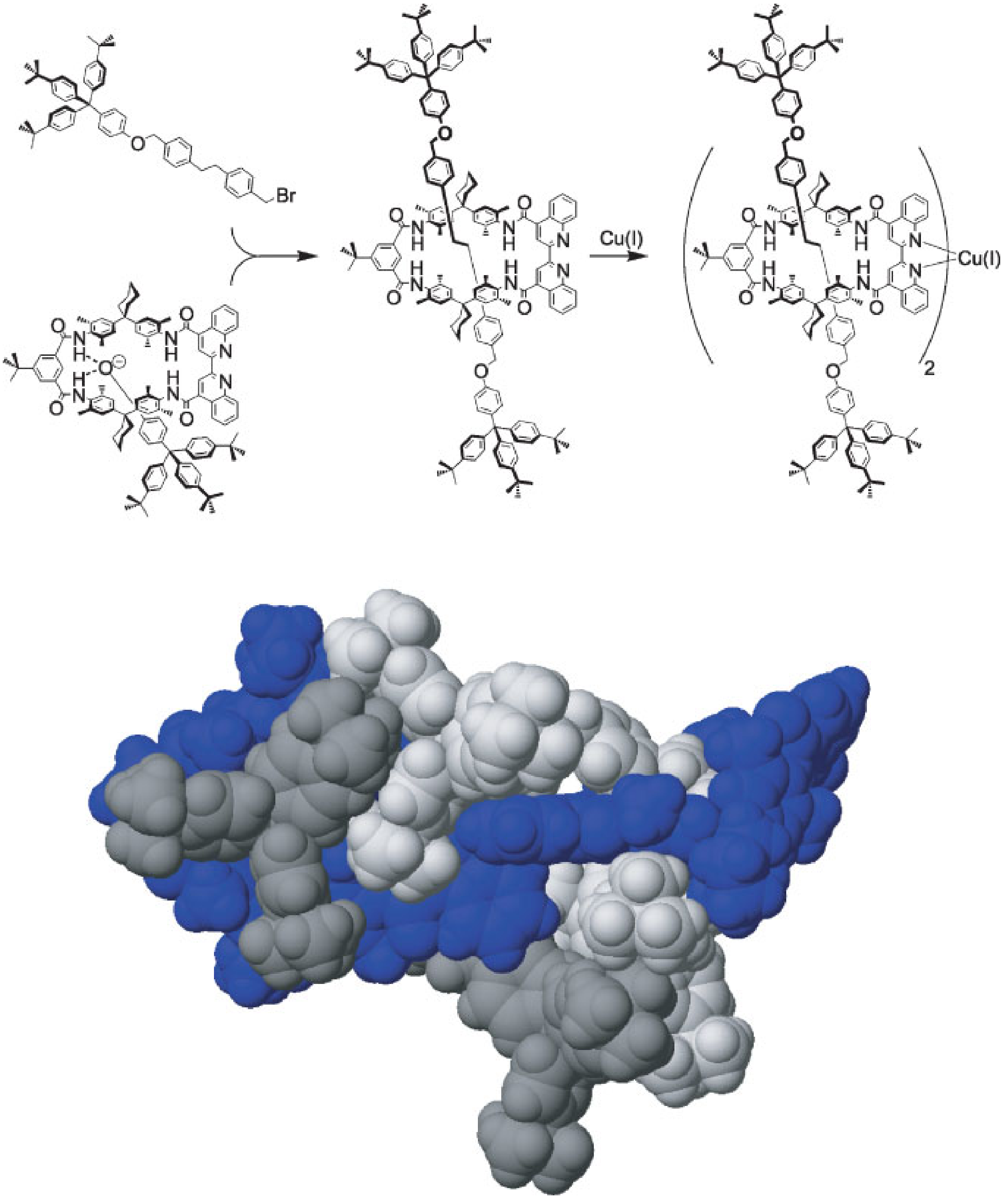


Plate 1. Top: Anion-templated rotaxane synthesis utilizing a biquinoline-bearing wheel and subsequent dimerization of the rotaxane via Cu(I). Bottom: MM2 optimized structure of the rotaxane dimer held together by a central Cu(I) ion. Blue parts of the space-filling representation correspond to the two macrocyclic wheels, dark grey and light grey parts represent the two axles threaded through the two perpendicular macrocycles

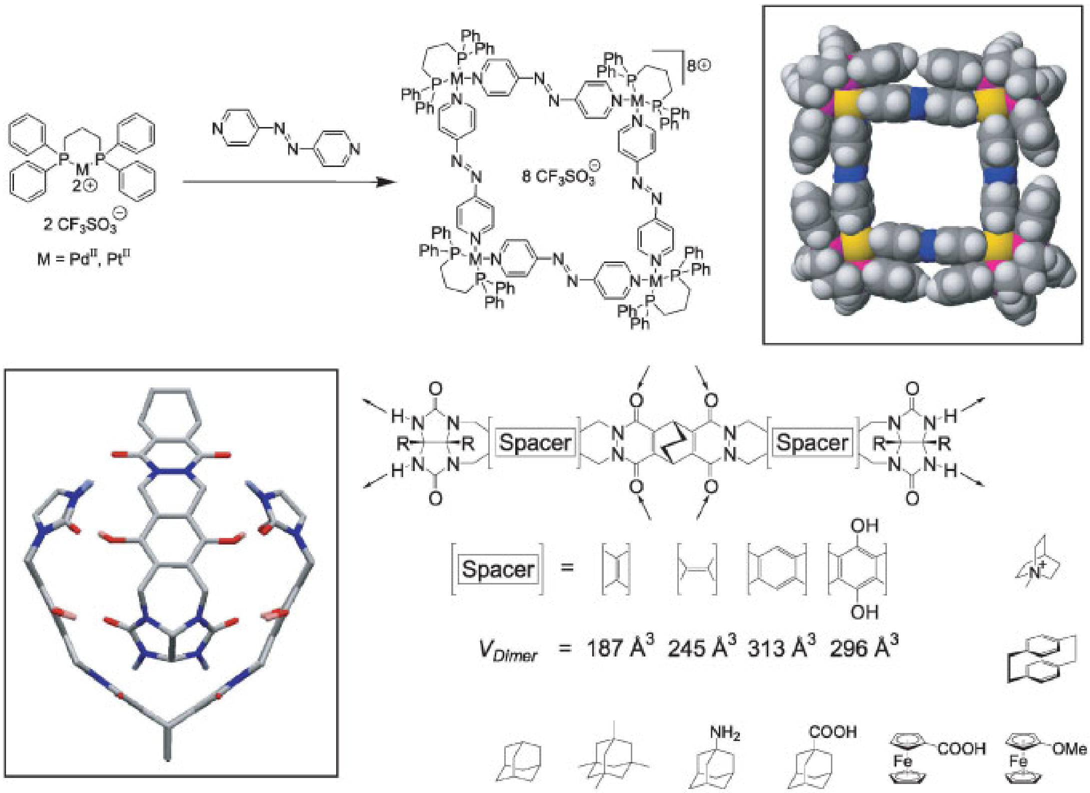


Plate 2. Top: Self-assembly of a molecular square containing azopyridine ligands and force field minimized structure of the product in space-filling representation. Bottom: Molecular formulae of the four softball monomers which, due to spacers of different lengths, have inner cavities of different volumes. Typical guests are shown that have been used to fill the cavities. Arrows indicate hydrogen bond donors and acceptors. The inset on the left shows a force field minimized structure of one of the softballs

self-assembling complexes that contain multiple copies of the same building blocks requires precise size information. Owing to a high degree of symmetry, other methods often yield ambiguous data leaving the question of stoichiometry unanswered. In this instance mass spectrometry is a very valuable tool yielding very precise data even for mixtures, provided that the intact ionization of the species under study can be performed successfully.[27]

Beyond a merely analytical application of mass spectrometry, it also enables supramolecular complexes in the gas phase to be examined and thus provides information about the structure of supramolecular complexes, their reactivity or their thermochemistry. In particular, the comparison of thermochemical data from gas phase and solution experiments could provide a profound insight into the role of solvation (see Ref. 28, for example, for a discussion of the best fit concept of cation/crown complexes).

We have been able to address the structural topic with a study on how to distinguish the topology of macrocycles and catenanes, such as those shown in Scheme 4 and similar analogues.[29] Indeed, the fragmentation pattern in a tandem MS experiment, in which the ions are selected by mass and subjected to collisional activation, are clearly indicative of the topology. While all monocyclic species exhibit an intense loss of a neutral water molecule, the catenane undergoes ring cleavage followed by loss of one of the two macrocycles, which are no longer intertwined after dethreading. Another structural issue that could successfully be resolved by mass spectrometric means is the structural integrity of hydrogen-bonded capsules (Plate 2, left).[30] The two monomers of this 'softball' are C-shaped and are held together by hydrogen bonds, thus generating a cavity, the inside of which can be filled with guests.[31] With positively charged guests, intact ionization is possible and experiments with deformed capsule monomers, oversized guests and heterodimer formation provide evidence for a capsular structure. Collision experiments give rise to covalent bond cleavages competing to some extent with guest release, which supports the assumption that the guest is tightly bound inside the cavity. Supramolecular squares (for a selection of reviews see Ref. 32) can serve as the last example for the utility of mass spectrometry.[33] These species can not only be studied with respect to their structure, but also their reactivity can be examined. After cleavage of the macrocycle, one free end can favor one of all possible fragmentation reactions through what could be called a supramolecular neighbor group effect, giving rise to a triangle in a true gas-phase reaction.

CONCLUSIONS

With these four aspects of our approach to functional supramolecular species, we combine synthetic supramolecular chemistry with mass spectrometry as a specific method for elucidating the properties of the supramolecular species under study. Although this account gives an overview of a research program we started only recently, we consider that implementing functionality into these structures is one of the primary goals, in order, finally, to be able to construct devices for technical applications.

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