

Topologically novel multiple rotaxanes and catenanes based on tetraurea calix[4]arenes

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Calix[4]arenes bearing at their wide rim four urea residues easily form hydrogen bonded dimeric capsules. This has been used to preorganise alkenyl functions attached to these urea groups for their controlled connection *via* metathesis reaction. Multimacrocyclic tetraurea derivatives are thus obtained in excellent yields *via* heterodimers which are formed exclusively with tetratosylurea derivatives. Heterodimerisation of such bis- and tetraloop tetraureas leads analogously to multicatenanes, or to rotaxanes by stoppering. Huge macrocycles are detached from tetraloop derivatives by cleavage of the urea function.

Introduction

Topologically nontrivial molecules,¹ such as catenanes, knots,² Borromean rings,³ Möbius strips⁴ or K₅-molecules⁵ have attracted the interest of (synthetic) chemists for a long time from a purely “intellectual” point of view. Not only their synthesis provides challenges, but also their description in terms of topological (stereo) isomerism, topological chirality *etc.*

However, often there is also some “practical” use of such studies. It has been shown that topologically very complex molecules (DNA) exist in nature, being essential for correct

transcription processes.⁶ Mechanically interlocked molecules, especially catenanes and rotaxanes⁷ have been constructed also as prototypes for various molecular devices (switches, molecular machines,⁸ actuators^{9,10}), for information storage, *etc.* And this would not be the first case in which purely “intellectual curiosity” leads to important practical implications in the end.

Catenanes and rotaxanes

The first controlled synthesis of catenanes by Schill and Lüttringhaus was based on the prearrangement of reactive groups *via* covalent attachment.¹¹ A linear precursor for the second macrocycle was bound to a prefabricated macrocyclic molecule. Two intramolecular ring closure reactions with an additional intra-annular functional group, sterically possible

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Myroslav O. Vysotsky was born 1971 in Kiev (Ukraine). He obtained his Diploma in Chemical Engineering of Organic Compounds in 1994 from the National Technical University of Ukraine “Kiev Polytechnical Institute”. Since 1994 he has worked at the Institute of Organic Chemistry of National Academy of Sciences of Ukraine (Kiev), where he obtained his PhD degree (Candidate of Sciences,) in 1998 for research on O-phosphorylated calixarenes under the supervision of Vitaly I. Kalchenko. He spent one year as The Royal Society/NATO post-doctoral fellow with

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Volker Böhmer, born 1941, studied chemistry at the Johannes Gutenberg-Universität Mainz. He received his PhD degree in Organic Chemistry in 1969 in the group of Hermann Kämmerer for research which used oligonuclear phenolic compounds as templates. With the exception of a stay as guest lecturer at the university in Le Mans he remained loyal to the university in Mainz, where he played a major role in the development of the Department for Teacher Trainees in Chemistry.

Familiar with phenolic resins, he was already involved in the field of calixarenes before this name was coined. Parallel to the stepwise synthesis he developed the fragment condensation for the preparation of inherently chiral, bridged, annelated and double calixarenes. His present research interests comprise self-assembly phenomena in general and their use to prepare topologically challenging molecules based on the calixarene skeleton. He is a member of the Sonderforschungsbereich 625 “From Single Molecules to Nanoscopically Structured Materials” and co-author of more than 250 scientific publications.

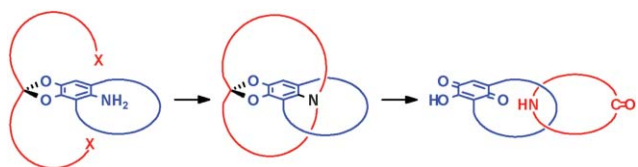


Fig. 1 Prearrangement *via* covalent links in the first rational synthesis of a [2]catenane.¹¹

only in *one* way, led to the desired multicyclic product (30%). Finally, the catenane was formed by breaking the covalent linkages between the two macrocycles (Fig. 1).

More recently the covalent approach was used again by Godt *et al.* to prepare [2]catenanes with large and thus freely moving rings.¹² Ring formation was achieved by oxidative coupling of acetylene groups within two rigid 2,6-aryl phenols held in the correct mutual position *via* a connecting carbonate link.

In spite of this “revival” of preorganisation *via* covalent bonds, the “breakthrough” in the synthesis of catenanes (and rotaxanes) came when metal coordination was used to self-assemble suitable building blocks in a correct orientation around a template. Meanwhile classical template syntheses for [2]catenanes were described by Sauvage *et al.*, using the tetrahedral coordination sphere of Cu(I) to arrange suitably functionalised phenanthroline derivatives¹³ (Fig. 2).

The strategy also allowed the first controlled synthesis of a trefoil knot¹⁴ and was very recently used to prepare a [3]catenane in which one ring is threaded through both rings of a “handcuff-like” compound.¹⁵ The preorganisation of suitable precursors within metal complexes was later extended to other ligands (*e.g.* terpyridines¹⁶ or 2,6-diiminopyridines¹⁷) also using cations with octahedral coordination spheres (Mn²⁺, Fe²⁺, Co²⁺, Ni²⁺, Zn²⁺, Cd²⁺, Hg²⁺).¹⁷

Simultaneously, with the progress of “supramolecular chemistry”¹⁸ other reversible interactions were either applied by design or understood as the driving force behind initially unexpected results or observations. Hydrogen bonding between amides of isophthalic acid and/or 2,6-pyridine diacid was used by Hunter¹⁹ and Vögtle²⁰ to synthesise catenanes and knots. In countless publications Stoddart and his group combined π - π -stacking (donor-acceptor interactions) and hydrogen bonding, to synthesise a myriad of catenanes, including a [5]catenane (“olympiadane”).²¹ Recently Beer *et al.* described the synthesis of [2]catenanes using the preorganisation of diamides derived from isophthalic acid (and its pyridinium analogue) by chloride anions as template.²² Coordination to the anions *via* hydrogen bonds was assisted by π - π stacking (and further hydrogen bonding) in this case.



Fig. 2 Controlled synthesis of a [2]catenane; prearrangement of the linear precursors *via* coordination to a metal cation as template.¹³

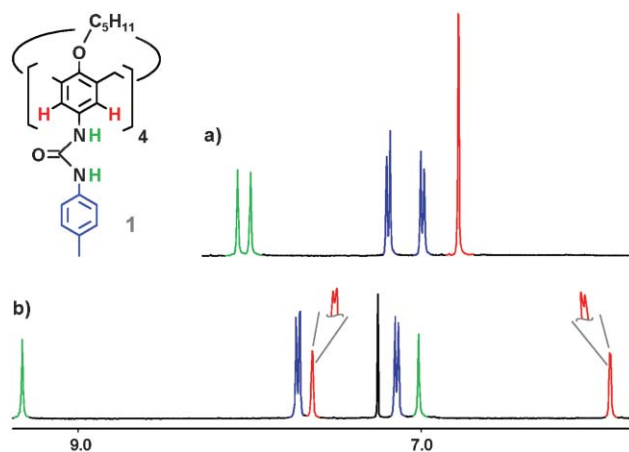


Fig. 3 Sections of the ¹H NMR spectra of a tetraurea **1** in (a) DMSO-*d*₆ and (b) chloroform-*d*₁.

Many of these template syntheses of catenanes²³ start with a (prefabricated) macrocyclic compound which is preorganised with a linear precursor in an assembly often named a “*pseudo* rotaxane”.²⁴ Thus, rotaxanes can be obtained (for instance by stoppering²⁵) using quite similar strategies as outlined for catenanes. On the other hand, the self-assembly of non-cyclic precursors may even lead to such sophisticated mechanically interlocked compounds, like Borromean rings.²⁶

Hydrogen bonded capsules of tetraurea calix[4]arenes

It is now roughly a decade ago, that Rebek and Shimizu reported for the first time, that calix[4]arenes substituted at their wide rim by four urea residues form dimeric capsules, in aprotic, apolar solvents such as chloroform or benzene, which are able to (reversibly) include suitable guest molecules.²⁷ The unique structure of these dimers (see Fig. 4), in which the two calix[4]arenes are connected *via* their wide rim and held together by a seam or belt of hydrogen bonded urea functions was first deduced from their ¹H NMR spectra (see Fig. 3). In polar, hydrogen bond breaking solvents (*e.g.* DMSO-*d*₆, THF-*d*₈ or pyridine-*d*₅) a singlet for the aromatic protons of the calixarene is in agreement with (the expected) C_{4v}-symmetry. In apolar solvents two *meta*-coupled doublets for the aromatic

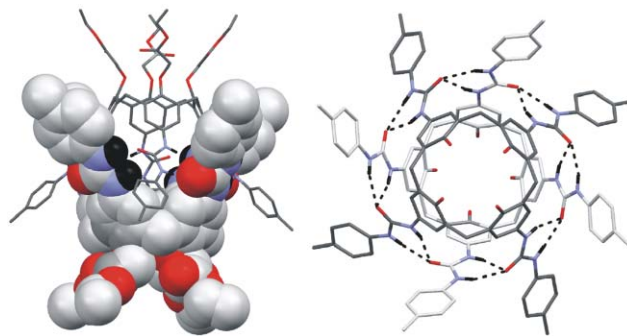
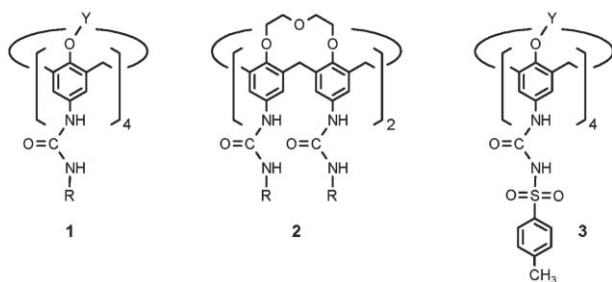


Fig. 4 Dimeric capsules of tetraurea-calix[4]arenes **1** (R = tolyl; Y = CH₂-COOEt): side and top view (OY are omitted) of the X-ray structure.²⁹

protons clearly indicate C_4 -symmetry for the single calixarene and S_8 -symmetry for the dimer. The signal for one of the NH-protons is strongly downfield shifted, indicating strong hydrogen bonds, while the guest inclusion (often the solvent itself) is indicated by upfield shifted signals.

The existence of dimers in solution was unambiguously confirmed by the formation of heterodimers in solutions containing two different tetraurea derivatives.²⁸ A single crystal X-ray structure^{29,30} was totally in agreement with the structure predicted or better designed by Rebek and Shimizu. Both calix[4]arenes fixed by the dimerisation in a “regular C_4 -symmetrical cone” conformation, are turned by 45° around the common fourfold axis and their urea residues are pointing in opposite directions; see Fig. 4.

The (more or less) statistical formation of heterodimers is not general, however. Tetraureas **2** derived from a calix[4]arene rigidified in a very regular cone conformation by two short crown ether chains, do *not* combine to form heterodimers with **1**,³¹ while tetraosyl ureas **3** form *exclusively* heterodimers in a stoichiometric mixture with tetraarylureas **1** ($R = Ar$).³² And also the directionality of the hydrogen bonded belt, which is seen for neutral guests even at elevated temperatures, is usually not observed for organic cations as guests at room temperature.³³



The thermodynamic stability of the dimers is difficult to assess, since conditions for a simple equilibrium between monomer and dimer do not exist. Kinetic measurements under high dilution (0.05–0.5 μM) by fluorescence resonance energy transfer (FRET) between tetraurea calix[4]arenes labelled at the narrow rim by appropriate coumarine dyes led to rate constants for the formation and dissociation from which association constants up to $\sim 10^9 \text{ M}^{-1}$ could be derived.³⁴

Rate constants derived from NOESY-NMR studies in benzene solution ($c = 3\text{--}5 \text{ mM}$) led to values of $k_1 = 0.25\text{--}0.5 \text{ s}^{-1}$ for the dissociation/recombination and for the guest exchange.³⁵ Further kinetic studies revealed that the rate of the guest release or exchange depends not only on the structure of the calixarene,³⁶ but also on the guest and on the solvent.³⁷

Preorganisation

As pointed out above, the appropriate preorganisation of functionalised building blocks by suitable templates is an essential requirement for the successful synthesis of catenanes and rotaxanes.

The mutual arrangement of the two calixarenes within a dimer, in which the interdigitating urea groups R point (alternatingly) in opposite directions, offers such a unique preorganisation. The high (thermodynamic as well as kinetic) stability of the dimers suggests that this preorganisation may

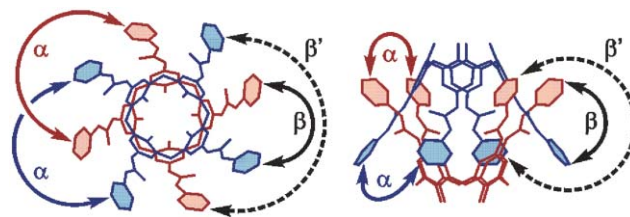


Fig. 5 Potential covalent connections between urea residues belonging to the same (α) or to different calixarenes (β, β').

be used to connect these residues R by controlled and well defined reactions between functional groups attached to the urea groups.

As illustrated in Fig. 5, a potential reaction may link neighbouring residues within the same calixarene (α -connection), leading to additional macrocyclic structures within this calixarene. It may, however, also occur between the two calixarenes (β -connection), forming covalently linked “double calix[4]arenes”.

Symmetry properties

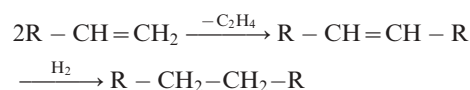
Before we discuss such reactions, it will be useful to consider the symmetry properties of those dimers. As mentioned already, the S_8 -symmetrical homodimer of a tetraurea consisting of identical phenolic units **A** is composed of two enantiomers with C_4 -symmetry. Consequently a heterodimer with a calixarene consisting of four units **B** must be chiral. However, this chirality is only due to the directionality of the hydrogen bonded belt of the urea functions.

A calixarene consisting of two different phenolic units **A** and **B** (this difference may be due to the ether residues Y or to the urea residues R or both) in alternating order **ABAB** is C_{2v} -symmetric (time averaged). In this case the dimer is chiral (D_2 -symmetry) also without the directionality of the hydrogen bonds, just by the mutual arrangement of the two non-chiral calixarenes, and thus it is justified to name this “supramolecular chirality”. The directionality of hydrogen bonds reduces the symmetry from D_2 to C_2 ,³⁸ but it does not create new stereoisomers.

For calix[4]arenes of the **AABB**- and **ABBB**-types two regioisomers exist which have C_2 - and C_1 -symmetry, respectively. Fig. 6 summarises this discussion and introduces a graphical representation of the dimers in which the calixarenes are symbolised by regular squares with the phenolic units at the corners.

Choice of the reaction

In principle all chemical reactions may be used for a covalent connection of urea residues, as long as they can be conducted under conditions under which the hydrogen bonded dimers exist. We have chosen for our studies olefin metathesis,³⁹ which gives (after hydrogenation of the initially formed double bonds) a stable, inert aliphatic connection:



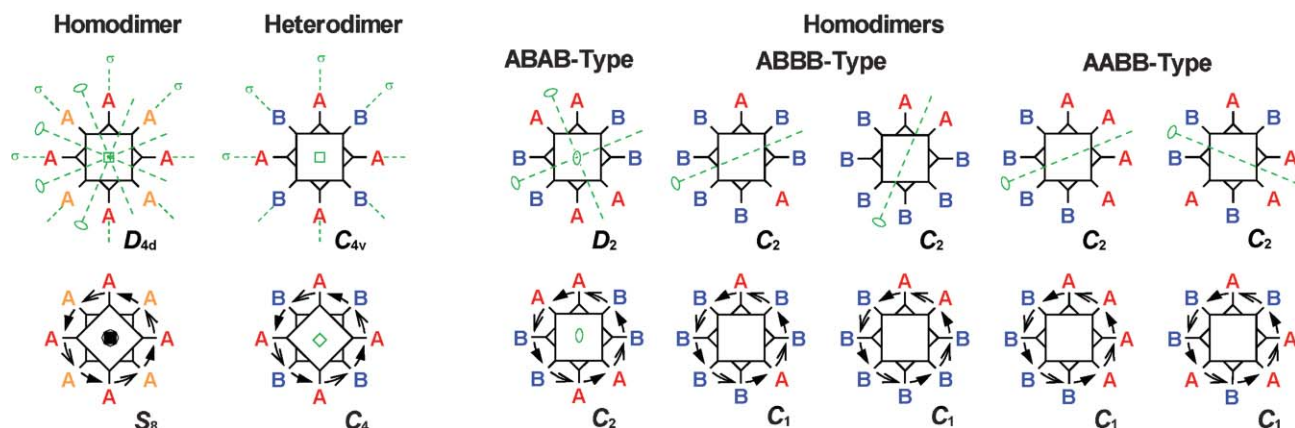


Fig. 6 Symmetry properties of the homodimers and heterodimers of tetraurea derivatives. Calix[4]arenes are represented by squares with the phenolic units at the corners. Symmetry elements are indicated (green), symmetry classes are given with and without directionality of the hydrogen bonded belt shown by arrows.

Various examples from the literature demonstrate its utility for intramolecular connections in syntheses of bridged macrocycles,⁴⁰ dendrimers with covalently linked shells,⁴¹ as well as for reactions within self-assembled structures⁴² including nanotubes,⁴³ which can be covalently stabilised in this way.⁴⁴

First attempts

Tetraurea calix[4]arenes **1a** (Fig. 7) bearing a single alkenyl group $[-(\text{CH}_2)_6-\text{CH}=\text{CH}_2]$ per urea residue were easily synthesised, by acylation of the respective tetraamino calix[4]-arene **4** with *p*-nitrophenyl chloroformate, followed by aminolysis with *m*-alkenyloxy aniline.⁴⁵ For the metathesis reaction we used the commercial first generation Grubbs' catalyst under standard conditions in dichloromethane as solvent. A solution of the calixarene in benzene was added since benzene, as a good guest, should favour the dimerisation. The total concentration of **1a** was 10^{-4} M to suppress reactions *between* dimers. To avoid stereochemical complications due to the formation of *cis/trans* isomers the reaction product was hydrogenated before work up.

Nonetheless three reaction products were isolated which by their mass spectra proved to be isomers with the expected mass. To understand their structure it is useful to discuss the symmetry properties of the potential reaction products (Fig. 7).

Four α -connections lead to a bis[2]catenane **5** (for the name see below) with D_2 -symmetry, four β -connections to a tetrabridged capsule **7** with D_4 -symmetry, while the product **6** with C_2 -symmetry results for two connections of each type. In all cases twofold axes within the drawing plane are not observed under conditions where the directionality of the hydrogen bonded belt is kinetically stable. Consequently the symmetry is reduced to C_1 , C_2 and C_4 for **6**, **5** and **7** respectively. The ^1H NMR spectra for the reaction products in solvents such as benzene or chloroform, which are also included as guests in the dimeric capsules, are entirely in agreement with these symmetries. Thus, the products obtained could be easily identified. With tetraethyl ammonium cations as guests (see also below), the directionality of the hydrogen bonds changes rapidly on the NMR-timescale,³² and

consequently the spectra reflected the higher symmetry indicated also in Fig. 7, which can be seen as additional proof.

It is noteworthy, that in the case of the tetrabridged capsule **7** racemisation is possible by dissociation and recombination of the two calixarene substructures, while the other two isomers with catenated structures cannot racemise without breaking covalent bonds.

Guest exchange and internal guest mobility

The cavities of dimeric capsules are large enough ($190\text{--}200 \text{ \AA}^3$) to include small molecules as guests. In fact, the presence of a

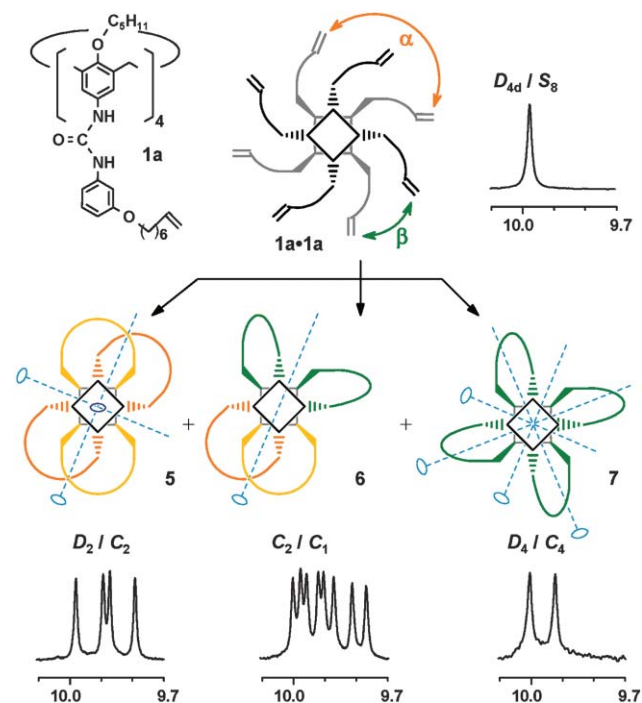


Fig. 7 Symmetry of the starting dimer **1a·1a** and of the potential reaction products formed by metathesis (α - and β -connections) and subsequent hydrogenation.⁴⁵

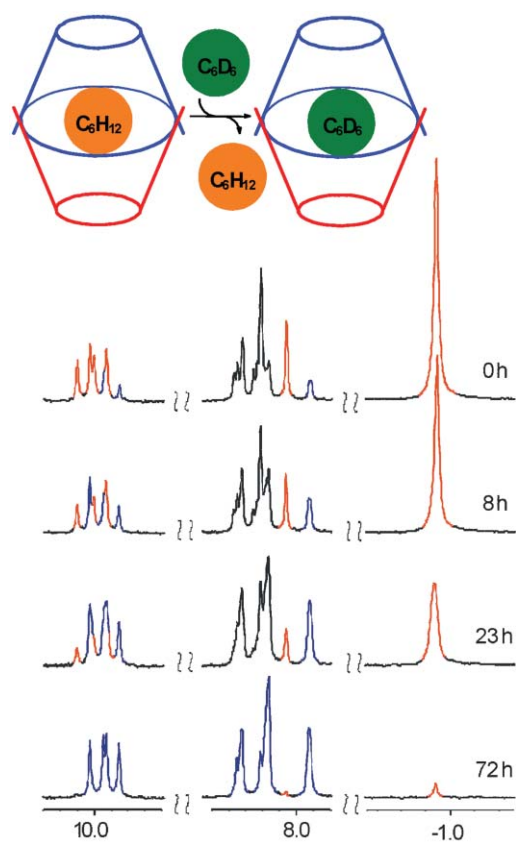


Fig. 8 Schematic representation of the guest exchange and section of the respective NMR-spectrum, showing the decreasing peak of the included, non-deuterated guest (C_6H_{12}).⁴⁵

suitable guest (often the solvent) is a necessary condition for the dimerisation, since capsules without a guest do not exist.

Evaporation of a solution of a tetraurea of type **1** in a suitable solvent (*e.g.* cyclohexane) usually leads to a solid (crystalline) residue for which the inclusion of solvent is easily shown by its upfield shifted signal(s). Monitoring these signals as a function of the time offers an easy way to determine the rate of the guest release (Fig. 8). In most cases the overall process, kinetically a first order reaction, is an exchange with the deuterated solvent as guest.³⁶ However, if the solvent molecule is too large, the (original) capsule may be destroyed with the same rate.³⁶

Such kinetic data for the exchange of cyclohexane with C_6D_6 (the solvent) are collected in Table 1. As expected, the first order rate constant is distinctly higher for dimers **1a** than for compounds **5–7**, for which a small but still significant increase is observed in this order.

Table 1 Rate constants k and half-lives $\tau_{1/2}$ for the exchange of C_6H_{12} with the solvent C_6D_6 and energy barriers for the reorientation of included Et_4N^+ at the coalescence temperature T_C

Compound	k/h^{-1}	$\tau_{1/2}/h$	$\Delta G^\ddagger/kJ mol^{-1}(T_C/K)$
1a	0.090	7.7	47 (265)
5	0.045	15	55 (306)
6	0.048	14	52 (292)
7	0.059	12	50 (278)

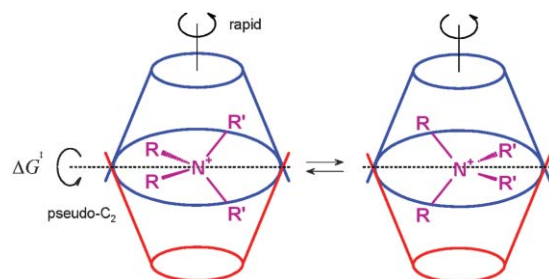


Fig. 9 Mobility of the Et_4N^+ cation within a hydrogen bonded capsule. While the rotation around the molecular axis is fast, the energy barrier for the exchange of the two types of methyl groups can be deduced from VT-NMR.

While most of the included guests (*e.g.* benzene, cyclohexane, chloroform) are freely tumbling on the NMR-timescale inside the cavity of a capsule, this motion can be frozen for the tetraethyl ammonium cation as guest.³³ A single signal for the methyl groups at about -1.6 ppm splits into two signals at -0.2 and -3.3 ppm at low temperature.⁴⁶ This is interpreted as a motion which brings methyl groups oriented towards the aromatic π -electrons of the calixarenes into the less shielded “equatorial” position (the hydrogen bonded belt of the urea functions) and *vice versa* (Fig. 9). From the coalescence temperature the energy barriers ΔG^\ddagger for this process can be derived, which are also included in Table 1. Their decrease in the order **5** > **6** > **7** > **1a** indicates an increasing mobility in the same order, in agreement with the expectations which suggest the most rigid structure for the bis[2]catenane **5**.

Improved synthesis of bis[2]catenanes

To obtain a variety of bis[2]catenanes in larger quantities which allow a comparative determination of their properties it was necessary to develop a better synthetic strategy, which suppresses the undesired β -connections. Starting with tetraurea derivatives in which adjacent urea functions are already covalently connected, avoids or reduces the number of potential β -connections.⁴⁷

Macrocyclic tetraureas can be prepared by conventional acylation of tetraamines under dilution conditions as shown in Fig. 10. Active bis(urethane)s **13** are preferable as reagents since they can be more easily purified and stored than bis(isocyanate)s. Boc-protection⁴⁸ allows the synthesis of bisloop compounds with two different rings. Such a “two-step” cyclisation can be useful, also, to ensure the connection of adjacent groups and to avoid *trans*-cavity bridging.

It has been shown earlier, that monolooop compounds **11** form selectively only one of the two regioisomeric homodimers, usually observed for tetraureas of the ABBB-type.³⁸ The other isomer would lead to a sterically (and thus energetically) very unfavourable overlap of the loops. For exactly the same reason bisloop compounds **12** do not form homodimers at all! The tendency to obtain all urea functions paired in dimers in apolar solvents thus leads to the exclusive and complete formation of heterodimers if **12** is combined with the equivalent amount of an “open chain” tetraurea **1**.

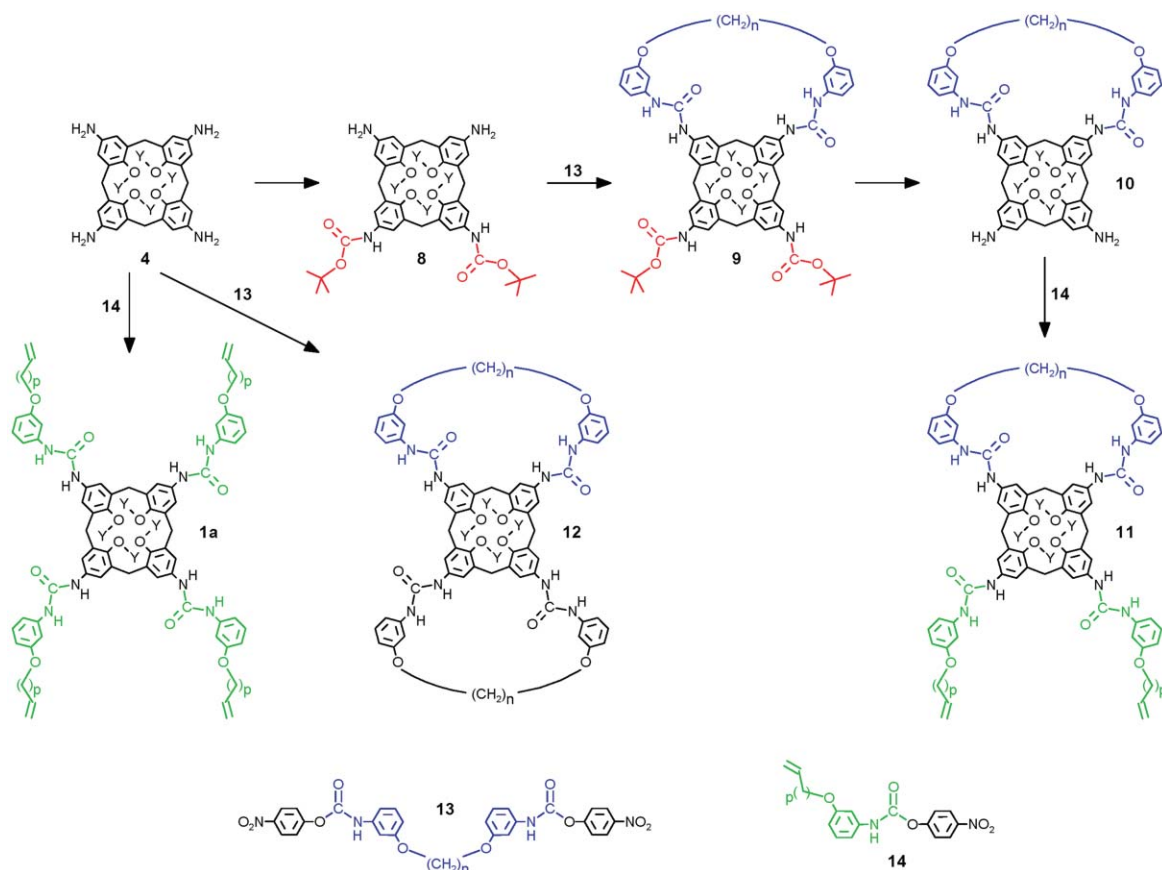


Fig. 10 Schematic representation of the synthesis of “open chain” and cyclic tetraurea calix[4]arenes.⁴⁷

As shown in Fig. 11, in principle *two* α -connections leading to the desired bis[2]catenane are possible in homodimers of **11** and only *one* β -connection, leaving two (isolated) double bonds unreacted (see below). The situation in heterodimers of **12** with **1a** is even better, since *all* possible covalent links within a dimer are α -connections, leading to the correct product.

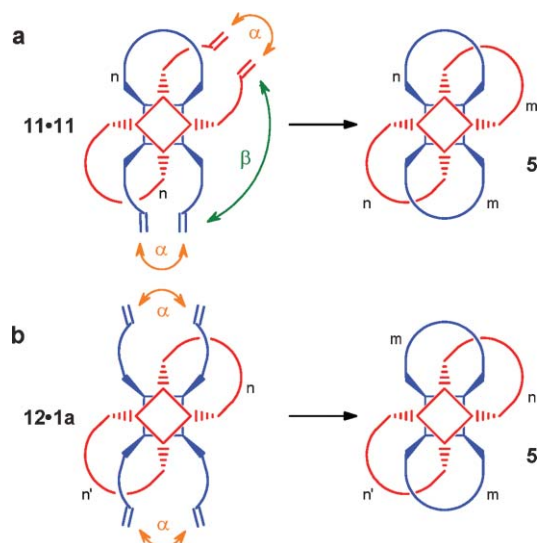


Fig. 11 Directed syntheses of bis[2]catenanes: (a) *via* homodimers **11**·**11**; (b) *via* heterodimers **12**·**1a**.

Consequently the yield of bis[2]catenanes reaches 50% on pathway (a) and up to 93–97% on pathway (b).

It should be emphasised, that both pathways are complementary, allowing for instance the synthesis of isomeric bis[2]catenanes with different length loops consisting of two identical or two different calix[4]arenes.⁴⁹

For one example ($n = m = 10$), the bis-catenated structure could be unambiguously proved by single crystal X-ray analysis (Fig. 12).⁵⁰ Since the crystals were obtained from $CHCl_3$ -methanol, the dimeric hydrogen bonded capsule is broken and the molecule is held together only by the interlocking rings. The conformation found in the crystal thus illustrates, also, that exchange of guests should be easily possible, even for rings with $n = 10$.

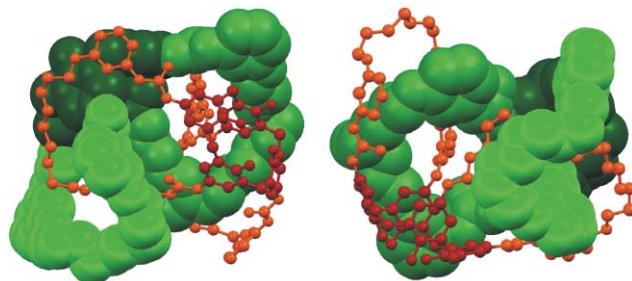


Fig. 12 Molecular conformation of bis[2]catenane **5** ($n = m = 10$) seen from two directions.

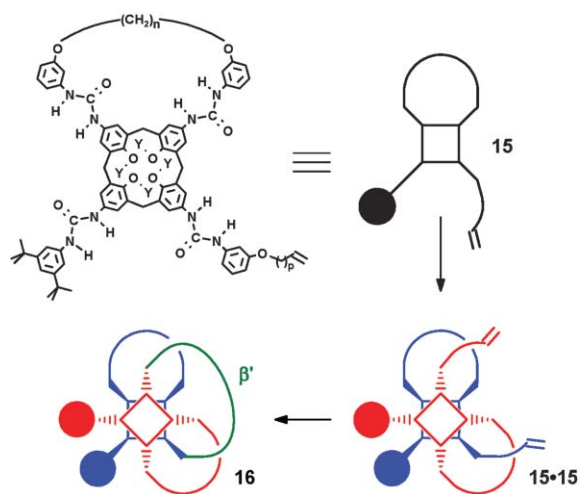


Fig. 13 Synthesis of topologically novel molecules **16** by metathesis of selectively formed homodimers **15-15** ($p \geq 9$).

Towards novel topologies

The bis[2]catenanes synthesised according to Fig. 11, [pathway (a)] are the only identified reaction products for “short” alkenyl groups (leading to loops with $n \leq 14$). For longer residues, however, the (chromatographically) isolated product seemed to consist of two isomeric compounds which could not be further separated. This led to the idea that, in addition to the covalent linkage of two adjacent groups of the two calixarenes (β -connection) the distal positions could also be linked (β' -connection, Fig. 5)

According to molecular models such a β' -connection would be possible. To check, if it is also realistic under the conditions of the metathesis reaction, we synthesised the monoloop monoalkenyl derivatives **15** ($n = 10$ or 8 and $p = 9$). Due to the bulky second urea residue, which cannot pass the loop, they form only one homodimer, in which the β' -connection is the only possible reaction (Fig. 13).

Metathesis was possible in all cases under the usual conditions and a single product was isolated (40–50%, after chromatographical purification), which according to the mass spectrum is the expected compound. Also the NMR-spectrum, showing for instance 16 m -coupled doublets for aromatic protons, is in agreement with a single compound with C_1 -symmetry.

To illustrate the topology of these compounds the graphical simplification shown in Fig. 14 is useful. The final

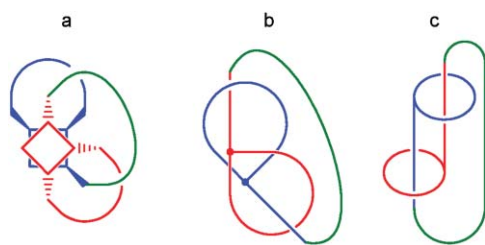


Fig. 14 Topology of **16**: (a) omission of bulky “open ended” urea residues; (b) “shrinkage” of the calixarene macrocycles to a point; (c) graphical rearrangement.

representation shows, that there are elements of rotaxanes⁹ and catenanes and also similarities to knots. Thus, while the β' -connection may be an undesired side reaction during the synthesis of bis[2]catenanes, it enables the preparation of novel interesting compounds with unprecedented topology.

Template synthesis of multimacrocylic tetraurea calix[4]arenes

As shown in Fig. 10, two cyclisation steps and the intermediate protection of two reactive positions may be necessary (or at least advantageous) to obtain bisloop compounds such as **12**. In general there is not only the problem of *trans*-cavity bridging, which is often the preferred reaction.⁵¹ Methyl ether derivatives may also assume the unfavourable partial cone conformation.⁵² And the correct intramolecular connection of two functional groups per phenolic unit at the wide rim of calix[4]arenes with both adjacent phenolic units definitely requires an improved strategy (see Fig. 15).

Again the dimerisation of tetraurea derivatives may be used to obtain an optimum arrangement of functional groups in space. As already mentioned tetraaryl- as well as tetratosylurea derivatives **3** form homodimers, but an equimolar mixture of both contains only and exclusively the heterodimer.⁵³ Although not yet understood in detail, this is well established for numerous examples.

We therefore studied the metathesis of **1a** in the presence of **3** (5–10% excess, to ensure that **1a** is completely converted to heterodimers) in benzene–dichloromethane. After the usual work up, using THF as a hydrogen bond breaking solvent, the desired bisloop derivative **12** was easily separated from **3** by column chromatography.⁵⁴ Various compounds of type **12** with different ring sizes ($n = 8, 10, 14, 20$) and different ether residues ($Y = \text{CH}_3, \text{C}_5\text{H}_{11}, \text{C}_{10}\text{H}_{21}$) were obtained⁵⁵ in yields up to 90–95%.

The great advantage of this template synthesis becomes evident when the metathesis reaction is carried out with octaalkenyl derivatives **1b** in heterodimers with **3** (Fig. 16). In this case tetraloop compounds **17a** are formed and isolated in 85–90% yield ($n = 8, 10, 14, 20$; $Y = \text{CH}_3, \text{C}_5\text{H}_{11}$). It seems at least difficult, if not impossible, to prepare such multimacrocylic compounds without **3** as template.

As shown by an X-ray structure (Fig. 17) the connecting loops keep the tetramethoxy calix[4]arene skeleton in the (unusual) pinched cone conformation. This follows also from ¹H NMR spectra, which show a pair of doublets for the methylene bridge protons also at higher temperature,

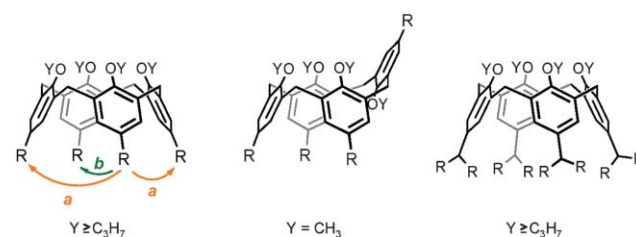


Fig. 15 Potential difficulties for the controlled intramolecular connection of functional groups R attached to the wide rim of a calix[4]arene.

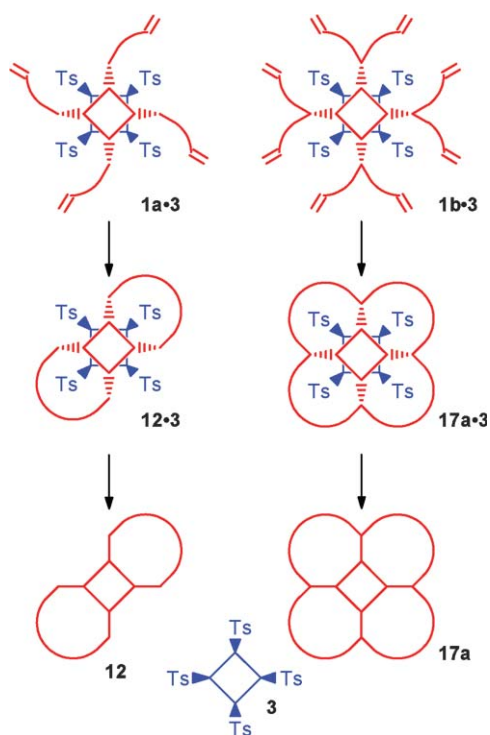


Fig. 16 Template synthesis of bis- and tetraloop derivatives.

indicating that a cone-to-cone interconversion does not take place.

It should be possible to extend this strategy (Fig. 18) to other reactions, as long as they occur under conditions under which the heterodimers exist, as well as to other structures. The triloop compound **18**, for instance, was easily obtained in 70% yield from the hexaalkenyl derivative **1d** of the **AABB**-type, while a tetraloop compound with two loops of different size and structure was formed in 55% yield from the **AAAB** tetraurea **1c**.⁵⁶ The latter example demonstrates also, that the structure of the loops is not restricted to pure alkane chains.

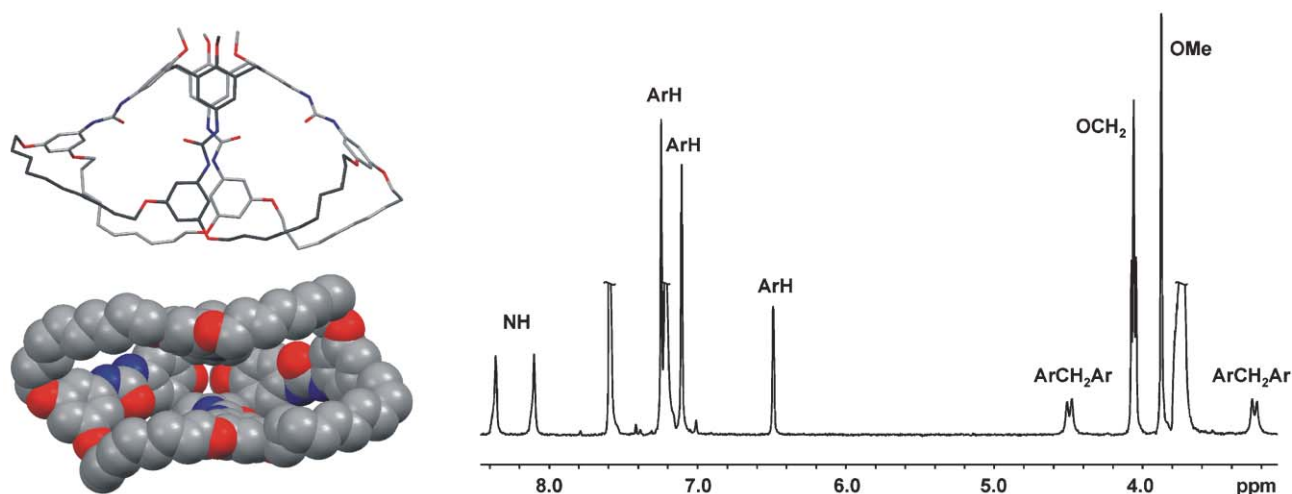


Fig. 17 Single crystal X-ray structure of tetraloop compound **17a** ($n = 10$, $Y = \text{Me}$) (left); section of the ^1H NMR spectrum of **17a** ($n = 14$, $Y = \text{Me}$), at $100\text{ }^\circ\text{C}$ in pyridine (right).

Giant macrocycles by double template synthesis

After various unsuccessful attempts to hydrolyse the urea links in **17a** under acidic or alkaline conditions, we found that a clean cleavage is easily possible by refluxing with acetic acid.⁵⁷ In this way huge macrocyclic molecules **19** are detached which would be difficult to synthesise by other strategies (Fig. 19). Up to now, the maximum ring size was 100 atoms, but still larger rings should be available analogously.

It is worth recalling the whole reaction sequence, leading to these “giant” macrocycles:

- In a first step a bifunctional molecule [a bis(alkenyl-oxo)-benzene] is attached (*via* urea links) to a first calix[4]arene (a tetraamine), which as template **I** determines the number of bifunctional molecules to be connected in the final macrocycle.

- A second calix[4]arene, the tetraatosylurea **3**, is used to arrange these functional groups appropriately in space (template **II**), thus ensuring their correct connection by metathesis reaction.

- Decomposition of the complex with template **II** by hydrogen bond breaking solvents and detachment from template **I** by hydrolysis releases the desired macrocycle.⁵⁸

The reaction sequence was used also to prepare macrocycles with ethylene oxide units and it has potential to prepare macrocyclic molecules consisting of different units in a predetermined sequence.

Multiple catenanes of “higher order”

The easy access to tetraloop tetraureas **17** paves the way for the synthesis of hitherto unprecedented molecules containing several catenated substructures. As expected, tetraloop compounds cannot form homodimers, but again the tendency to have all urea groups “saturated” by hydrogen bonds leads to the exclusive formation of heterodimers in 1:1 combinations with tetraalkenyl tetraureas **1a** or octaalkenyl tetraureas **1b**. The formation of dimers is slower for **1b** than for **1a**, and may be entirely impossible if the loops in **17** become too small.

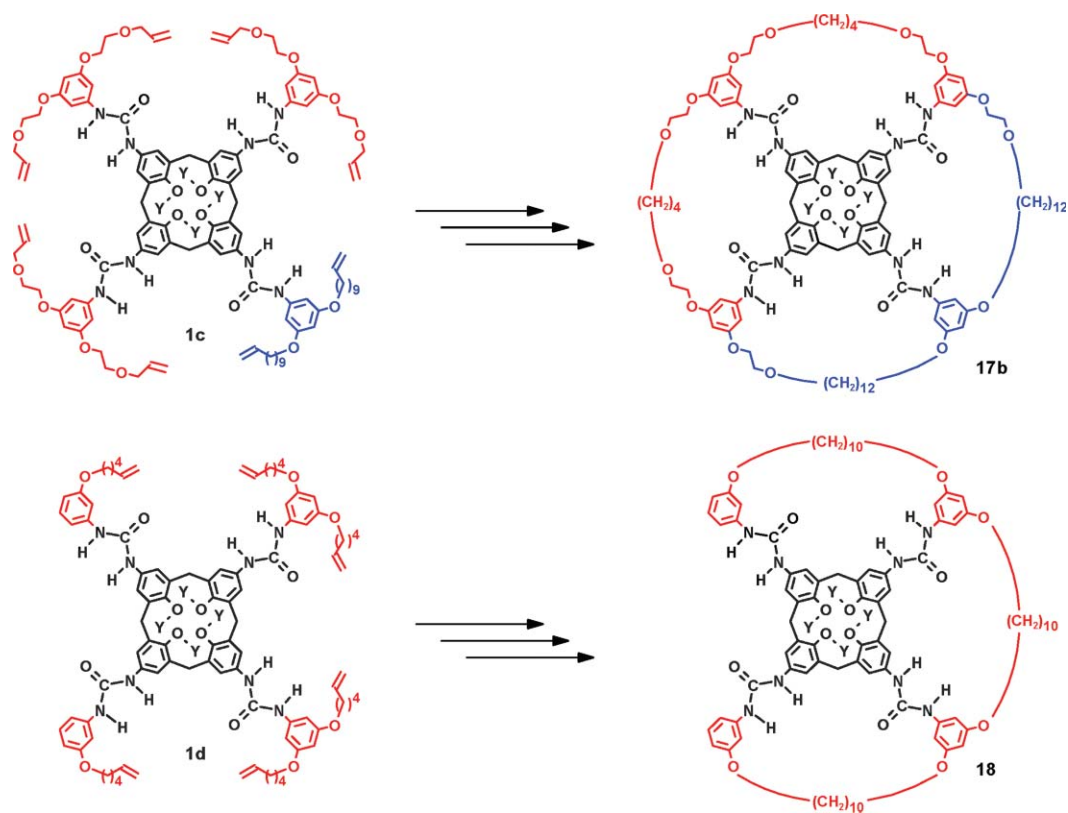


Fig. 18 Extension of the template strategy to the tetraloop compounds **17b** with different loops and triloop derivatives **18**, using tetraurea derivatives of AAAB and AABB type.

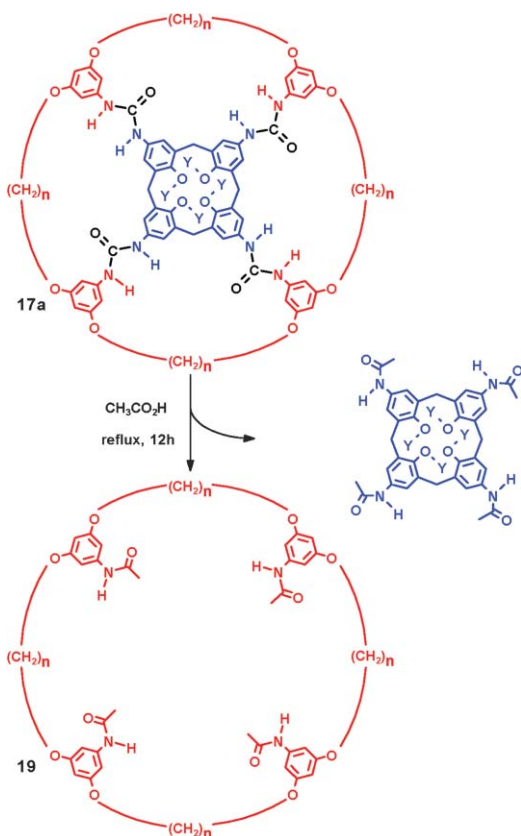


Fig. 19 Detachment of the huge macrocycles **19** from the calix[4]arene used as template.

Metathesis reaction of these heterodimers led to novel (hitherto not realised) catenated molecules in yields >50% after simple chromatographic purification.⁵⁹ As schematically shown in Fig. 20 two annulated rings of the tetraloop compound are penetrated by one ring of the newly formed bisloop compound in **20**. Since this structural element occurs twice, we have chosen the name “bis[3]catenane” for the whole assembly, although it consists of only two mechanically connected molecules. The two belts of four annulated rings of each calix[4]arene are interwoven in such a way in **21**, that each ring of one belt penetrates two adjacent rings of the other

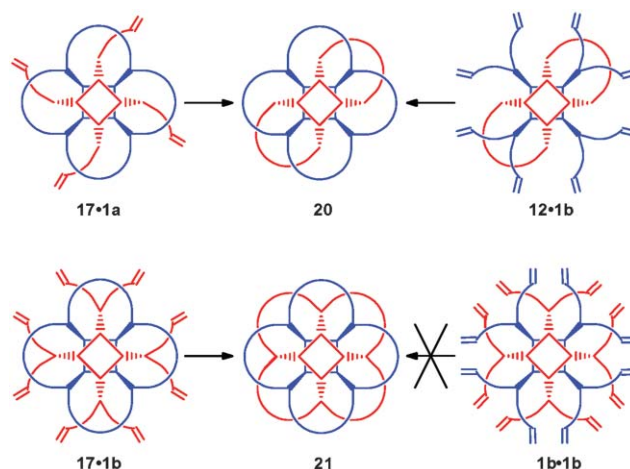


Fig. 20 Formation of bis[3]catenanes and of cyclic [8]catenanes.

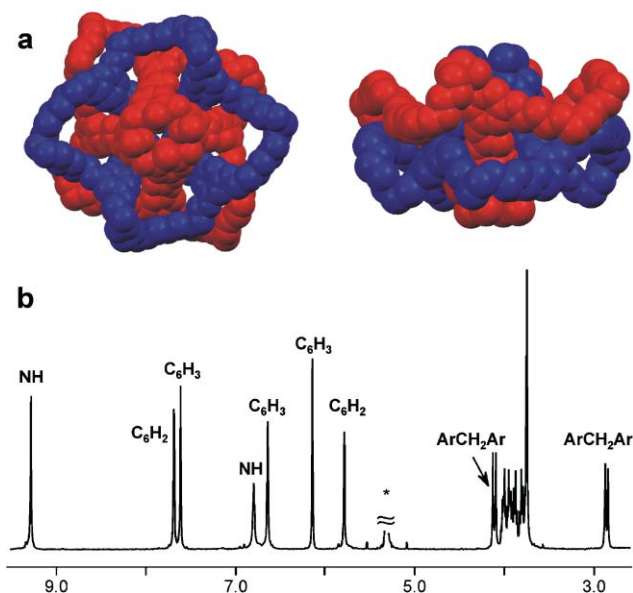


Fig. 21 Cyclic [8]catenane **21**: conformation in the crystalline state (a) and section of the ^1H NMR spectra (b) in CD_2Cl_2 .

belt. This structure is adequately described by the expression “cyclic [8]catenane”.

Compound **21** shows a rather simple ^1H NMR spectrum which can be considered as a structural proof [Fig. 21(b)]. Two singlets for NH-protons, two *m*-coupled doublets for the calixarene aryl protons and three *m*-coupled triplets for the 3,5-dialkoxyphenyl groups reflect the S_8 -symmetry which is also found in simple homodimers **1**·**1**. In contrast to such homodimers, which are decomposed by hydrogen bond breaking solvents into the C_{4v} -symmetrical calix[4]arenes, the spectra of **21** do not change essentially, if the solvent is changed from CDCl_3 or CD_2Cl_2 to $\text{THF-}d_8$ or pyridine- d_5 . Even at 100 °C two broad signals are observed for the aromatic protons of the calixarene part in pyridine- d_5 . This shows that the intertwining of the two calixarenes in **21** makes complete solvation of the urea functions and a free rotation around the Ar–NH σ -bonds still impossible.

On the other hand, high resolution mass spectra (Q-TOF) reveal that, for **20** and even for **21**, the exchange of guests is possible. Peaks for $0.5 \cdot (M + 2Na + C_6H_4F_2)$ obtained for both compounds from a mixture of 1,4-difluorobenzene–dichloromethane–methanol (1:1:0.4) cannot be explained otherwise, since difluorobenzene was not present during the synthesis.

It will be interesting to study such phenomena (internal mobility, guest exchange) as a function of the chain lengths in the catenated rings.

Multiple rotaxanes

The heterodimer formed from a bis- or tetraloop tetraurea and an open chain tetraurea may be regarded as a “pseudo rotaxane” held together by the hydrogen bonded belt of the urea functions. The attachment of bulky stopper groups under conditions under which these hydrogen bonds are stable should lead to bis- or tetrakis[2]rotaxanes, stable also

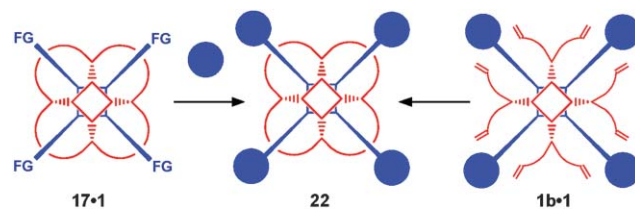


Fig. 22 Schematic representation of the formation of multiple rotaxanes by “stopping” and “clipping” procedures.

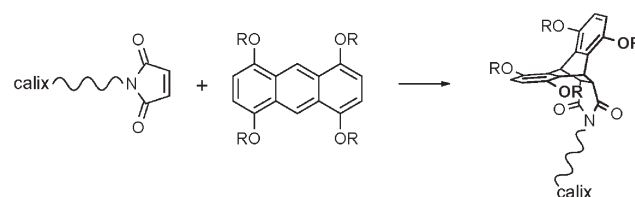


Fig. 23 Introduction of bulky stopper groups by Diels–Alder cycloaddition.

under hydrogen bond breaking conditions. As indicated schematically in Fig. 22, analogous rotaxanes should be available also from suitable heterodimers by “clipping”.

For the stopping process we have chosen the Diels–Alder cycloaddition between maleimide groups attached to the end of the urea residues and tetraalkoxy anthracenes (Fig. 23) which proceeds smoothly at 100 °C in toluene. The reaction can be easily followed in an NMR-tube by the disappearance of the $-\text{CH}=\text{CH}-$ protons. With 5–10% excess of the anthracene, the reaction is complete within 72 h, and fourfold [2]rotaxanes **22a** (for the nomenclature see above) are isolated in about 50% after chromatographic purification.⁶⁰ ^1H NMR spectra in $\text{THF-}d_8$ reveal that the rotaxanes cannot be split into the two calix[4]arene parts. ESI or MALDI-TOF mass spectra also show the expected molecular peaks.

The synthesis of two- or fourfold [2]rotaxanes *via* clipping reactions requires the exclusive (or at least predominant) formation of heterodimers between **1a** or **1b** with tetraureas bearing bulky stopper groups which could be developed again on the basis of arylsulfonyl ureas. Very recently, we found⁶¹ that the tetraloop compound synthesised according to Fig. 16 cannot be split from the tetraurea used as template by THF or similar solvents, if the connecting aliphatic chains in the loops become smaller than $-(\text{CH}_2)_8-$. Obviously the “rectangular” shape of the $-\text{NH}-\text{C}(\text{O})-\text{NH}-\text{SO}_2-\text{aryl}$ fragment makes a combination of four of them already bulky enough to hinder their slippage through such small rings. Therefore, these dimers can be regarded as the first examples of fourfold [2]rotaxanes formed by “clipping” (Fig. 24).

Conclusions and outlook

Dimeric capsules formed by tetraurea calix[4]arenes may not be used only for the (selective) inclusion of guests. The unique preorganisation of the urea functions and of reactive groups attached to them offers also the possibility to obtain topologically novel and interesting molecules. The covalent

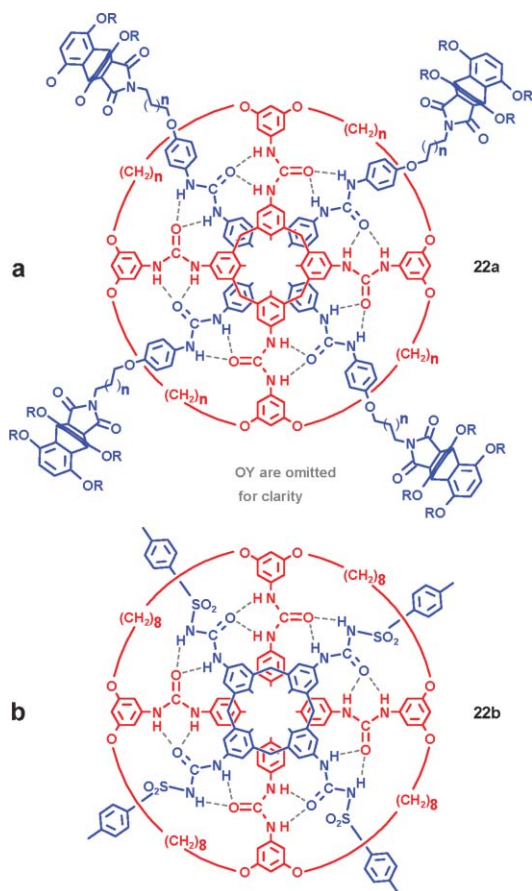


Fig. 24 Examples of rotaxanes obtained (a) by stoppering (Fig. 23) and (b) by clipping.

connection of functional groups is not necessarily restricted to olefin metathesis. In principle all reactions may be used, which can be carried out under conditions under which the hydrogen bonded dimers are stable.

The size of macrocycles available by the “double template” strategy might be also increased. If bifunctional fragments are attached to the urea residues R *via* covalent bonds which are easier to cleave than the urea function itself, the synthesis of macrocycles could be extended also to other structures and more sophisticated molecules.

Tetraurea calix[4]arenes in which urea functions are covalently linked to form loops cannot form dimers, in which these loops overlap. It can be supposed that sufficiently bulky urea groups can be found, which cannot penetrate loops of a certain size, which would create additional selectivities for the dimerisation. The homodimerisation of **15** in which the smaller urea residue is threaded through the loop can be taken as a first example. Thus, various self-sorting processes can be envisaged, leading to well defined self-assembled supramolecular structures from a mixture of programmed building blocks. The formation of a uniform dendritic assembly ($M = 25800 \text{ g mol}^{-1}$) based on the exclusive heterodimerisation of aryl and tosylureas and the independent dimerisation of tripodal triureas⁶² and calixarene based tetraureas may be taken as first examples.⁶³

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