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Template synthesis of multi-macrocycles by metathesis reaction†‡

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Selective heterodimerisation of tetraurea calix[4]arenes containing four or eight ω-alkenyl groups with a tetratosyl urea calix[4]arene has been effectively used to synthesize multi-macrocycles *via* metathesis reaction.

Macrocyclic molecules are usually obtained from linear, bifunctional precursors. To avoid undesired polymerisation, the reaction often has to be conducted under "high dilution" conditions. A suitable preorganisation of the reacting species (*via* reversible noncovalent bonds) by a "template" may lead to drastic increases of the yield. This is well established/understood in numerous cases[1] and well appreciated in others.[2] Preorganisation can be achieved also *via* covalent attachment to a suitable template molecule,[3] as shown recently by the spectacular synthesis of cyclic phenol ethers.[4]

The situation is even more complicated, if several covalent links have to be formed within a precursor molecule in a well defined way. High dilution alone, preventing intermolecular reactions, cannot be used to suppress undesired intramolecular connections. Take as an example a calix[4]arene fixed in the *cone* conformation in the form of its tetraether and functionalized at the wide rim. Intramolecular connection of these functional groups by a bifunctional reagent will lead in $\frac{2}{3}$ of all cases to a bridging of adjacent phenolic units and in $\frac{1}{3}$ to a transcavity bridging between opposite units§ (Fig. 1).

This situation may be improved, if by a suitable template the calix[4]arene can be "prearranged" in a way which precludes transcavity bridging. Then the bis-macrocyclic derivative in which adjacent phenolic units are connected should be the only product of an intramolecular reaction.

Tetraurea derivatives of calix[4]arenes form dimeric capsules in apolar solvents held together by a seam of hydrogen bonds (Fig. 2).[5]¶ In such a dimer the opposite urea residues R of each calixarene are effectively separated, while adjacent urea residues may be covalently connected *e.g.* by metathesis reaction between ω-alkenyl groups.[6]

It is well established also that calix[4]arenes substituted by four tosylurea functions at their wide rim (**3**) form exclusively heterodimers in the presence of an equimolar amount of a tetraarylurea (*e.g.* **1**, **2**), although the reasons for this heterodimerisation are not yet understood in detail.[7] Thus, **3** may be used as a template to orient the alkenyl groups of **1** in the heterodimers **1·3** in a way favoring the desired connection of adjacent residues.‖ In fact, **4b** could be obtained by metathesis reaction followed by hydrogenation in 66% yield, using **3** as template,** while the analogous

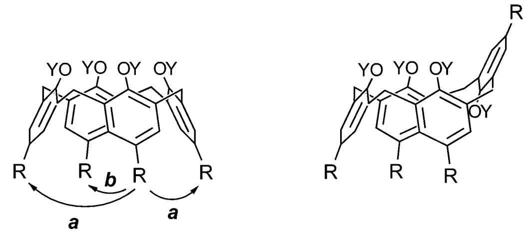


Fig. 1 Two possible intramolecular connections (*a* and *b*) of residues R in a calix[4]arene fixed in the *cone* conformation (Y > Et). For a derivative preferring the *partial cone* conformation (Y = Me) a complete connection of adjacent residues R (*a*) is highly unlikely.

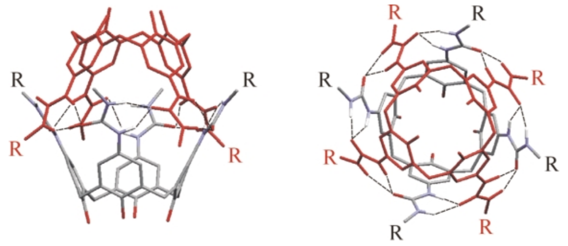
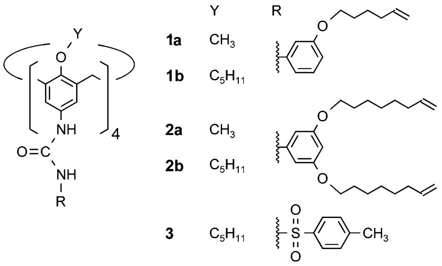
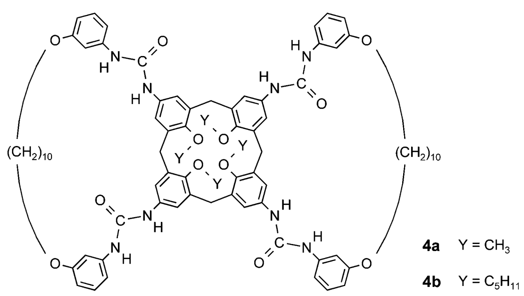
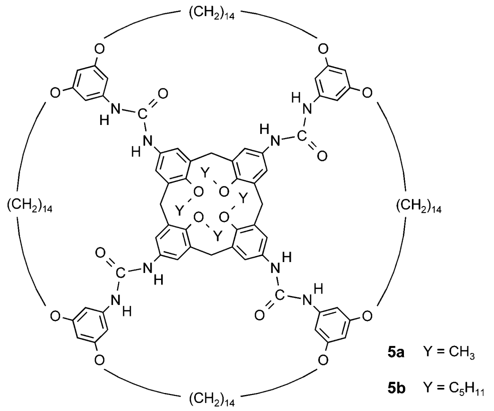


Fig. 2 Schematic representation of a calix[4]arene urea dimer (side- and top-views); an included guest is omitted for clarity; hydrogen bonds are represented by dashed lines.





4a Y = CH$_3$
4b Y = C$_5$H$_{11}$



5a Y = CH$_3$
5b Y = C$_5$H$_{11}$

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† Electronic supplementary information (ESI) available: ^{1}H NMR and ESI-MS spectra of multi-macrocycles **4** and **5**. See http://www.rsc.org/suppdata/cc/b4/b402719a/
‡ Dedicated to Julius Rebek, Jr. on the occasion of his 60th birthday.

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reaction was unsuccessful in the absence of **3**. For the tetramethoxy derivative **1a** the template **3** additionally induces the *cone* conformation[8] necessary for the sterically correct connections.[9]

The highly exceptional potential of the template synthesis is further demonstrated by fourfold metathesis (followed by hydrogenation) of the octa-alkenyl derivatives **2** leading to the tetramacrocyclic derivatives **5** in yields of up to 65%.†† Intramolecular metathesis without template was not attempted in these cases, since a successful reaction seems even more unlikely than in the case of **1**.

The structure of the multi-macrocyclic compounds **4** and **5** was confirmed by ESI MS and unambiguously established by their simple ^{1}H NMR spectra showing C_{2v}- and C_{4v}-symmetry.‡‡ Obviously the *cone* conformation is fixed in the tetramethyl ether derivatives **4a** and **5a**, at least on the NMR timescale up to 55 °C in THF-d_8, as can be seen from the pairs of doublets for the protons of the methylene bridges (Fig. 3). Elongation of the ether chains connecting the urea residues R should lead to conformational flexibility again.

We have demonstrated that tetra- and octa-alkenyl derivatives of calix[4]arenes can be efficiently preorganised by heterodimerisation of the appropriate tetraurea derivatives. Since these hydrogen bonded dimers can be easily destroyed by hydrogen bond breaking solvents, the multi-macrocyclic derivatives formed by metathesis within these dimers can be separated from the template and isolated (after hydrogenation) by chromatography in yields of up to 66%†† and quantities sufficient for further syntheses. Their use in the preparation of rotaxanes and catenanes is presently being studied, as well as the cleavage of the urea links in **5**, which should lead to large (functional) macrocycles. Furthermore it should be possible to use the preorganisation of tetraurea derivatives in such heterodimers for other covalent connections.

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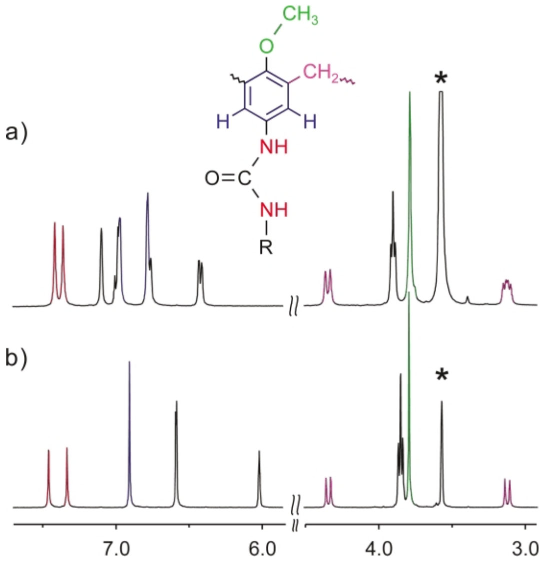

Fig. 3 ^{1}H NMR (400 MHz, THF-d_8, 55 °C) spectra of **4a** (a) and **5a** (b). Different structural groups are indicated with different colours. Signals of the solvent are indicated with asterisks.

Notes and references

§ These statistical values assume an entirely intramolecular reaction and an equal probability for the first group to react with the other three groups. For practical reactions these probabilities may be different for various reasons.

¶ Necessarily this requires the inclusion of a suitable guest.

‖ The exclusive formation of heterodimers was proved by ^{1}H NMR.

** *A typical procedure*: A mixture of **3** (0.37 g, 0.24 mmol) and **1b** (0.33 g, 0.20 mmol) in benzene (50 mL) was stirred at 40 °C under nitrogen for two days. 800 mL of dichloromethane and the Grubbs' catalyst[10] [bis-(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride from Strem, 41 mg] were added to this mixture. After two days of stirring at 20 °C, the solvent was evaporated. The residue was dissolved in THF, a solvent which destroys the hydrogen bonded dimer, and evaporated again. Finally, the hydrogenation of the crude product was carried out in THF (40 mL) with hydrogen (1 atm) in the presence of PtO_2 (80 mg). The desired **4b** was obtained after chromatographic separation (eluent: THF/hexane 2:3) and crystallization from THF/methanol (0.20 g, 66%). mp > 250 °C (decomp.). ^{1}H NMR (THF-d_8, 400 MHz, 25 °C): δ (ppm) = 7.49 (s, 4H, N**H**), 7.47 (s, 4H, N**H**), 7.07 (d, 4H, ^4J = 2.0 Hz, Ar$_{meta}$-**H**), 6.98 (t, 4H, ^3J = 8.2 Hz, Ar$_{meta}$-**H**), 6.90 (d, 4H, ^4J = 2.6 Hz, Ar$_{calix}$-**H**), 6.79 and 6.76 (dd, 4H, ^3J = 8.1 Hz; ^4J = 1.4 Hz, Ar$_{meta}$-**H**), 6.74 (d, 4H, ^4J = 2.4 Hz, Ar$_{calix}$-**H**), 6.42 and 6.40 (dd, 4H, ^3J = 8.1 Hz; ^4J = 1.6 Hz, Ar$_{meta}$-**H**), 4.44 (d, 4H, ^2J = 12.9 Hz, Ar–CH_2–Ar *ax*), 3.89–3.85 (m, 16H, OCH_2–), 3.08 (d, 2H, ^2J = 13.2 Hz, Ar–CH_2–Ar *eq*), 3.06 (d, 2H, ^2J = 13.2 Hz, Ar–CH_2–Ar *eq*), 1.96 (m, 8H, –CH_2–), 1.77 (m, 8H, –CH_2–), 1.49–1.43 (m, 24H, –CH_2–), 1.30 (m, 16H, –CH_2–), 0.96 (brt, 12H, ^3J = 7.0 Hz, –CH_3).

†† ^{1}H NMR spectra of crude products **4** and **5** suggest their formation in yields > 90%.

‡‡ Considering also the calixarene skeleton **4** represents a tri-macrocyclic and **5** a penta-macrocyclic compound; the outer ring in **5** consists of 76 atoms. For a synthesis of giant macrocycles see ref. 11.

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