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Novel template effect for the preparation of [2]rotaxanes with functionalised centre pieces†

Pradyut Ghosh,[ab] Oliver Mermagen[a] and Christoph A. Schalley*[a]

[a] *Kekulé-Institut für Organische Chemie und Biochemie, Universität Bonn, Gerhard-Domagk-Str. 1, D-53121 Bonn, Germany. E-mail: c.schalley@uni-bonn.de*

[b] *Central Salt & Marine Chemicals Research Institute, G. B. Marg, Bhavnagar 364002, India*

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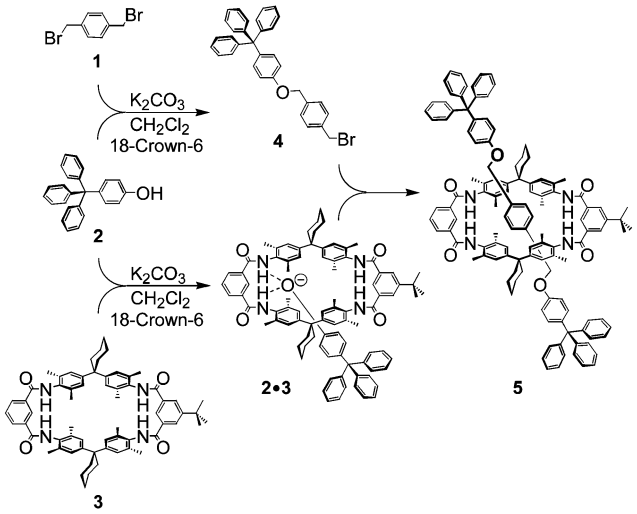
A novel anion-templated synthesis permits the preparation of [2]rotaxanes with a tetralactam wheel through which axles are threaded that are functionalised at their center pieces; the wheel protects these groups efficiently against modifications.

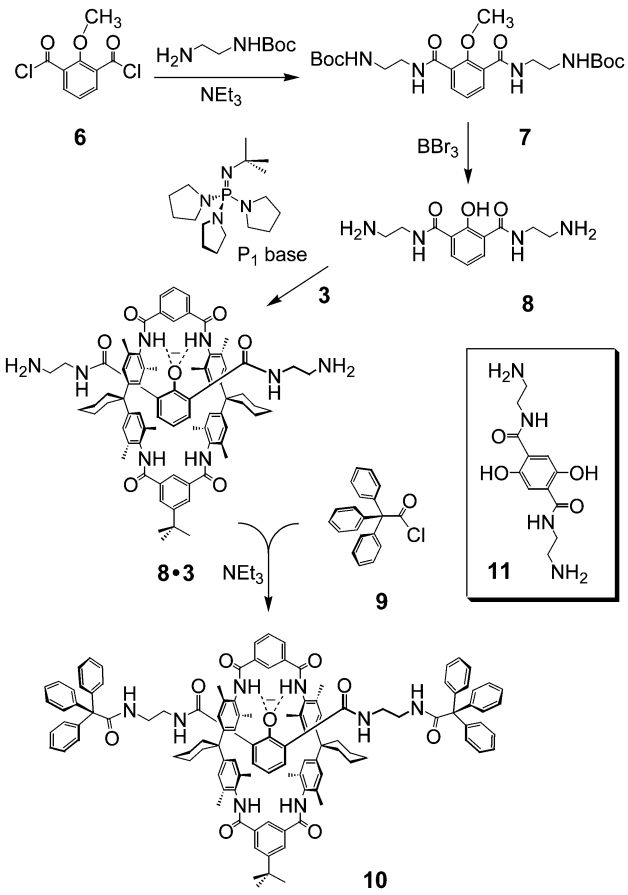
Since the mid-1980s, the use of template effects[1] boosted the preparation and examination of interlocked molecules such as catenanes, rotaxanes, and knots.[2] Quite a variety of different templated syntheses have been developed during the last 15 years; most prominent among them are those that utilise metal coordination,[3] π-donor–π-acceptor complexes,[4] or hydrogen-bonding to ammonium cations,[5] amides,[6] or phenolate anions.[7] However, despite the much better understanding of non-covalent interactions, it is still difficult to design and predict the formation of host–guest complexes suitable for interlocking one molecule within the other.

Recently, we discovered that the anion template effect reported by Vögtle and coworkers[7] (Scheme 1) depends much on the particular nature of the stoppers.[8] While larger trityl phenol stoppers **2** give high yields of rotaxanes such as **5** (40–95% depending on the axle centre piece), smaller di-*tert*-butyl phenol stoppers generate the corresponding rotaxanes in much lower yields (with some centre pieces even < 5%). This is mainly due to the fact that the phenolate binds to macrocycle **3** with exactly the same oxygen atom at which the reaction with the semi-axle **4** takes place. The phenolate oxygen is buried inside the wheel's cavity and thus protected against attack of the semi-axle depending on the conformation of the wheel.



Scheme 1

In order to circumvent these problems, we designed centre pieces **8** and **11** which bear a phenolate mediating the template effect and two sites for stopper attachment remote from the wheel's cavity (Scheme 2). Deprotonation of the phenolate is carried out with Schwesinger's P_1 base[9] which simultaneously is sufficiently basic for a complete deprotonation *and* provides good solubility of the resulting salt even in dichloromethane. Such non-competitive solvents are necessary since they do not interfere with the hydrogen bonding mediating the template effect. Other bases such as K_2CO_3/18-crown-6 or NaH were tested without greater success. In the presence of P_1 base, the centre pieces yield orange solutions in dichloromethane due to the formation of the phenolate. Upon addition of the wheel, the colour changes to light yellow indicating the formation of complexes **8·3** or **11·3**, respectively. The final step is then attachment of the two triphenylacetic acid chloride stoppers **9** at the primary nitrogen atoms by amide bond formation to yield [2]rotaxanes **10** (from **8**) and **12** (from **11**) in 20–30% yield. The rotaxane structure is confirmed by typical upfield shifts (*e.g.* $\Delta\delta$ = 0.9 ppm for the *meta*-protons of the central phenol) of the proton signals for the centre pieces in the ^{1}H NMR spectra and by surprisingly clean, almost completely fragment-free MALDI mass spectra (Fig. 1). For similar rotaxanes like **5**, often the protonated wheel is observed as an abundant fragment after cleavage and dethreading of the axle in the gas phase.



Scheme 2

† Electronic supplementary information (ESI) available: Experimental section and ^{1}H NMR titration curves. See http://www.rsc.org/suppdata/cc/b2/b208361b/

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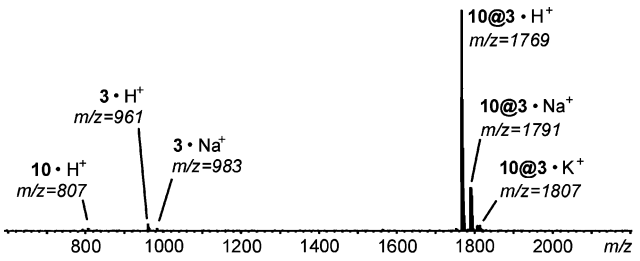

Fig. 1 MALDI mass spectrum of rotaxane **10**.

In order to get an idea why the yields of rotaxanes are not higher than this although the binding of a phenolate in the wheel[10] is rather strong (K = 2.200 ± 700 M^{-1} for **8·3** in DMSO:CH_2Cl_2 = 1:1), a Monte Carlo conformational search among 1000 structures was performed with the Amber* force field[11] implemented in the MacroModel 7.1 program.[12] It resulted in a minimal energy conformation of **8·3** as shown in Fig. 2. Clearly, the phenolate oxygen forms two *intra*molecular hydrogen bonds with the amide protons of the axle centre piece. This preorganises the centre piece allowing the two amide carbonyls to interact *via* four hydrogen bonds with the wheel so that both arms of **8** point to the same side of the wheel. Attachment of the stoppers then leads to formation of a non-intertwined axle-wheel complex rather than the rotaxane. This complex can easily dissociate into the free components. If this scenario holds true, the yields can likely be enhanced by appropriate design of suitable, more rigid centre pieces.

One of the remarkable properties of these rotaxanes is the centre piece equipped with a functionality which was expected to permit 'post-threading' modifications after the preparation of the rotaxane. Rotaxanes **10** and **12** both bear phenolic hydroxyl groups which could be modified and equipped with additional substituents. At least, a small reagent is expected to be able to proceed to the core of the rotaxane axle and *e.g.* alkylate the phenol oxygen atom. However, no methylation with CH_3I took place at the centre piece irrespective of the base used. This result not only indicates that the wheel efficiently shields the centre piece against chemical modifications,[13] it also adds another piece of evidence in favor of the rotaxane structure with the axle centre piece deeply buried inside the wheel.

In conclusion, a novel template effect has been designed permitting the synthesis of rotaxanes functionalised at the centre piece. The positions mediating the template effect and the sites for stopper attachment have been separated from each other, so that steric problems due to the shielding of the wheel do not play a role any more. Further research on centre piece design should significantly improve the yields of rotaxanes and makes our approach a candidate for an efficient synthetic route to rotaxane

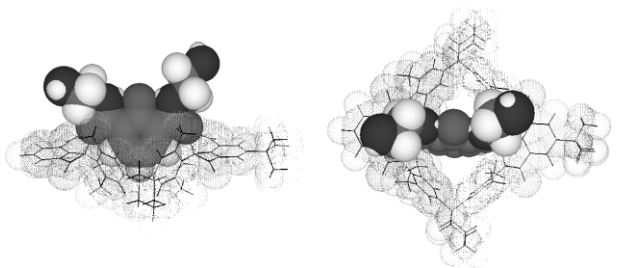

Fig. 2 Lowest energy conformation of the **8·3** complex out of 1000 structures minimised in a Monte Carlo conformational search. Side view (left) and top view (right); the wheel is shown as dotted surface, the centre piece by space filling representation.

formation. Rotaxanes with functional groups in the axle centre have been used to control molecular motion[14] and thus are of great potential use in the design of molecular machinery. In particular, the conversion of phenols to phenolates inside a wheel capable of hydrogen bonding may greatly affect the mobility of the axle inside the wheel. Studies in this respect are under way and will be reported in due course.

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