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Synthesis of diastereomeric trianglamine-β-cyclodextrin-[2]-catenanes

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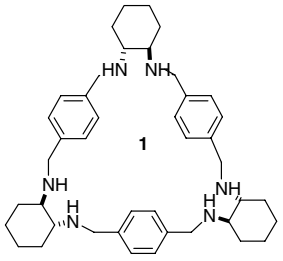
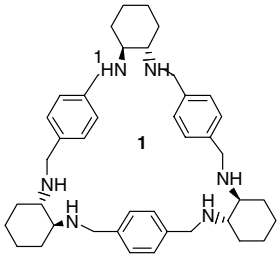
Abstract—The synthesis of novel diastereomeric [2]-catenanes derived from β-cyclodextrin and an enantiomeric trianglamine is described using a [3+3] cyclocondensation reaction.

1. Introduction

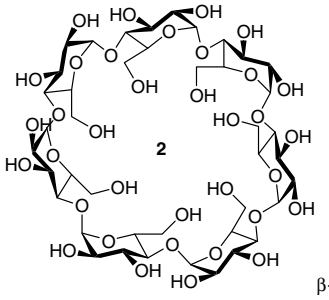
The development of supramolecular chemistry has been mainly driven by the availability of suitable macrocyclic receptors. Once a class of macrocyclic receptors with a unique shape, distinct architecture and set of functional groups becomes widely available from natural or synthetic sources, they start to inspire the imagination of supramolecular chemists in order to devise and synthesise novel sophisticated receptors, molecular machines and devices.[1] Gawronski et al.[2] have recently introduced a new synthetic strategy for the synthesis of large



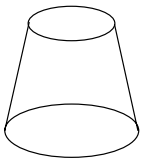
2*R* 3*R* 12*R* 13*R* 22*R* 23*R*-Trianglamine (*all-R*)-**1**



2*S* 3*S* 12*S* 13S 22*S* 23*S*-Trianglamine (*all-S*)-**1**



β-cyclodextrin



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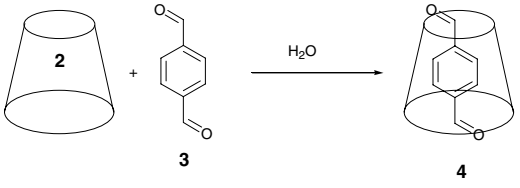
poly-imine *meta*- and *para*-cyclophane type macrocycles using a [3+3] cyclocondensation strategy. We have studied the scope and limitation of this unusual macrocyclisation leading to trianglimine macrocycles in detail and reported on several extensions of this chemistry including the reduction to give trianglamine macrocycles **1**.[3–5] Other isolated examples of [3+3] cyclocondensation strategies have been reported.[6–9] As a logical extension of our previous work, we wondered whether trianglimine macrocycles, which are characterised by an unusually large central hole, could be used to obtain interlocked molecules such as catenanes employing macroycles such as β-cyclodextrin **2** that are complementary in size.

In this letter, we report on the extension of the [3+3] cyclocondensation concept in order to obtain a trianglamine β-cyclodextrin catenane. Catenanes are interlocked molecules whose unique features offer promise in the design of molecular equivalents of bearings, joints, motors and other analogues of macroscopic assemblies composed of interlocked mechanical parts.[10–12]

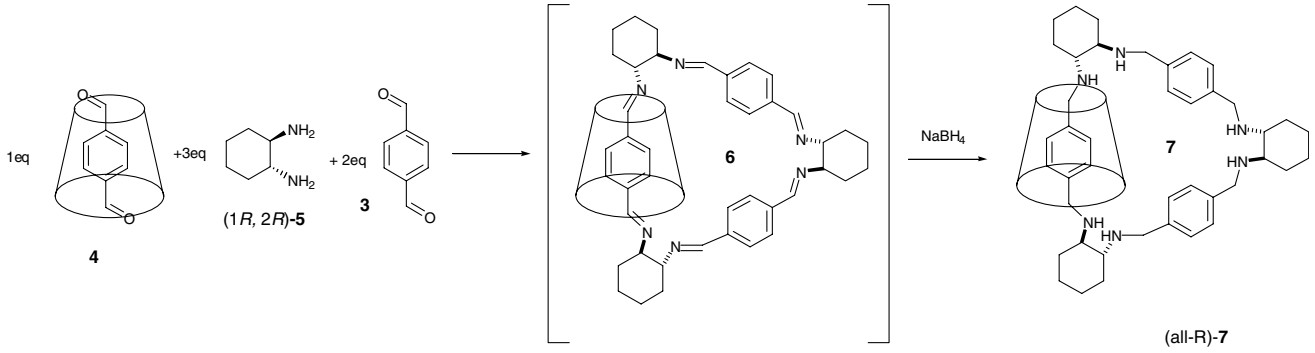
[3+3] Cyclocondensation between diamine (1*R*,2*R*)-**5** and aromatic dialdehydes such as terephthalaldehyde **3** gives, under standard conditions at 0.05 M concentration in a variety of solvents the macrocyclic trianglimines independent of the nature of the dialdehyde.[2–5] Using one or other enantiomer of diaminocyclohexane allows the synthesis of both enantiomers of the macrocycle, for example, *all-R*-**1** or *all-S*-**1.**

The group of Simionescu has reported that pseudorotaxane based materials can be obtained using β-cyclodextrin, terephthalaldehyde and aromatic diamines, presumably via inclusion complexes of β-cyclodextrin and terephthalaldehyde **4**.[13]



Other polyrotaxanes based on CD inclusion complexes of dialdehydes have been reported by the groups of Geckeler and Liu.[14,15] Encouraged by this report, we prepared an inclusion complex **4** between terephthalaldehyde **3** and β-cyclodextrin **2** in 72% yield from its constituents, that could subsequently be employed in a [3+3] cyclocondensation reaction.

[3+3] Cyclocondensation reaction of three equivalents of diamine (1*R*,2*R*)-**5** or (1*S*,2*S*)-**5** 2 equiv of terephthalaldehyde **3** and 1 equiv of the inclusion complex **4** in methanol gave after 48 h at room temperature, a mixture of 75% trianglimine macrocycle[2] along with 25% catenane **6** as judged by the crude ^{1}H NMR spectrum and ESI mass spectrum. Other stoichiometries employed led to reduced amounts of the catenane. Addition of further β-cyclodextrin **2** to the reaction mixture failed to increase the yield of the [2]-catenane. We failed, however, to isolate hexa-imine catenane **6** by various chromatographic methods presumably due to the reversible ring opening of the trianglimine imine linkages. Direct in situ reduction of the crude reaction mixture with $NaBH_4$, however, gave a mixture of trianglamine **1** and [2]-catenane (*all-R*)-**7** and (*all-S*)-**7** in a reasonable isolated yield of 18%.[16]



The two diastereomeric [2]-catenanes (*all-R*)-**7** and (*all-S*)-**7** (the stereochemical descriptors relate to the absolute configuration of the trianglamine only) could be isolated using preparative thin layer chromatography. Both diastereomeric catenanes exhibited identical ^{1}H NMR, IR and mass spectra. They could only be distinguished by their circular dichroism spectra. Compound (*all-R*)-**7** showed a bisignate CD curve, typical for the observed exciton splitting,[2,6] characterised by negative chirality, whereas (*all-S*)-**7** was characterised by a positive chirality curve. The circular dichroism spectra of (*all-R*)-**7** showed a maximum at 249 nm, a minimum at 287 nm and an intersection at 269 nm. As expected all protons of the trianglamine macrocycle in **7** are nonequivalent in the ^{1}H NMR spectrum, due to the asymmetry of the β-cyclodextrin. This observation also indicates that the β-cyclodextrin is stationary and does not move around the trianglamine on the NMR time scale. The β-cyclodextrin produces one set of signals for the seven repeating units. As expected for an inclusion compound of an aromatic compound with a β-cyclodextrin H-5 of the catenane cyclodextrin

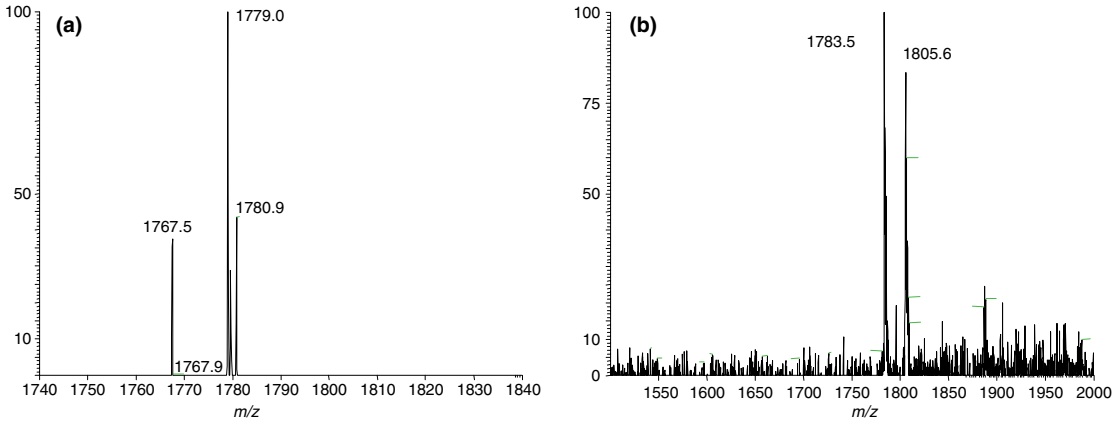


Figure 1. Expanded ESI mass spectra of [2]-catenane (*all-R*)-**7** from methanol solutions: (a) in negative ion mode; (b) in positive ion mode.

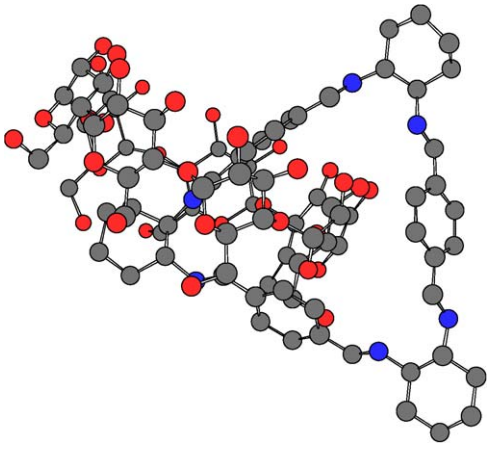


Figure 2. MM-2 minimised structure of (*all-R*)-**7** (cyclodextrin on the left and trianglamine on the right).

is found shifted downfield at 3.8 ppm if compared with the parent β-cyclodextrin at 3.48 ppm. H-3 of the β-cyclodextrin-catenane is found shifted highfield at 3.48 ppm when compared with β-cyclodextrin (at 3.58 ppm) again due to the aromatic induced shift.[16,17] Unfortunately; due to the low solubility of the compound no ^{13}C NMR data could be obtained. Most importantly, the ESI mass spectrum recorded in the negative ion mode showed the expected molecular ion at *m*/*z* 1780.9 (M−H $C_{84}H_{129}N_6O_{35}$) (Fig. 1). The positive ion mode ESI mass spectra showed exclusively two strong molecular ions at *m*/*z* 1783.5 (M+H $C_{84}H_{131}N_6O_{35}$) as expected for the molecular ion of the [2]-catenane and at *m*/*z* 1805 a strong signal corresponding to a mono-sodium adduct (M+Na $C_{84}H_{130}N_6O_{35}Na$).

Figure 2 shows a minimised MM-2 molecular model of the catenane (*all-R*)-**7** indicating the perfect complementarity in size of the two interlocked macrocycles. The diameter of the internal hole of β-cyclodextrin was reported to be in the order of 7.8 Å,[17] whereas the size of the trianglamine central hole was reported to be around 10.5 Å.[3,4]

In conclusion, we have successfully applied the concept of [3+3] cyclocondensation chemistry to the synthesis of a novel type of [2]-catenane. We have shown that a trianglamine macrocycle can be incorporated in more sophisticated molecular assemblies. [2]-Catenanes synthesised are to our knowledge the first examples of [2]-catenanes reported using two distinct enantiomerically pure interlocked macrocycles and the first set of diastereomeric catenanes, in which both enantiomers of one of the ring components have been successfully utilised.

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16. *Synthesis of catenane* **7**: Adduct **4** (710 mg, 1 mmol) was dissolved in 10 ml methanol and 340 mg (3 mmol) (1*R*,2*R*) diaminocyclohexane was added to the solution followed by 270 mg (2 mmol) terephthalaldehyde. The solution was stirred for 48 h at room temperature and the solvent reduced to 5 ml. THF (5 ml) was added to the solution followed by 28 mg $NaBH_4$ (6.2 mmol). The solution was stirred for another 6 h at room temperature and the solvent removed in vacuum. Water (10 ml) was added and the aqueous layer extracted with 20 ml chloroform to remove noncatenane trianglamine. The aqueous layer was removed in vacuum and the crude mixture purified by preparative TLC using methanol as the solvent to give the title product **7** as a white powder; mp does not melt up to 360 °C; CD (MeOH, *c* 0.005) λ_{max} 249 nm, λ_m 267 nm, λ_{min} 289 nm; ^{1}H NMR δ_H (500 MHz in D_2O): 7.32–7.09 (m, 12H, Ar), 4.70 (d, *J* 3.5, 7H, H-1(CD)), 4.23–4.02 (m, 6H, CH_2N), 3.81 (dd, *J* 9.3, 2.3, 7H, H-5(CD)), 3.68–3.80 (m, 6H, CH_2N), 3.48 (t, 7H, *J* 9.3, H-3(CD)), 3.24 (dd, 7H, *J* 9.2, 3.5, H-2(CD)), 3.12 (dd, *J* 9.2, 8.6, 7H, H-4(CD)), 3.48 (m, 14H, H-6(CD)), 1.05–2.22 (m, 36H, cyclohexane); IR *v* 3410, (OH), 3350 (NH+OH) cm^{-1}; calcd for $C_{84}H_{130}N_6O_{35}$: C, 56.5; H, 7.29; N, 4.71. Found: C, 56.7; H, 7.52; N, 4.6; MS: *m*/*z* ($C_{84}H_{130}N_6O_{35}$) (ESI, negative ion mode): 1780.9, MS: *m*/*z* (M−H: $C_{84}H_{129}N_6O_{35}$) (ESI, positive ion mode): 1783.5 (M+H).
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