A Novel Class of Neutral Chiral Cyclophanes from α,α′-Trehalose

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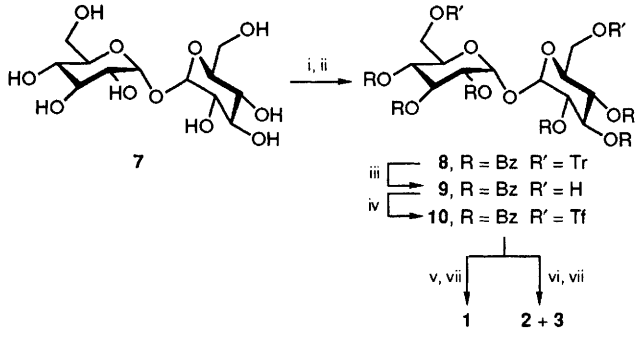
The synthesis and preliminary complexation studies of a new class of chiral cyclophanes **1–6**, with properties comparable to cyclodextrins and cyclophanes, is described.

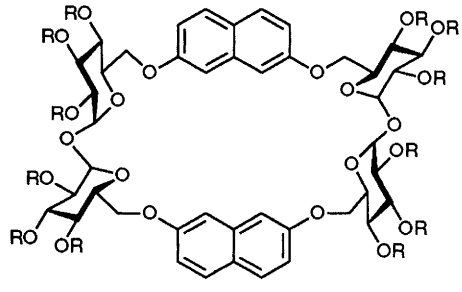
Cyclodextrins[1] and cyclophanes[2] have been used as model receptors to study the driving forces for molecular recognition of neutral organic molecules in aqueous media.[3] Water solubility of cyclophanes is provided by ionic centres located near to or remote from the cavity, while in cyclodextrins the water solubility is conferred by the hydroxy groups of the glucose moieties.

Our goal is the synthesis and study of a new type of receptor endowed with the requirements of cyclodextrins (chirality, neutrality and lipophilic cavity) and those of cyclophanes (additional aromatic interactions). These new receptors may allow us to study the influence of aromatic and hydrophobic interactions on the strength and selectivity of binding in a hydrophilic surrounding and should help to clarify uncertainties about the physical forces that govern molecular recognition in water.[4]

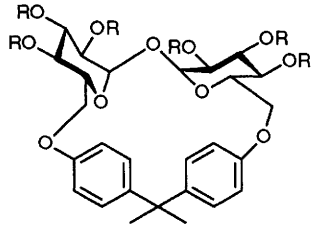
Syntheses of optically active cyclophanes have been reported.[5] In two cases,[5e,f] monosaccharides have been used to prepare chiral neutral cyclophanes, but, to the best of our knowledge, no data on their complexing properties have been reported. We have now used disaccharides, which are more conformationally restricted than monosaccharides and, besides, will confer chirality and water solubility to the cyclophanes prepared from them. Here, we describe a short synthesis of new chiral glycophanes[6] **1–6** incorporating α,α′-trehalose, a disaccharide with C_2 symmetry, and the first evidence for aromatic complexation with unchanged molecules in aqueous media. Polar cavities, crown ether type, incorporating α,α′-trehalose have been previously prepared by linking one hydroxy group of each monosaccharide unit with a polyethylene glycol chain.[7] According to Corey–Pauling–Koltun (CPK) models a lipophilic cavity similar to that of cyclodextrins could be obtained by linking positions 6 and 6′ of α,α′-trehalose with an aromatic segment (naphthyl, diphenyl, *etc.*).



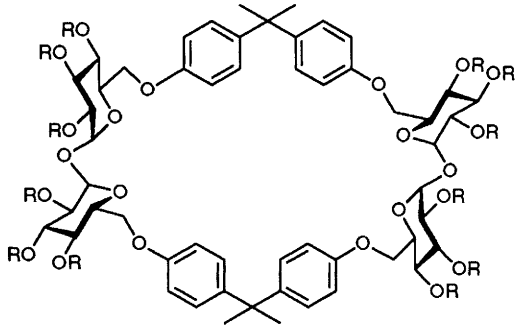
Scheme 1 *Reagents and conditions*: i, TrCl, py, 40 °C; ii, BzCl, room temp.; iii, *p*-TsOH, MeOH–Cl_2CH_2 (60%); iv, Tf_2O, DBMP, Cl_2CH_2, 0 °C v, **10**, Cs_2CO_3, DBMP, 2,7-dihydroxynaphthalene, THF (12% based on **9**); vi, **10**, Cs_2CO_3, DBMP, 4,4′-isopropylidenediphenol, THF (15 and 16% respectively based on **9**); vii, NaMeO, MeOH (85, 90 and 90% respectively); Tr = trityl, py = pyridine, Ts = toluenesulfonate, Tf = trifluoromethanesulfonyl, DBMP = 2,6-di-*tert*-butyl-4-methyl-pyridine, THF = tetrahydrofuran



1, R = H
2, R = Bz



3, R = H
4, R = Bz



5, R = H
6, R = Bz

For the synthesis of compounds **1–6**, α,α′-trehalose **7** was converted into the 6,6′-diol **9** in three steps with 60% overall yield (Scheme 1). Diol **9** was transformed to the ditrifluoromethanesulfonate derivative **10**, which was directly used without further purification. The protected trehalo-6,6′-phanes **2**,**4** and **6** were obtained by cyclization of ditrifluoromethanesulfonate **10** with the corresponding diphenol. Thus, reaction of **10** with 2,7-dihydroxynaphthalene (THF, DBMP, Cs_2CO_3, room temp.) gave after 3 days the bis-trehalo-6,6′-phane **2** in 12% yield {fast atom bombardment mass spectroscopy (FABMS): *m/z* 2182 $[M + H]^+$}. Debenzoylation of **2** gave in 85% yield the glycophane **1** (FABMS: *m/z* 933 $[M + H]^+$). Similarly, the cyclization of **10** with 4,4′-isopropylidenediphenol gave the mono-trehalo-6,6′-phane **4** (15%, FABMS: *m/z* 1159 $[M + H]^+$) and the bis-trehalo-6,6′-phane **6** (16%, FABMS: *m/z* 2319 $[M + H]^+$) which were separated chromatographically (flash silica gel, eluent: 2 : 1 hexane–ethyl acetate). Deprotection of **4** and **6**, gave the hydroxy free mono- and bis-trehalo-6,6′-phanes **3** and **5**, respectively, in 90% yield.

Glycophanes **1–6** are highly symmetric as confirmed by their NMR spectra. The CPK model of **1** resembles those of cyclodextrins, the cavity diameter being ≈6.5 Å from naphthalene to naphthalene and ≈5.2 Å from trehalose to trehalose. Glycophane **1** in 1 : 1 water–methanol forms complexes with electron-deficient aromatic guests (4-NO_2-phenol, Paraquat, picric acid) as observed by ^{1}H NMR spectroscopy. Upfield shifts for the aromatic protons of the host [chemically induced shift (CIS) : 0.3–0.75 ppm] and downfield shifts for H-1 and H-2 (CIS : 0.13–0.3 ppm) of the α,α′-trehalose moiety were observed, indicating a parallel orientation of both host and guest aromatic rings. However, no significant complexation was observed with electron-rich aromatic guests (phenol, 4-OH-toluene). The association constants determined by ^{1}H NMR binding titration[8] were: 4-NO_2-phenol (<10 $dm^3\ mol^{-1}$), Paraquat (≈30 $dm^3\ mol^{-1}$), picric acid (≈120 $dm^3\ mol^{-1}$). This result indicates the influence of donor–acceptor π-stacking interactions in the complexation. This result is the first example of complex formation between a synthetic neutral cyclophane and neutral molecules in aqueous medium.

The synthetic strategy used for **1–6** will allow the preparation of a variety of glycophanes with recognition sites comparable to cyclodextrins as far as hydroxy groups and hydrophobic cavity are involved. The chiral recognition properties of these now available glycophanes are being studied in detail.

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