Pergamon

Tetrahedron, Vol. 53, No. 34, pp. 11859-11868, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00759-X

New Supramolecular Hosts: Synthesis And Cation Binding Studies of Novel Tröger's Base-Crown Ether Composites

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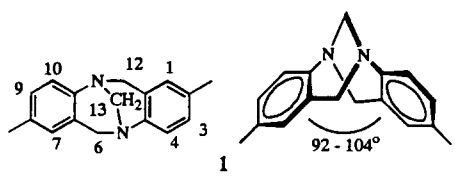
Abstract:. **A simple and straightforward synthesis of a novel class of supramolecular hosts containing the Tröger's base moiety is reported. The cation binding properties of these macrocycles were investigated using Cram's picrate extraction method.** © 1997 Elsevier Science Ltd.

2,8-Dimethyl-6H,12H(5,11)-methanodibenzo[b,f][1,5]diazocene (**1**, Fig. 1), first prepared by Tröger[1] in 1887, has recently been attracting the attention of chemists, especially, in the area of biomimetic and bioorganic chemistry. It is a rigid and very easily available molecule, obtained by acid-promoted condensation of *p*-toluidine and formaldehyde. Historically, it was the first amine proven to have a rate of configurational inversion slow enough to allow resolution into its enantiomeric components.[2]



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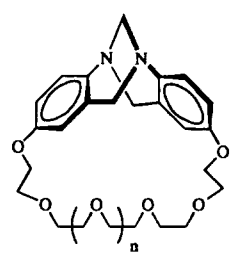
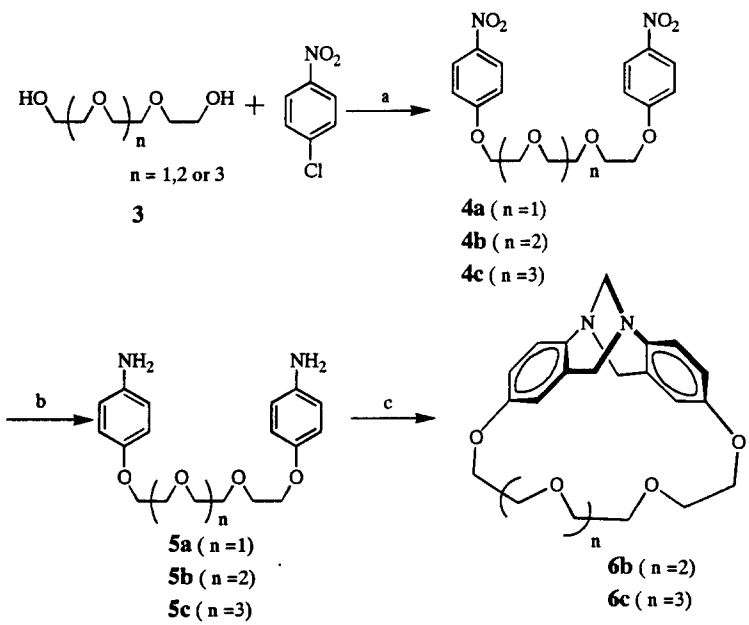


2a (n=1)
2b (n=2)
2c (n=3)

Figure 1

The methanodibenzodiazocine unit has a hinge region in the form of the five saturated atoms of the central rings and the phenyl rings of the base are oriented approximately at right angles to each other.[3] Much attention has been focussed on the synthesis of molecules with recognition sites on either side of the dibenzodiazocene hinge for the selective binding of guests.[4] Studies of clathrate formations with this kind of molecular armatures in a variety of solvents have also been reported.[5] More recently, Tröger's base derivatives incorporating potential DNA-interacting substituents have received much impetus.[6] A porphyrin containing Tröger's base has been prepared and its binding with several α, ω diamines studied.[7] Very few macrocycles have been constructed with the Tröger's base unit as an integral part of the macrocycle.[8] Of these, to the best of our knowledge, there have been no reports of the construction of macrocycles incorporating both Tröger's base unit and crown ether framework. These molecules would form an interesting class of synthetic receptors for the uptake of appropriate cations. In this paper we report a simple and facile synthesis of oxygen macrocycles (**2**, Figure 1) bearing the Tröger's base moiety and a study of their cation binding properties.

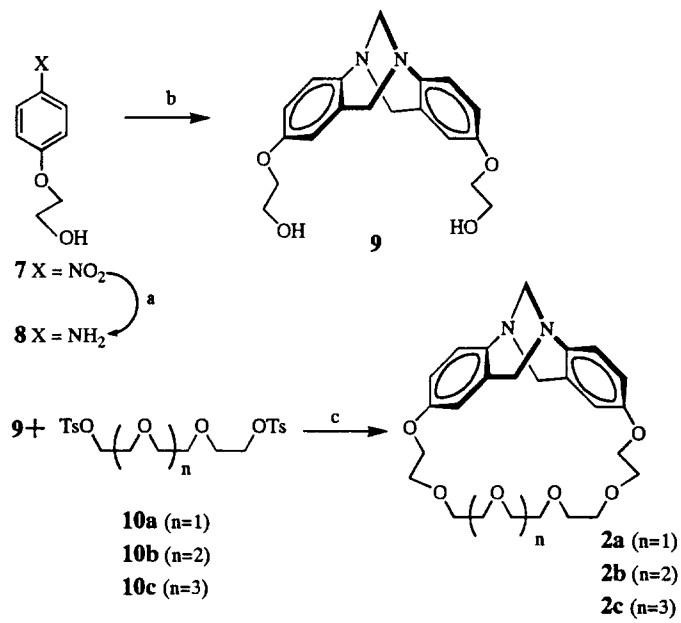
Synthesis. Synthesis of the macrocycles can be envisaged in two ways. The polyether framework can be assembled first and then the macrocycle tied up by condensation of the amine ends. Alternately, the Tröger's base frame can be fabricated first followed by closure of the macrocycle with the appropriate polyether chain.



Scheme 1 *Reagents and conditions:* a) NaH, DMF, reflux, 24h; b) $SnCl_2 \cdot 2H_2O$, EtOH, reflux, 12h; c) HCHO, HCl, EtOH, rt, 48h.

Adopting the first strategy, we set out to synthesise the polyether frame. The bis(4-nitrophenoxy) ethers (**4a - c**) of the corresponding glycols **3** were made by nucleophilic substitution on 4-nitrochlorobenzene. The nitro group was then reduced, under the conditions mentioned in Scheme 1, to obtain the corresponding diamines (**5a - c**).[9] Attempts were made to construct the 1,5-diazocene ring by employing the acid promoted condensation of formaldehyde with the diamines.[10] Efforts to condense the diamine **5a** (n = 1) with formaldehyde, in order to obtain the corresponding macrocycle were not successful. This could be due to the short ether chain in **5a**. The condensations of **5b** and **5c** with formaldehyde were then tried. The crude ^{1}H NMR spectra of the reaction mixtures showed the presence of signals characteristic of the 1,5-diazocene unit. However, attempts to obtain pure products were unsuccessful due to the presence of inseparable polar by-products.

Having failed to obtain the macrocycles in a pure form by the first pathway, we then concentrated our efforts on the second strategy. Accordingly, 2-(4-nitrophenoxy)ethanol (**7**) was synthesised as reported in the literature[11] and reduced to 2-(4-aminophenoxy)ethanol (**8**) in the usual manner (Scheme 2). This was then condensed with formaldehyde under the same conditions as above, to procure **9** in 25% yield.



Scheme 2 *Reagents and conditions:* a) $SnCl_2 \cdot 2H_2O$, EtOH, reflux, 12h; b) HCHO, HCl, EtOH, rt, 48h; c) NaH, Cs_2CO_3, DMF, reflux, 36h.

The macrocyclisation was undertaken employing tri-, tetra- and pentaethylene glycol ditosylates (**10a-c**). At the outset, **9** was heated with the ditosylates **10a-c** and NaH in DMF and the corresponding macrocycles **2a-c** were obtained after purification in 25, 32 and 20% yields, respectively.

The absence of the hydroxyl band and the appearance of a characteristic strong ether band at 1100 cm^{-1} in the IR spectrum marked the macrocyclisation. The ^1H NMR spectrum showed no significant changes in the 1,5-diazocene unit. The polyether signals were distinct at δ 4.09-3.63 in all the macrocycles. In the ^{13}C NMR spectrum, the disappearance of the signal at 61.55 ppm (C-*C*-OH), was again indicative of ring closure. The ^{13}C NMR spectra of all the macrocycles were fully in consonance with the symmetry present in these molecules. Lastly, all compounds gave satisfactory elemental analyses.

Encouraged by this, the synthesis of the macrocycles was done under various conditions in order to improve the yields in the macrocyclisation step. Addition of cesium carbonate improved the yields, but not to a very large extent.

Cation Binding Studies. Having thus achieved a simple and straightforward synthesis of a novel class of oxygen macrocycles, efforts were addressed to study their binding abilities, especially their cation complexation affinities. With a reasonable assumption that the oxygen macrocycles **2a-c** are potentially capable of co-ordinating alkali metal cations, we chose to work with Li^+, Na^+, K^+ and Cs^+ ions. A tetrahedral ion, NH_4^+ ion was also added to the list to see if it shows any special binding affinities. Evaluation of the cation binding properties was done by using Cram's picrate extraction method.[12] Chloroform solutions of the macrocycles **2a-c** were used to extract aqueous solutions of the metal picrates by a technique described in the experimental section.

Table 1. Log K_s values

Cation	Host 2a	Host 2b	Host 2c
Li^+	4.65	5.13	4.82
Na^+	4.61	5.02	4.98
K^+	4.70	4.97	5.09
Cs^+	4.52	4.96	4.80
NH_4^+	4.60	4.84	4.83

The log K_s values obtained from the extraction studies are presented in Table 1. From the data it is clear that all the macrocycles show reasonably good extraction capabilities and binding affinities with all the cations studied. However, no particular selectivity towards any specific cation was observed. The particularly low selectivity of the hosts towards cations of different sizes reflects on the high flexibility present in the macrocycle. This kind of low discrimination of cations of different radii is characteristic of stretched macrocycles[13] and podands.[14]

In order to further understand the extraction data and cavity sizes of the macrocycles **2a-c**, their optimised conformations were determined at AM1 level using HYPERCHEM for windows software. The optimised structures are shown in Figure 2.

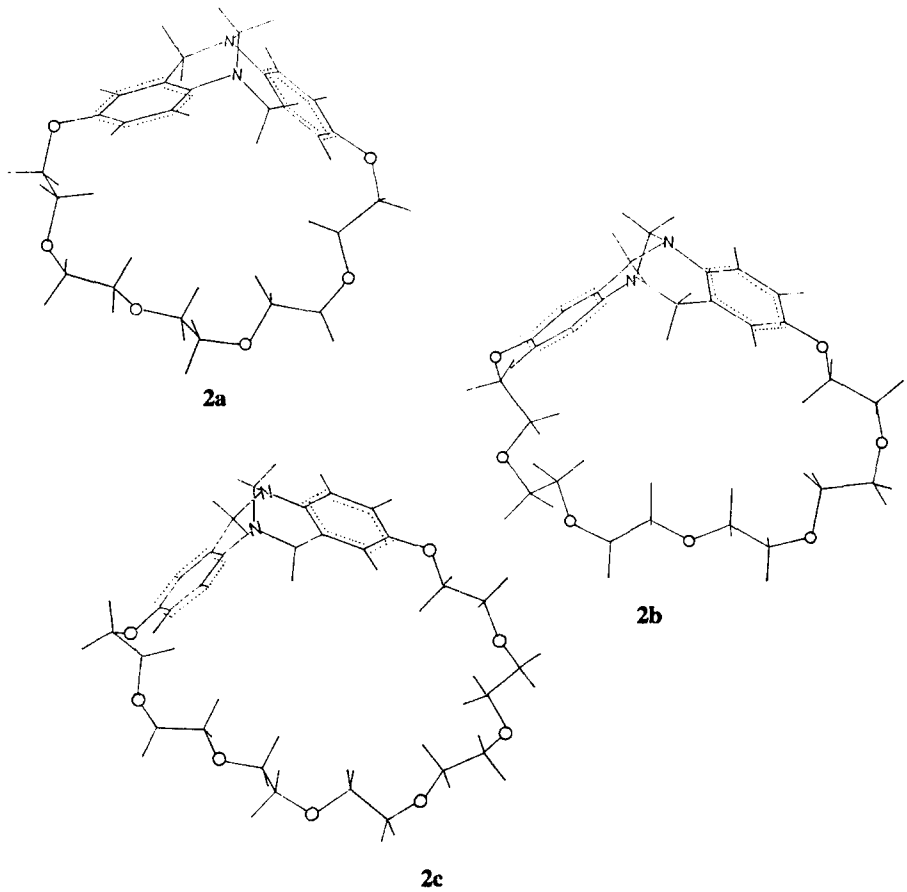


Figure 2. AM1 optimised structures of hosts **2a-2c**

The objective was to determine the cavity dimensions. The two planes containing the hinge of the Tröger's base are at an angle of 113^0. This rules out the participation of the phenolic oxygens in the complexation. The distance between the next set of diagonal oxygen atoms was taken as a measure of the effective cavity size offered for complexation. This distance was found to vary from 9.3-11.8 Å. As is clear from the above distances, the incorporation of Tröger's base unit distorts the macrocycle to the extent that the ether oxygens are forced into a non-optimal orientation for complexation. The binding, therefore, cannot be selective. The experimental results are in agreement with this.

In conclusion, a simple and straightforward synthesis of novel class of supramolecular hosts **2a-c** has been realised. The picrate ion extraction studies of these macrocycles reveal good cation extraction capabilities but poor selectivities due to their flexible cavities.

Experimental Section

Melting points were determined on a SUPERFIT melting point apparatus and are uncorrected. IR spectra were recorded on JASCO FT-IR 5300 instrument. ^{1}H-(200 MHz) and ^{13}C-NMR (50 MHz) spectra were recorded on BRUKER AF-200 NMR spectrometer in chloroform-d solutions with tetramethylsilane (TMS) as an internal standard. Elemental analyses were obtained using PERKIN-ELMER model 240C-CHN analyser.

2-(4-nitrophenoxy)ethanol was prepared as reported in the literature[11] from 2-chloroethanol and 4-nitrophenol. This was then reduced using $SnCl_2 \cdot 2H_20$ to obtain 2-(4-aminophenoxy)ethanol.

2,8-bis(2′-hydroxy)ethoxy)-6H,12H-5,11-methanodibenzo [b,f] [1,5] diazocene (9).[10] The amine **8**, (2.0 g, 13.1 mmol) and 37% solution of formaldehyde (7.4 ml) in 18 ml ethanol were cooled to 0^0 and then conc. HCl (6.5 ml) was added . The mixture was stirred at rt for 48 h. The reaction mixture was then reduced to half the volume under vacuum and poured into 150 ml water. To this 25 ml aq. ammonia was added. The reaction mixture was extracted with dichloromethane (3 × 100 ml). The organic layers were washed with saturated sodium bicarbonate solution (3 × 50 ml). The solvent was removed under reduced pressure. The crude product was chromatographed on a silica gel column with ethyl acetate as the eluent. The product obtained was crystallised from ethanol to afford **9** (610 mg, 25%): m.p. 162-164^0 ; IR (KBr): 3379, 2930, 1614, 1576, 1495, 1454, 1277, 1230, 1159, 1080, 922, 837, 760 cm^{-1} ;^{1}H NMR: δ 7.09-7.05 (d, J = 8 Hz, 2H), 6.78-6.72 (m, 2H), 6.45-6.44 (d, 2H), 4.68-4.60 (d, J = 16.7 Hz, 2H), 4.29 (s, 2H), 4.10-4.02 (d, J = 16.8 Hz, 2H), 3.99-3.94 (t, 4H), 3.91-3.86 (t, 4H), 3.15 (bs, 2H); ^{13}C NMR: 155.26, 141.33, 128.76, 126.11, 114.68, 112.0, 69.55,

67.30, 61.55, 58.94 ppm. Analysis: Calcd for $C_{19}H_{22}O_4N_2$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.72; H, 6.46; N, 8.20.

Synthesis of the macrocycles 2a, 2b and 2c. a) General procedure for synthesis: The dibenzodiazocene **9** (200 mg, 0.58 mmol) was dissolved in 4 ml of DMF and added dropwise to a stirred suspension of sodium hydride (60 mg, 1.17 mmol) in 2 ml of DMF. The reaction mixture was then stirred at rt for 1 h. To this mixture, the corresponding ditosylate (0.58 mmol) was then added in 4 ml of DMF. The resulting solution was heated at 120^0 for 72 h. The reaction concoction was quenched with water and extracted with dichloromethane (3 × 50 ml). At the outset, purification by silica gel column chromatography was attempted. However, nothing could be eluted from the column in substantial amounts due to very strong adsorption on to the column. The chromatography was therefore performed on basic alumina. First, ethyl acetate was eluted to remove any unreacted diol and the product collected by eluting with 5-10% methanol in ethyl acetate. Often, the products of required purity were obtained only after a second chromatography. All the products were obtained as gums.

Yields: **2a** = 67 mg, 25%

2b = 94 mg, 32%

2c = 63 mg, 20%

b) The procedure adopted was same as that described above except that 2 eq. of cesium carbonate was added.

Yields: **2a** = 70 mg, 26%

2b = 120 mg, 41%

2c = 70 mg, 25%

c) The reaction was carried out as in the case of (b), but under dilute conditions. The dianion of dibenzodiazocene **9** (200 mg, 0.58 mmol) was prepared in 30 ml of DMF. The ditosylate (0.58 mmol) in 30 ml of DMF was added to the anion under nitrogen atmosphere over 4h. The resulting solution was heated at 120^0 for 72 h. The solvent was removed from the reaction mixture under reduced pressure, followed by the usual work-up and purification.

Yields: **2a** = 70 mg, 26%

2b = 93 mg, 32%

2c = 80 mg, 27%

Physical data for the macrocycle 2a.

IR (neat): 3052, 2880, 1613, 1493, 1246, 1128, 964, 833, 735 cm^{-1}; ^1H NMR: δ 7.06-7.01 (d, J = 8.8 Hz, 2H),

6.78-6.73 (m, 2H), 6.43 (s, 2H), 4.67-4.59 (d, J = 16.8 Hz, 2H), 4.24 (s, 2H), 4.06-3.98 (m, 6H), 3.72 (bs, 4H), 3.63 (bs, 12H); ^{13}C NMR: 155.30, 141.18, 128.66, 126.00, 114.72, 111.98, 70.87, 70.70, 69.81, 67.75, 67.26, 58.95 ppm. Analysis: Calcd. for $C_{25}H_{32}O_6N_2$: C, 65.77; H, 7.06; N, 6.14. Found: C, 65.82; H, 7.12; N, 6.18.

Physical data for the macrocycle 2b.

IR (neat): 3053, 2880, 1612, 1493, 1271, 1097, 964, 926, 833, 735 cm^{-1}; ^{1}H NMR: δ 7.05-7.01 (d, J = 8.6 Hz, 2H), 6.76-6.72 (d, 2H), 6.43 (s, 2H), 4.67-4.58 (d, J = 17.06 Hz, 2H), 4.27 (s, 2H), 4.09-4.01 (m, 6H), 3.77 (m, 4H), 3.63 (bs, 16H); ^{13}C NMR: 155.27, 141.12, 128.72, 125.90, 114.61, 111.88, 70.76, 70.60, 70.56, 69.61, 67.64, 67.23, 58.87 ppm. Analysis: Calcd. for $C_{29}H_{40}O_8N_2$: C, 64.78; H, 7.25; N, 5.60. Found: C, 64.65; H, 7.21; N, 5.55.

Physical data for the macrocycle 2c.

IR (neat): 3053, 2878, 1612, 1575, 1493, 1271, 1246, 1186, 1109, 964, 735 cm^{-1}; ^{1}H NMR: δ 7.05-7.01 (d, J = 8.6Hz, 2H), 6.77-6.71 (d, 2H), 6.43-6.42 (d, 2H), 4.66-4.57 (d, J = 16.73 Hz, 2H), 4.26 (s, 2H), 4.07-3.98 (m, 6H), 3.79-3.74 (t, 4H), 3.63 (bs, 20H); ^{13}C NMR: 155.31, 141.15, 128.65, 125.96, 114.68, 111.94, 70.80, 70.62, 69.76, 67.68, 67.27, 58.91 ppm. Analysis: Calc. for $C_{29}H_{40}O_8N_2$: C, 63.95; H, 7.40; N, 5.15. Found: C,64.12; H, 7.38; N, 5.25.

Complexation studies of 2a-c with unipositive cations: Determination of the association constants by UV method. [12] The association constants were determined using picrate salts of Li^+, Na^+, K^+, Cs^+ and NH_4^+. All the picrate salts were prepared as reported[15] in the literature by the action of picric acid on the corresponding metal hydroxides or carbonates. The salts were recrystallised from appropriate solvents and dried in high vacuum prior to use. All UV measurements were made on a UV-160A SHIMADZU Spectrophotometer at 26-30^0. Spectral grade solvents were used throughout. Aqueous solutions of the picrate salts were made in distilled and deionised water. The solutions of Li^+, Na^+, K^+ and NH_4^+ picrates were 0.015 M and that of Cs^+ was 0.010 M (relatively poor solubility in water) for the extraction experiments. The host solutions were prepared in chloroform and were 0.075 M. Typically, four complexation experiments were run simultaneously for each cation with a given host. In a centrifuge tube, 0.5 ml of the metal picrate was transferred using a Gilson micropipettor, followed by 0.2 ml of the host solution. The centrifuge tube was then closed by a septum to prevent evaporation. The contents of the tube were then thoroughly mixed by means of a vortex mixer for 2 min. The solutions were then subjected to high speed centrifugation for 10 min. to obtain a clear bilayer separation. The aqueous layer was separated from the chloroform layer. An aliquot (0.05 ml) of

the chloroform layer was transferred by a microlitre syringe into a 5 ml volumetric flask and diluted upto the mark by adding acetonitrile. The UV absorption of each aliquot was measured against the blank at 380 nm. The concentration of the picrate salt in the chloroform layer was calculated based on Beer's law. From this, the molar ratios of the host to picrate in the chloroform layer (R) were determined. The association constants were calculated employing equation 1, written for the equilibrium represented by the following expression.

$$[H_i]_{CHCl_3} + [G_i^+]_{H_2O} + [X^-]_{H_2O} \rightleftharpoons [G^+.H.X^-]_{CHCl_3}$$

$$K_a = \frac{R}{(1-R)\, K_d \left[(G_i)_{H_2O} - R\,(H_i)_{CHCl_3}\, V_{CHCl_3}/V_{H_2O} \right]^2} \qquad (1)$$

where, R = Molar ratio of the picrate to the host in $CHCl_3$

$(G_i)_{H_2O}$ = Initial picrate concentration

$(H_i)_{CHCl_3}$ = Initial concentration of the host

V_{CHCl_3} = Volume of $CHCl_3$

V_{H_2O} = Volume of H_2O

The distribution coefficients (K_d), representing the distribution of the picrate salt between chloroform and water in the absence of the host, reported by Cram were used in all calculations. The logarithmic values of the association constants thus determined are listed in Table 1.

Acknowledgements: A. M. thanks UGC (New Delhi) for the financial assistance in the form of a research fellowship. A sample of cesium carbonate from Chemtall GMBH (Germany) is gratefully acknowledged. We acknowledge the COSIST programme in School of Chemistry for the instrumental facilities.

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(*Received in UK* 15 *May* 1997; *revised* 30 *June* 1997; *accepted* 3 *July* 1997)