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A Bis(Crown-Ether) Analogue of Tröger's Base: Recognition of Achiral and Chiral Primary Bisammonium Salts.

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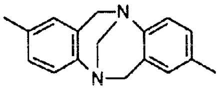
Abstract: A C_2-symmetric bis(18-crown-6) analogue (**2**) of Tröger's base (**1**) has been synthesized. In a series of achiral primary bisammonium salts, compound **2** binds heptane-1,7-diylbis(ammonium chloride) most strongly. Moderate enantioselective discrimination in the complexation of L-cystine dimethyl ester dihydrochloride with *rac*-**2** was observed. © 1998 Elsevier Science Ltd. All rights reserved.

The incorporation of a Tröger's base[1] (**1**) motif in a receptor gives the latter a helical shape with a rigid, concave cavity. Such properties are advantageous for enantioselective recognition.



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Analogues of Tröger's base have been used as receptors for a variety of substances. Thus, macrocyclic analogues of Tröger's base have been used to coordinate phenols and *p*-toluenesulfonic acid[2a] and to complex polar benzenoid guests.[2b] Some optically pure macrocyclic analogues achieve enantio- and diastereomeric discrimination of neutral aliphatic and alicyclic substrates,[3] including terpenes.[4] Bis(carboxylic acid) analogues recognize adenine and biotin derivatives, trimethylene- and dimethyleneurea,[5] as well as 2-aminopyrimidine.[5,6] A bis(zinc(II)porphyrin) analogue has impressively been synthesized and acts as a receptor for diamines and, in optically resolved form, achieves very high enantiomeric discrimination of benzylic esters of histidine and lysine.[7] A bis(*N*-pyridylbenzamide) analogue was successful in the recognition of dicarboxylic acids.[8] Macrocyclic crown-ether analogues complex a variety of monovalent cations.[9]

The syntheses of analogues of Tröger's base is hampered by the special electronic requirement of the aniline in the condensation reaction with formaldehyde in hydrochloric acid (or equivalent reagents).[10] Only a few substrates have successfully been employed including 5-amino-1,10-phenanthroline,[11] anilines substituted with electron-withdrawing heterocycles,[12] aminoacridine[13] and 10-aminobenzo[*b*][1,7]phenanthroline,[13a] as well as some other groups of aromatic amines such as 2-aminoporphyrin[7] and 5-aminopyrazoles.[14] It is of interest to find new aniline derivatives that are able to condense with formaldehyde to give analogues of Tröger's base because that broadens the scope of the condensation and gives access to new molecules with a chiral cavity.

Finding new receptors for organic ammonium salts are important in the perspective that bioactive molecules such as amino acids, peptides and proteins exist partly as ammonium ions in aqueous solutions[15] and for the enantioselective separation of small chiral primary ammonium salts. It is well established that primary ammonium ions are effective complexation partners for 18-crown-6 derivatives.[16a] The bonding forces constitute a combination of charge-dipole and hydrogen-bonding interactions.[16b] Quite a few existing receptors for primary bisammonium ions are based on bis-crown ethers.[17,18] However, only a few chiral bis(crown-ether) derivatives are known including bis-crown ethers of biphenyl,[19] diphenanthrylnaphtalene,[20] malonic acid[21] and calixarene[22] of which only one has been employed in the enantiomeric recognition of chiral primary bisammonium salts.[20] Thus, there is room for new approaches.

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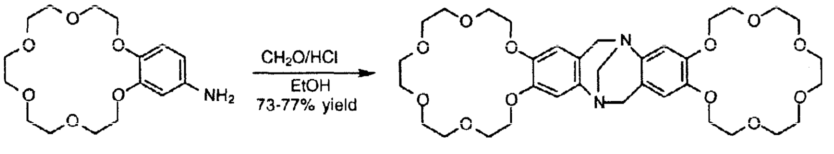
We here report the synthesis of a new Tröger's base analogue: a rigid C_2-symmetric bis(crown-ether) (**2**) (Scheme) and initial recognition studies using **2** as a receptor for achiral and chiral primary bisammonium salts.

We noticed that the commercially available 4'-aminobenzo-18-crown-6 (**3**) condensed with formalin in HCl/EtOH to give the linear symmetric bis(18-crown-6) analogue of Tröger's base (**2**), hence, increasing the spectrum of available analogues to include a 3,4-dioxosubstituted analogue of Tröger's base. The condensation proceeded smoothly following the Wilcox protocol[10c] on a 1.5 mmol scale of 4'-aminobenzo-18-crown-6 (Scheme). After work-up with Me_4NOH, the product was purified on a Bio-Beads SX-1 size-exclusion column [MeCN:toluene (1:1)] and finally recrystallized from acetone, giving **2** in 76% yield.[23]



Scheme

Theoretically, the condensation may give rise to three geometrical isomers: one with linear symmetry (**2**), one symmetric and one unsymmetrical. Inspection of the ^{1}H-NMR spectrum of the crude condensation product revealed only two aromatic singlets, confirming that only **2** was formed.

The aptitude of various bisammonium ions, $[H_3N(CH_2)_nNH_3]^{2+}$; n = 2-12, for complex formation with **2** was investigated computationally using the MM3* force field.[24] The parameters of the intermolecular interactions being crude, only qualitative conclusions could be drawn. The rather flexible crown-ether part of **2** enabled it to accommodate guests with a wide range of N···N distances. However, it was clear from the calculations that with all chain lengths tested, the guest must complex with the endo face of **2**. With $n < 5$, the strain energy was appreciable, whereas complexes with longer guests were relatively unstrained. Complexes with long-chain guests should be disfavoured entropically. Due to the V-shape of the host, complexes with the low energy all-*transoid* conformation of the guest were most easily accommodated if their number of methylene-groups was odd. For that reason, the optimum chain length was predicted to be a low, odd number (n = 5 or 7).

Following the results from the modelling experiment, the constants of association (K_{bis}, eq. 1) of **2** with a series of bisammonium salts, $[H_3N(CH_2)_nNH_3]Cl_2$; n = 4-8, in MeOH-d_4:$CDCl_3$ (1:1) were determined by ^{1}H-NMR. Due to low solubility, shorter chains could not be employed. Initial investigations revealed that the association constants were too high to allow a direct determination. These association constants were instead determined indirectly by competition with a more weakly binding salt, methylammonium chloride, for which the two association constants ($K_{1,mono}$ and $K_{2,mono}$, eqs 2 and 3) could be determined by direct measurements.[25]

$$\mathbf{2} + [H_3N(CH_2)_nNH_3]^{2+} \rightleftharpoons [\mathbf{2}\text{-}H_3N(CH_2)_nNH_3]^{2+} \qquad K_{bis} \qquad (1)$$

$$\mathbf{2} + [CH_3NH_3]^{+} \rightleftharpoons [\mathbf{2}\text{-}H_3NCH_3]^{+} \qquad K_{1,mono} \qquad (2)$$

$$[\mathbf{2}\text{-}H_3NCH_3]^{+} + [CH_3NH_3]^{+} \rightleftharpoons [CH_3NH_3\text{-}\mathbf{2}\text{-}H_3NCH_3]^{2+} \qquad K_{2,mono} \qquad (3)$$

The association constants of the complexation of **2** with methylammonium chloride were found to be much lower than those of the bisammonium salts (see Table). Upon complexation, the methyl groups experienced an upfield shift of 0.12 ppm in ^{1}H-NMR, whereas the aromatic protons were shifted downfield by ca. 0.05 ppm for each guest. The complexation of butylammonium chloride with **2** was also investigated to verify that the alkyl chain in itself did not influence the results significantly. The association constants were similar (see Table), as were the effects on the ^{1}H-NMR shifts of the aromatic and the α-protons. The remaining butyl protons showed an even stronger shielding (ca. 0.2 ppm), indicating that they were situated above the aromatic ring.

The association constants of the complexation of **2** with the primary bisammonium salts are shown in the Table. The deshielding of the aromatic protons in ^{1}H-NMR is similar to that found for the monoammonium salts, ca. 0.1 ppm. The shielding of the α-protons is stronger, ca. 0.2-0.4 ppm. An even more dramatic effect is seen for the remainder of the alkyl chain, with upfield shifts consistently > 0.4 ppm. The largest changes are seen for the β-protons when n = 5 or 7 (0.8 and 0.7 ppm, respectively). This is consistent with the binding mode shown in Figure, where the β-protons are clearly positioned on top of the aromatic ring. With n = 6, the largest upfield change is shown by the γ-protons, indicating that the straight-chain conformation cannot fit perfectly into the V-shaped receptor.

Table. Association Constants (M^{-1}) of the complexation of **2** with Bisammonium Salts ($[H_3N(CH_2)_nNH_3]Cl_2$) and Monoammonium Salts in MeOH-d_4:$CDCl_3$ (1:1) at 25 °C .[25]

ammonium salt	n	$K_{bis}\cdot 10^{-6}$	$K_{1,mono}\cdot 10^{-6}$	$K_{2,mono}\cdot 10^{-6}$
butane-1,4-diylbis(ammonium chloride)	4	0.5[a,b]		
pentane-1,5-diylbis(ammonium chloride)	5	0.70[b]		
hexane-1,6-diylbis(ammonium chloride)	6	2.6[b]		
heptane-1,7-diylbis(ammonium chloride)	7	7.8[b]		
octane-1,8-diylbis(ammonium chloride)	8	3.7[b]		
methylammonium chloride			0.0074	0.00052
butylammonium chloride			0.006[a]	0.0005[a]

[a]Less accurate value because of fewer available data points. [b]Titrations done at $[Cl^-]_{tot}$ = 74 mM.

The results show that bisammonium salts with n = 6-8 bind almost equally strongly to compound **2**. However, a slight preference for n = 7 in binding to **2** is observed, coordinating ca. 10 times more strongly than n = 4-5 to **2**. An energy-minimized representation of $[2\text{-(heptane-1,7-diylbisammonium)}]^{2+}$ is shown in Figure.

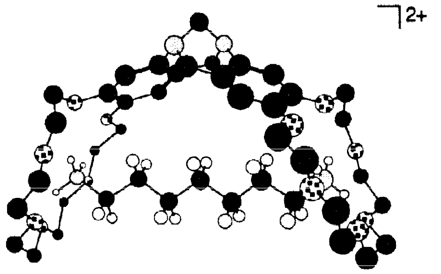


Figure. Chem3D representation of the energy-minimized structure of $[2\text{-(heptane-1,7-diylbisammonium)}]^{2+}$.

The nitrogens in receptor **2** are not significantly protonated under the conditions employed. Even though their lone pairs are not completely conjugated with the aromatic system, these nitrogen atoms are still sufficiently similar to that of aniline to have low basicity. A minimal protonation of the free host by the ammonium salt may occur, but should not have any influence on the observed results.

The enantiomeric discrimination of the new C_2-symmetric receptor **2** with chiral primary bisammonium salts was investigated using racemic **2** and enantiopure primary bisammonium salts in an initial ^{1}H-NMR investigation. Thus, upon complexation of the dimethyl ester dihydrochloride of L-cystine (C_2-symmetric) and the methyl ester dihydrochloride of L-lysine to *rac*-**2**, respectively, the protons of both **2** and the amino acid derivatives were shifted as for the simple bisammonium salts, indicating strong coordination. In additon, the ^{1}H-NMR spectrum at a 1:1 ratio of L-cystine dimethyl ester dihydrochloride and *rac*-**2** revealed that the aromatic protons as well as the protons belonging to the methylene bridges were doubled compared to free **2**, demonstrating the formation of two strong diastereomeric complexes (L-*R* and L-*S*) exclusively. At a 1:2 ratio, the two diastereomeric complexes were in fast exchange with respective enantiomer of free **2** as seen from the shift change and line broadening of the protons in the ^{1}H-NMR spectrum. The diastereomeric selectivity of the complexation (enantiomeric recognition) was calculated from the ^{1}H-NMR spectra and was found to be 62:38 for the 1:2 ratio of L-cystine dimethyl ester dihydrochloride and *rac*-**2**.[26] Despite that the enantiomeric recognition is modest, immobilizing enantiopure **2** on a chromatographic column would most likely separate *rac*-cystine into its antipodes. In contrast to the results above, no enantiomeric discrimination was observed in the complexation of L-lysine methyl ester dihydrochloride with *rac*-**2**.

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23. Selected data for **2**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 8 H), 3.68-3.78 (m, 16 H), δ 3.84-3.89 (m, 4 H), 3.89-3.94 (m, 4 H), 4.003 (A part of AB, J_{AB} = 16.44 Hz, 2 H), 4.03-4.08 (m, 4 H), 4.10-4.15 (m, 4 H), 4.25 (s, 2 H), 4.567 (B part of AB, J_{AB} = 16.44 Hz, 2 H), 6.40 (s, 2 H), 6.65 (s, 2 H); HRMS (EI$^+$, 70 eV) calcd for $C_{35}H_{50}N_2O_{12}$: 690.3365. Found: 690.3363; Anal. calcd for $C_{35}H_{50}N_2O_{12}$: C, 60.86; H, 7.30; N, 4.06. Found: C, 60.86; H, 7.29; N, 3.96.
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25. *Determination of association constants:* The changes in ^{1}H-NMR shift of all guest and aromatic host protons in relation to those of the pure compounds were measured for several total concentrations of **2** and guest in MeOH-d_4:$CDCl_3$ (1:1) at 25 °C. For each such pair of total concentrations, the expected concentrations of all species were calculated from a postulated set of association constants (eqs 1-3), whereupon the regression between the concentrations calculated and the shifts observed was calculated. The regression was optimized by varying the association constants. In direct measurements, 2.5-25 mM of **2** was combined with 2-100 mM of methylammonium chloride, yielding 75 shift differences. In the indirect measurements, 2.5-25 mM of **2** and 2.5-25 mM of bisammonium salt were buffered with methylammonium chloride to a constant chloride concentration of 74 mM, yielding ca. 100 measured shift differences in each case. The regression was optimized by varying the bisammonium association constant. Variations of the postulated constants by 10% led to a significantly diminished regression.
26. A solution of *rac*-cystine has been extracted with an enantiopure host in 66% optical yield.[20]