Tetrahedron Letters,Vol.27,No.46,pp 5563-5566,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

NEW APPROACHES TO SYNTHETIC RECEPTORS. SYNTHESIS AND HOST PROPERTIES OF A WATER SOLUBLE MACROCYCLIC ANALOG OF TRÖGER'S BASE

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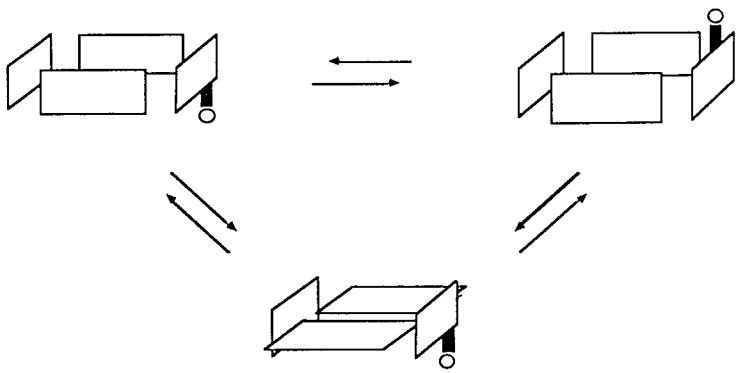
A water soluble, macrocyclic Tröger's base analog has been prepared and found to form association complexes with benzenoid substrates.

In the last decade, pioneering work by Koga, Murakami, Tabushi and Whitlock demonstrated that simple water soluble cyclophanes were capable of forming inclusion complexes with benzenoid and naphthalenoid substrates.[1] More recently, Diederich has refined this approach to synthetic receptors and has prepared a water soluble cyclophane which has a high affinity (K_d = 10^{-4} to 10^{-5}) for naphthalenoid substrates.[2] The known water soluble cyclophanes are flexible molecules in which the constituent benzenoid rings are freely rotating. (Figure 1) More rigid cyclophanes will allow an exploration of the relationship between rigidity and specificity and will support rational investigations of structure-activity relationships for these receptors.[3]

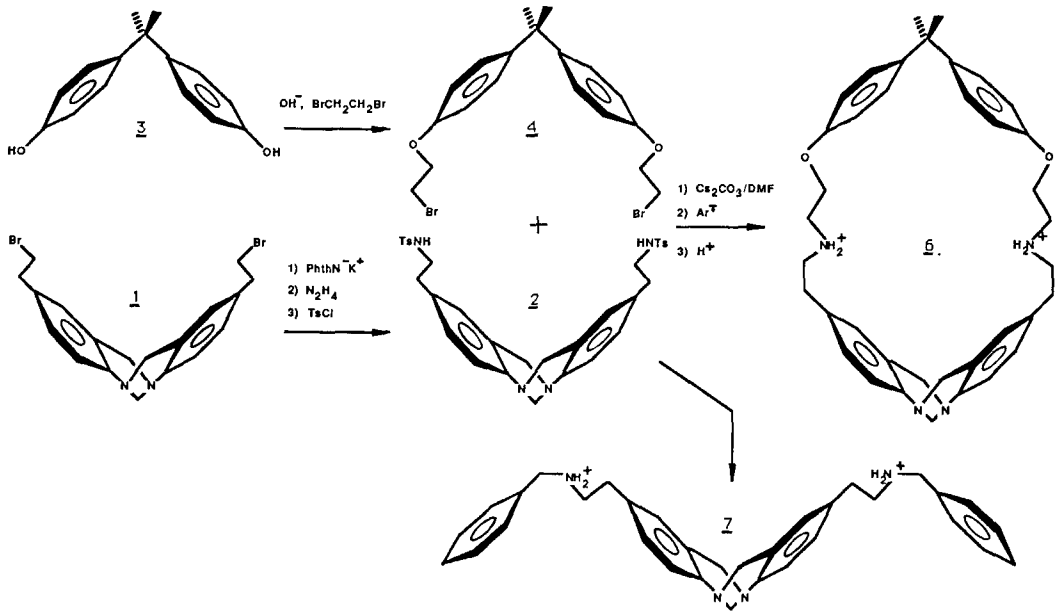
Figure 1. Schematic illustration of how rotational equilibria in water soluble cyclophanes can change the structure of a synthetic receptor.



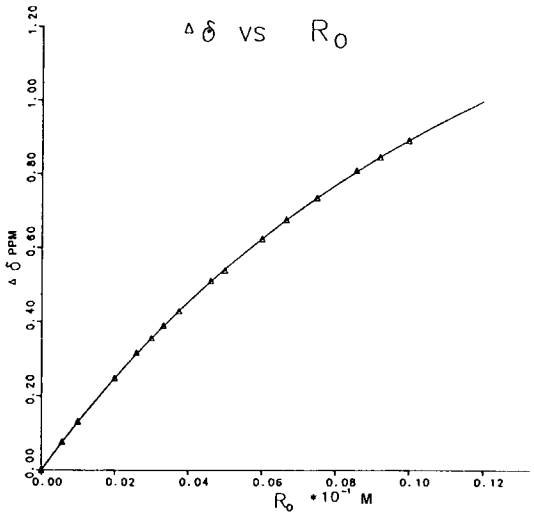
Tröger's base analogs are relatively rigid molecules in which two aromatic rings are held in a position well suited to the preparation of lipophilic pockets.[4] This paper describes the synthesis of a macrocyclic analog of Tröger's base and data for binding of this relatively rigid and chiral synthetic receptor to four benzenoid substrates.

The synthesis of the receptor began with the previously described dibromide 1 which was converted by conventional procedures to the bis-sulfonamide 2 in 60% overall yield.[4,5] (Chart 1) A solution of bis-sulfonamide 2 and dibromide 4 in DMF was added dropwise to a mixture of Cs_2CO_3 and DMF at 90°C under nitrogen. The macrocyclic bis-sulfonamide 5 was obtained in 55% yield. Reductive fragmentation of the bis-sulfonamide (0.1 M Na^+anthacene$^{\cdot-}$, DME, 0°C) afforded the diamine 6 which was purified by gradient elution ion exchange chromatography. (0.5-2.0% $NH_4^+Cl^-$, 1:1 $CH_3OH:H_2O$) By a similar route a control substance, diamine 7 was prepared and purified.

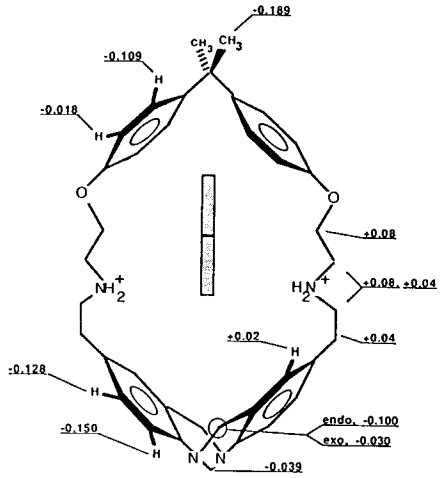
Chart 1.



Host properties of these diamines were determined in D_2O at 25°C at pD 1.8 in a DCl/KCl buffer. Figure 2(a) illustrates the effect of the synthetic receptor 6 (up to 10 mM receptor) on the chemical shift (TSP in D_2O external standard) of the aryl proton in 1,3,5-trimethylphenol (3 mM). Under these conditions, a 15 mM concentration of the control diamine (7) caused only a 0.1 ppm shift of the aryl proton. The large chemical shifts induced by the macrocyclic diamine are characteristic of inclusion complex formation.[1a-c,1i,2b] Added support for inclusion of the substrate within the cavity is provided by the substrate induced changes in host chemical shifts. [Figure 2(b)] In particular, the benzylic protons on the dibenzodiazocene which are *endo* are shifted far more than the benzylic protons *exo* to the macrocycle.[6] The receptor chemical shift changes indicate the time averaged position of the included (substrate) aryl group is as shown, and that "π-stacking", or a coplanar arrangement of the receptor and substrate aryl rings, is not favored.



(a)



(b)

Figure 2. (a)Change in ^{1}H-NMR resonance (H-3) of 2,4,6-trimethylphenol as a result of added receptor. Observed (Δ) and calculated (——) data. (b)Change in ^{1}H-NMR of receptor (3×10^{-3} M) induced by addition of p-cyanophenol (2×10^{-2} M). (+,upfield shift; -,downfield shift)

The magnitude of the synthetic receptor induced chemical shift may be shown to be a function of $\Delta\delta_{max}$ (the saturation value for receptor induced shift), R_o (the initial receptor concentration), S_o (the initial substrate concentration), and K_d (the dissociation constant):

$$\Delta\delta = \frac{\Delta\delta_{max}}{S_o}\left[\frac{R_o}{2} + \frac{\Sigma}{2}\left[1 - \sqrt{\frac{R_o^2 - 2R_o\Delta}{\Sigma^2} + 1}\right]\right] \qquad \Sigma = S_o + K_d \qquad \Delta = S_o - K_d$$

A curve fitting algorithm, implemented on a VAX 11/780 at the University of Texas, uses the above relationship together with experimental data to provide both K_d and $\Delta\delta_{max}$. Figure 2(a) includes a comparison of the calculated and observed variation of $\Delta\delta$ as a function of R_o. Using this method, dissociation constants for the synthetic receptor with four benzenoid substrates have been determined. (Table 1)

Table 1. Data for Binding of Four Substrates to Synthetic Receptor 6.

Substrate	K_d (M)	ΔG_{assoc}	$\Delta\delta_{max}$ (H-3)
4-methylphenol	2.37×10^{-2}	2.1 kcal/mol	2.13 (ppm)
2,4,6-trimethylphenol	1.33×10^{-2}	2.7 "	2.23 "
4-cyanophenol	1.28×10^{-2}	2.5 "	2.27 "
p-toluenesulfonic acid	4.00×10^{-3}	3.1 "	2.18 "

In summary, a macrocyclic Tröger's base derivative has been shown to afford inclusion complexes with benzenoid substrates. Dissociation constants for these complexes have been determined by use of a non-linear curve fitting procedure which avoids the approximations required in, for example, Benesi-Hildebrand treatments of complexation phenomena.[7] This new synthetic receptor shows a free energy of association for benzenoid substrates in the range of 2-3 kcal/mol at 25°C.

The data obtainable by these methods will be useful for testing computer models of association phenomena in aqueous systems. Rebek has observed unique properties associated with convergent functional groups on a rigid framework.[8] Our future work will examine the effect of rigidity on the host properties of cyclophanes and will evaluate the binding of other substrates to this and additional Tröger's base derived synthetic receptors.

Acknowledgment. The program used for data analysis was written by R. Bukownik. Support for this project was provided by the National Institutes of Health. Additional support was provided by the Robert A. Welch Foundation.

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5. New compounds had elemental compositions and spectral properties in accord with the indicated structure.

6. The *endo* and *exo* benzylic protons appear as an AB quartet. Irradiation of the bridging methylene ($-NCH_2N-$) caused a pronounced enhancement of the downfield doublet and little enhancement of the upfield doublet. The downfield doublet was thus assigned to the *exo* pair of protons and the upfield doublet ascribed to the *endo* protons.

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(Received in USA 4 August 1986)