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A Ditopic Azacryptate Proton Cage

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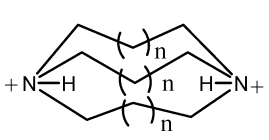
A tosylated azacryptand readily protonates at the bridgehead amines, becoming a potential ditopic anion receptor. The *in-in* conformation of the amines facilitates encapsulation of two bromide guests and represents the first structural evidence that a proton cage cryptate can bind two anions internally.

The concept of a proton cage emerged with the introduction of macrobicyclic diaza katapinands, **1**, of Park and Simmons,[1] and was exploited even further with the introduction of the proton cryptates, **2**.[2] The bridgehead amines of these two classes of macrocycles readily become protonated and can form *in-in*, *in-out*, and *out-out* conformers. Furthermore, because of the more rigid structure imparted by the arms joining the two tertiary amines, the protons in the *in-in* conformation are shielded, and hence rates of deprotonation are diminished. The effect has been termed "proton cage".[3]



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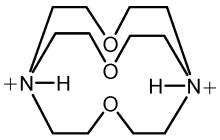

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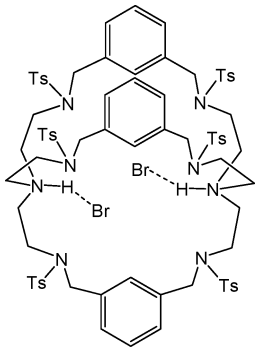
This type of shielding of the protonated amines allows for more control on their chemistry and has led to explorations in the photoinduction of long-lived proton transfer states in cryptands[3] and in the membrane transport of anions using katapinands and tosyl-protected azacryptands.[4] Indeed with the exception of this latter report, protection by tosyl groups has been primarily viewed as an undesirable nuisance, but a necessary part of the synthetic pathway to many aza-containing macrocycles. While Lehn and co-workers postulated binding of a halide within the proton cage in membrane transport,[4] this is the first structural evidence that tosylated azacryptands bind not just one, but two halides simultaneously within the bicyclic cavity.

One focus of our research group is the binding of anions by polyaza macrocycles.[5] More recently we have explored systematic ways to increase the affinity of anion receptors, including exploring the binding capabilities of new amide and thioamide macrocycles and cryptands,[6] and mixed amide/quaternized amine receptors.[7] It is this latter aspect that led us to revisit the tosylated azacryptands, with the possibility of introducing charge complementarity in these ligands by altering the protonation tendencies of the secondary amines. As a result, we synthesized the protected azacryptand, **L**, derived from a simple Schiff base condensation between tren and isophthalaldehyde, and isolated crystals of the free base, **L**, and the dihydrobromide salt, H_2**L**$(Br)_2$.



H_2**L**$(Br)_2$

L was synthesized from the reaction of the precursor amine[8] with *p*-toluenesulfonyl chloride in CH_3CN using

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(1) (a) Park, C. H.; Simmons, H. E. *J. Am. Chem. Soc.* **1968**, *90*, 2428−2429. (b) Simmons, H. E., Park, C. H. *J. Am. Chem. Soc.* **1968**, *90*, 2429−2431.

(2) (a) Cheney, J.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1972**, 487−489. (b) Cheney, J.; Kintzinger, J. P.; Lehn, J.-M. *Nouv. J. Chim.* **1978**, *2*, 411−418. (c) Smith, P. B.; Dye, J.; Cheney, J.; Lehn, J.-M. *J. Am. Chem. Soc.* **1981**, *103*, 6044−6048.

(3) Kuldovà, K.; Corval, A.; Trommsdorff, H. P., Lehn, J.-M. *J. Phys. Chem. A* **1997**, *101*, 6950−6854.

(4) Dietrich, B.; Fyles, T. M.; Hosseini, M. W.; Lehn, J.-M.; Kaye, K. C. *J. Chem. Soc., Chem. Commun.* **1988**, 691−692.

(5) Llinares, J. M.; Powell, D.; Bowman-James, K. *Coord. Chem. Rev.* **2003**, *240*, 57−75.

(6) (a) Kang, S. O.; Llinares, J. M.; Powell, D.; VanderVelde, D.; Bowman-James, K. *J. Am. Chem. Soc.* **2003**, *125*, 10152−10153. (b) Hossain, A. Md.; Kang, S. O.; Llinares, J. M.; Powell, D.; Bowman-James, K. *Inorg. Chem.* **2003**, *42*, 5043−5045.

(7) Hossain, M. A.; Kang, S. O.; Powell, D.; Bowman-James, K. *Inorg. Chem.* **2003**, *42*, 1397−1399.

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K_2CO_3 as a base.[9] Yellow crystals suitable for X-ray analysis formed after slow diffusion of Et_2O into a $CHCl_3$ solution.[10] H_2**L**$(Br)_2$ was obtained by dissolving 0.15 g of **L** in 10 mL of a mixture of $CHCl_3$/MeOH (1:1, v:v) and adding HBr (48%) until the solution reached a pH of 2.0. A fine, white precipitate formed, was filtered off, and was dissolved in MeOH,[11] followed by slow diffusion of Et_2O to obtain crystals suitable for X-ray analysis.[12]

The crystal structure of **L** contained the neutral azacryptand along with 1.5 molecules of a disordered CH_3CN and 0.183 molecule of $CHCl_3$. Both the cryptand and $CHCl_3$ sit on the crystallographic 3-fold axis. The crystal structure of H_2**L**$(Br)_2$ consists of the diprotonated **L**, two bromides, and 1.87 molecules of disordered $CHCl_3$. Each of the bromides lies off-center between two of the cryptand arms and is hydrogen bonded with one of the *endo*-oriented amine protons. The similarities between the two crystal structures are striking as can be seen in Figure 1, **A** and **B** for the neutral ligand and **C** and **D** for the bromide complex. For example, both of the cryptands are close to the same size, despite the fact that one is protonated. The distance between the bridgehead amines, N(1)−N(16), is 5.006 Å in **L**, while in the protonated form this distance is 5.200 Å. The elongation in the bromide complex is probably due to electrostatic repulsion of the two *endo*-oriented protons, as well as the incorporation of the two relatively large halides within the arms of the cryptand. The hydrogen bond distances in the bromide complex are 3.058(4) Å for N(16)···Br(1) and 3.128(4) Å for N(1)···Br(2). The structure of the bromide complex differs from many of the protonated azacryptand structures in that here there are only the two hydrogen-bonding sites.

The affinity of **L** for bromide in the presence of two equivalents of TsOH was investigated using ^{1}H NMR. Before the addition of the bromide salt, an NH proton signal was not observed. However, upon addition of *n*-Bu_4NBr, an NH signal appears at 9.34 ppm. The fact that the NH proton is seen only in the presence of bromide indicates that the anion also serves to stabilize the protonated amine, as noted by others.[13] A subsequent ^{1}H NMR titration of **L** in $CDCl_3$ (Figure 2) indicated that bromide only weakly binds with the protonated ligand (K_s = 254 M^{-1}).[14] As anticipated no

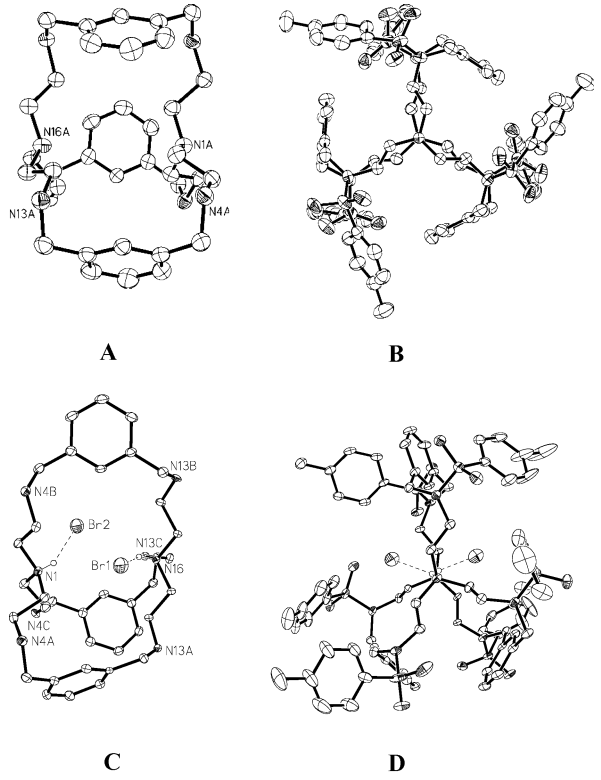

Figure 1. ORTEP diagrams showing two views of **L** (**A** and **B**) and H_2**L**$(Br)_2$ (**C** and **D**). **A** and **C** are views of the cavity with tosyl groups omitted for clarity. **B** and **D** are views down the bridgehead amine groups. Thermal ellipsoids are at 50% probability.

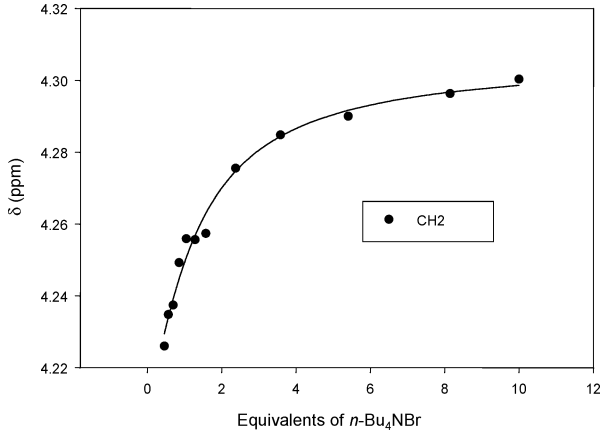

Figure 2. ^{1}H NMR titration of **L**·2TsOH with *n*-Bu_4NBr in $CDCl_3$.

(8) Clifford, T.; Danby, A.; Llinares, J. M.; Mason, S.; Alcock, N. W.; Powell, D.; Aguilar, J. A.; García-España, E.; Bowman-James, K. *Inorg. Chem.* **2001**, *40*, 4710−4720.

(9) The precursor amine (3.00 g, 5.02 mmol) was dissolved in 175 mL of CH_3CN and heated to 80 °C. K_2CO_3 (10.4 g, 75.3 mmol) was added as a solid, and the solution was stirred and refluxed for 20 min, after which solid TsCl (11.4 g, 60.2 mmol) was added. A precipitate began to form within several hours, and after refluxing for 48 h, a light brown precipitate was filtered off and washed in warm EtOH. The product was isolated as a white precipitate and dried *in vacuo*. Yield: 7.4 g, 97.0%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81 (t, 12H, NCH_2), 2.49 (s, 18H, CH_3), 2.81 (t, 12H, NCH_2CH_2), 4.08 (s, 12H, CH_2Ar), 7.07 (s, 3H, Ar*H*), 7.24 (d, 6H, Ar*H*), 7.35 (t, 3H, Ar*H*), 7.42 (d, 12H, Ts), 7.80 (d, 12H, Ts). ^{13}C NMR (100.61 Hz MHz, $CDCl_3$): δ 21.8, 47.7, 53.4, 54.7, 127.5, 128.6, 129.1, 129.5, 130.2, 136.2, 137.0, 143.9. FAB MS: *m*/*z* 1523.6 $[M + H]^+$. Anal. Calcd for $C_{78}H_{90}N_8O_{12}S_6$: C, 61.47; H, 5.95; N, 7.35. Found: C, 61.59; H, 6.05; N, 7.33.

(10) Crystal structure data for $C_{78}H_{90}N_8O_{12}S_6$·$1.5C_2H_3N$·$0.183CHCl_3$: M_w = 1607.50, trigonal, *R*3, a = 21.9335(6), b = 21.9335(6), c = 65.463-(3) Å, α = 90°, β = 90°, γ = 120°, V = 27273.6(16) Å^3, d_{calcd} = 1.174 g/cm^3, Z = 12, R ($I > 2\sigma(I)$) = 0.0624, wR (F^2 all data) = 0.2124, and GOF on F^2 = 0.910.

(11) Yield: 0.13 g, 80%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.53 (s, 18H, CH_3), 3.17 (t, 12H, CH_2), 3.40 (t, 12H, NCH_2CH_2), 4.40 (s, 12H, CH_2Ar), 7.21 m, 9H, Ar*H*), 7.34 (s, 3H, Ar*H*), 7.43 (d, 12H, Ts), 7.81 (d, 12H, Ts), 9.34 (s, 2H, N*H*). Anal. Calcd for $C_{78}H_{92}N_8O_{12}$-Br_2S_6: C, 55.64; H, 5.51; N, 6.66. Found: C, 55.28; H, 5.60; N, 6.69.

(12) Crystal structure data for $C_{78}H_{92}Br_2N_8O_{12}S_6$·$1.87CHCl_3$: M_w = 1909.59, triclinic, $P\bar{1}$, a = 15.2308(10), b = 16.0947(11), c = 19.8831-(14) Å, α = 96.720(2)°, β = 107.374(2)°, γ = 102.707(2)°, V = 4449.5(5) Å^3, d_{calcd} = 1.628 g/cm^3, Z = 2, R ($I > 2\sigma(I)$) = 0.0780, wR (F^2 all data) = 0.2507, and GOF on F^2 = 1.053.

(13) Micheloni, M. *J. Coord. Chem.* **1988**. *18*, 3−19.

(14) ^{1}H NMR spectra were recorded on a Bruker AM 500 spectrometer at 500 MHz. Each titration was performed by 20 measurements in $CDCl_3$ at room temperature. Aliquots from a stock solution of *n*-Bu_4N^+ salts (50 mM) were gradually added to the initial solution of ligand (5 mM). All proton signals were referenced to an external TMS standard in a capillary tube. The association constants K were calculated by a nonlinear regression curve fitting program with SIGMAPLOT.

binding was observed in the absence of TsOH, due to the lack of any electrostatic and hydrogen-bonding interactions.

While **L** does not show a high affinity for binding bromide, we detected a slightly stronger interaction with Cl^- ($K \approx 470\ M^{-1}$) and no interaction with I^-. Such findings are anticipated due to the heightened hydrogen-bonding tendencies of Cl^- and lessened tendencies of I^- compared to Br^-. We did observe some interaction with F^-, but no amine proton resonance signals, and were unable to calculate the binding constant due to spectral complexity. We have observed exceedingly strong binding of F^- with other cryptands.[6]

In conclusion, protective tosylation has generally been considered a necessary evil in the synthesis of a variety of amine-based receptors. However, by virtue of the same chemistry that allows the tosyl group to protect amines from further condensation, its protecting influence can be used to shift protonation to less accessible sites. The protonation of the two remaining amines provides a ditopic anion receptor with charge complementarity for monovalent halides or potentially a monotopic receptor for divalent anions. The isolation and characterization of the ditopic, *in-in* dibromide complex also demonstrates the important role that the anions play in stabilizing the protons on the apical nitrogen in these large azacryptands. Furthermore, because of the bulky tosyl groups which make these receptors less water soluble than simple amines, they may be of utility in applications such as liquid−liquid extraction. This finding thus provides structural and NMR corroboration to the capability of these systems for binding anions, and that binding does further shield the NH protons so that they are readily visible in the NMR spectra. While these receptors have yet to show superiority over other anion receptors, they serve as an example of an overlooked class of potential anion receptors.

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Supporting Information Available: Two crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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