Selective Anion Binding by a Macrocycle with Convergent Hydrogen Bonding Functionality

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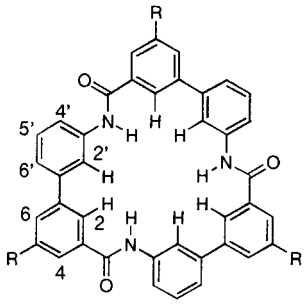
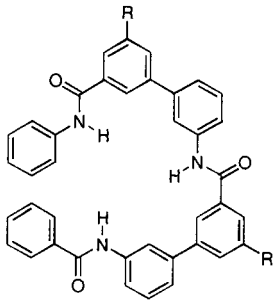
Received November 8, 2000

A key problem in supramolecular chemistry is the design of synthetic receptors with convergent binding groups that are arranged to match the functionality of the guest molecule.[1] Such receptors should have not only high affinity but also the improved selectivity that is important for sensing applications. In particular, many anions have diverse geometries that offer a possible route to the development of shape-selective anion receptors.[2] Although we and others[3] have made extensive use of hydrogen bonding to recognize anions, rarely have the binding groups been arranged in a convergent and rigid manner. Notable exceptions include the bicylic cyclophane[4] of Anslyn that binds planar anions and the calix[4]pyrrole[5] of Sessler that exploits four hydrogen bond donors to bind the spherical fluoride anion. To expand the type of anions that can be targeted by this strategy we have prepared a novel macrocyclic anion receptor with C_3 symmetry that binds tetrahedral anions such as sulfate and phosphate with high affinity. Although several artificial receptors for these important[2a] anions have been reported,[6,7] few have the combined features of rigid, convergent, and geometrically optimal binding groups.



1a R = CO_2Et
b R = NHBoc



2 R = CO_2Me

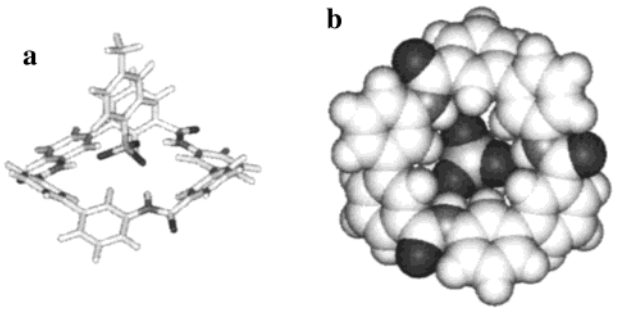


Figure 1. The calculated structure of the 1:1 complex between **1** and *p*-tosylate anion: (a) a side view and (b) a bottom view with CPK representation. The lowest energy conformation of the macrocycle was used as an initial structure for the calculation with the MM2 force field. R groups are omitted for clarity.

Macrocycle **1** was synthesized starting from 5-substitutied-3′-nitro-3-biphenylcarboxylic acid, which in turn was prepared from the coupling reaction between 3-nitrophenylboronic acid and the corresponding 3-iodobenzoic acid. Functional group manipulation and stepwise coupling of the monomeric unit gave the linear trimer that was cyclized to the corresponding macrocycle **1**.[8] This design projects into the center of the cavity three amide groups that serve as hydrogen bonding donors for anion binding. A Monte Carlo conformational search[9] showed that the lowest energy conformer has a central hole ≈5 Å in diameter, lined only with hydrogen atoms, three from the amides and six from the aryl groups. The size of the hole and skewed arrangement of three amide protons are nicely matched to the size and shape of tetrahedral oxyanions, such as *p*-tosylate (Figure 1).

To determine the anion binding properties of the macrocycle, NMR titration experiments[10] were performed in 2% DMSO-d_6/$CDCl_3$ and the chemical shift data were analyzed by EQNMR, a nonlinear regression curve fitting program.[11] Titration of **1** with tosylate anion as its tetrabutylammonium salt gave 1:1 binding isotherms for the amide and aryl protons of **1** (Figure 2). The aryl protons of the anion showed ≈0.3 ppm upfield shifts upon binding due presumably to the ring current effect of the macrocycle. The 1:1 binding ratio was confirmed by a Job's plot.[10] The complexation induced chemical shift changes ($\Delta\delta$) of the macrocycle protons projecting into the central cavity (C2H, C2′H) are much larger than those of the externally directed protons. **1a** and **1b** showed similar binding affinities indicating the overall anion binding properties are not affected significantly by the functional groups outside the central cavity.

The other anions tested showed more complex binding behavior, which was characterized by initial upfield shifts

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10.1021/ja005772+ CCC: $20.00
Published on Web 02/20/2001

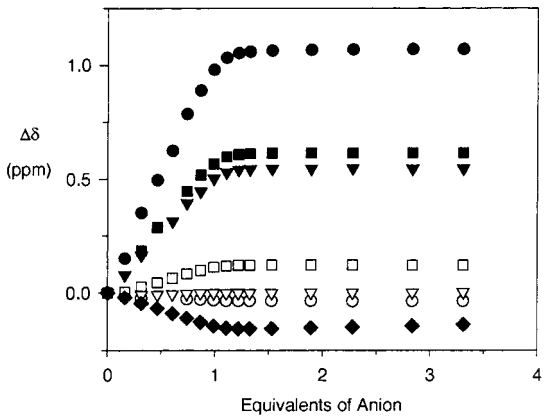

Figure 2. Change in ^{1}H chemical shift of **1b** with increasing pTsO$^-$ concentration in 2% DMSO-d_6/$CDCl_3$ (●, amide NH; ■, C2′H; ▼, C2H; □, C4′H; ▽, C4H; ○, C6H; ◆, BocNH). C5′H and C6′H, which overlap each other, showed little change (≈0.03 ppm). The assignment was done using COSY and NOESY experiments. The countercation was tetrabutylammonium, and the concentration of **1b** was 0.75 mM at 296 K.

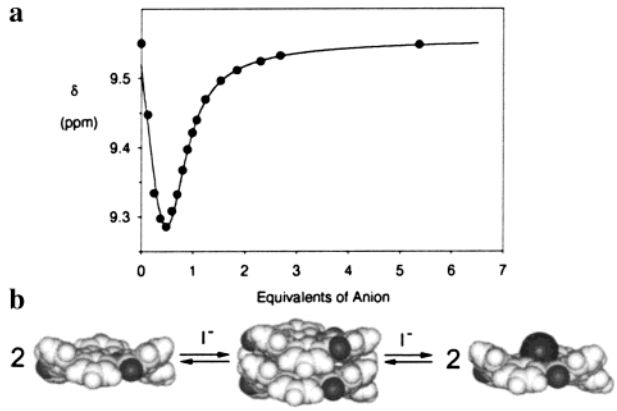

Figure 3. (a) Changes in the amide ^{1}H chemical shift of **1b** with increasing I$^-$ concentration. The data (●) were curve-fitted[11] to the multiple-equilibrium model involving 1:1 and 2:1 complexes of **1** with I$^-$. Conditions as in Figure 2 were used. (b) The multiple-equilibrium model used for the curve fitting. M_2I and MI structures were calculated by using the MM2 force field. The iodide anion of the M_2I complex is located between two macrocycles.

(especially of the amide protons) up to 0.5 equiv addition of anionic substrate. Above 0.5 equiv, the direction of the shift changed to downfield (Figure 3a). The binding isotherms of the amide and aryl protons fit a model of M_2I and MI complex formation (Figure 3b, M:macrocycle, I:ion) and the association constants of each equilibrium step were obtained.[12] Spherical halide, planar nitrate, and tetrahedral hydrogen sulfate and dihydrogen phosphate anions all showed this mode of binding (Table 1).[13] The even distribution of charge on these anions allows them to bind two equivalent macrocycles in a sandwich complex. This accounts for the large upfield shifts of the macrocycle protons in the M_2I complex from ring current effects in the π-stacked structures. I$^-$ showed much higher binding affinity than Cl$^-$, which has higher charge density. This selectivity can be explained by the large size and rigidity of the binding site. In the case of HSO_4^- and $H_2PO_4^-$, binding equilibria were slow on the NMR time scale and separate sets of ^{1}H peaks were observed for the M, MI, and M_2I complexes. In contrast, a linear analogue **2** showed much weaker binding to all anions tested.

Table 1. Association Constants (M^{-1}) of **1** with Tetrabutylammonium Salts at 296 K[a]

anion	**1a**[b]	**1b**[b]	**1b**[c]	**2**
I$^-$	1.3×10^5 (1.1×10^4)	1.2×10^5 (9.0×10^3)	<10	120[b]
Cl$^-$	8.8×10^3 (1.7×10^3)	7.6×10^3 (1.9×10^3)	<10	*d*
NO_3^-	4.6×10^5 (2.1×10^3)	*d*	20	620[b]
pTsO$^-$	2.6×10^5	2.1×10^5	780	*d*
HSO_4^-	slow equilibrium[e]	*d*	1.7×10^3	*d*
$H_2PO_4^-$	slow equilibrium[e]	*d*	1.5×10^4[f]	500[c]

[a] Determined by titrating a 0.5−1.0 mM macrocycle solution with salt solution. The salt solution contains macrocycle at its initial concentration to account for dilution effects. The association constant of the 2:1 complex ($MI + M \rightleftharpoons M_2I$) is included in parentheses when it is applicable. Estimated errors are within ±20%. [b] In 2% DMSO-d_6/$CDCl_3$. [c] In DMSO-d_6. [d] Not determined. [e] Slow equilibrium among free macrocycle; a 1:1 complex and a 2:1 complex were observed at room temperature. The association constants were not calculated. [f] Slow equilibrium was observed.

The $\Delta\delta$ values of the interior protons in the macrocycle are sensitive to the shape of the bound anion. While the tetrahedral anion complexes showed a large $\Delta\delta$ (0.8−1.1 ppm) of the amide proton, the other anion complexes showed small or negative $\Delta\delta$ (−0.35 to 0.05 ppm). In addition, the relative ratio between $\Delta\delta$ of C2H and C2′H ($\Delta\delta 2/\Delta\delta 2'$) was much larger for the planar (3.0) and spherical (2.2−2.8) anion complexes than the tetrahedral anion complexes (1.1−1.2), indicating a different binding mode for the different anions.

In a more competitive hydrogen bonding solvent such as 100% DMSO-d_6, the association constants decreased significantly and M_2I complex formation was not observed. The stability of the complexes with halide and nitrate anions decreased dramatically even in 50% DMSO-d_6/$CDCl_3$. However, tetrahedral anions such as pTsO$^-$, HSO_4^-, and $H_2PO_4^-$ retained strong binding in DMSO-d_6 with the $H_2PO_4^-$ complex still showing slow exchange on the NMR time scale.

In conclusion, we have synthesized a novel anion receptor based on the rigid disposition of hydrogen bonding groups in the interior of a macrocyclic scaffold. This convergent projection of dipoles enables the macrocycle to bind anions with size and shape selectivity and stable complexes were formed even in polar solvent. We are currently using this novel macrocycle as a building block in the formation of functionalized and more complex molecular receptors.

Acknowledgment. This work was supported by the National Institute of Health (GM35208).

Supporting Information Available: Synthetic schemes for **1**, selected NMR titration data, and a Job's plot (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Due to the directionality of macrocycle **1**, two diastereomers of the M_2I complex could be formed: parallel and antiparallel isomers. However, only single isomer formation was assumed for the association constant calculation. This assumption is supported by the observation of only a single set of ^{1}H signals for the M_2I complex under slow exchange conditions.

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