ORGANIC LETTERS

2006
Vol. 8, No. 15
3171−3174

Anion Binding to Monotopic and Ditopic Macrocyclic Amides

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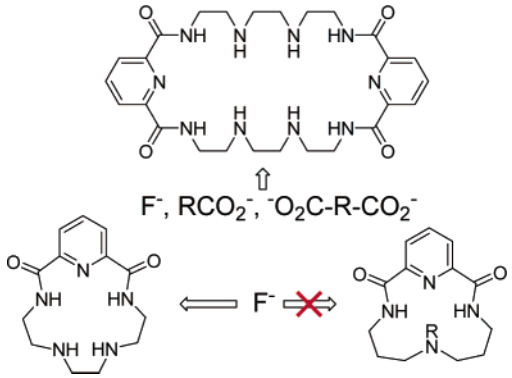
Received March 31, 2006

ABSTRACT



Binding of fluoride anion as well as carboxylic acid tetraalkylammonium salts by macrocyclic compounds of different size was studied by NMR in DMSO-d_6. It has been found that at least a 15-membered ring is necessary for successful recognition of fluoride. Larger macrocycles obtained in a [2 + 2] cyclization were shown to bind dicarboxylic acid salts. Effects of binding topicity are discussed.

Anion recognition is a rapidly expanding area of interest. Progress in this area has led to the design of strong and selective receptors for anion binding.[1−5] However, a full understanding of the principles that govern anion recognition has not been achieved. It became clear early on that multiple hydrogen-bonding interactions are necessary in high-affinity anion binding sites.[3,6] Charge and shape complementarity between the host and the anionic guests are also important. The overall ligand topology (e.g., acyclic vs macrocyclic vs macrobicyclic) has a profound influence on anion binding, and the majority of efficient anion binding receptors are based on the cyclic structures.[4,7]

Previous systematic studies identified the importance of ring size to anion binding affinity.[4,8,9] As the size of the macrocyclic ring gradually increases, certain large macrocyclic hosts become capable of binding more than one molecule of guest.[10,11] Despite these interesting findings, questions remain about topicity of anion binding in solution, especially in the case of larger rings.

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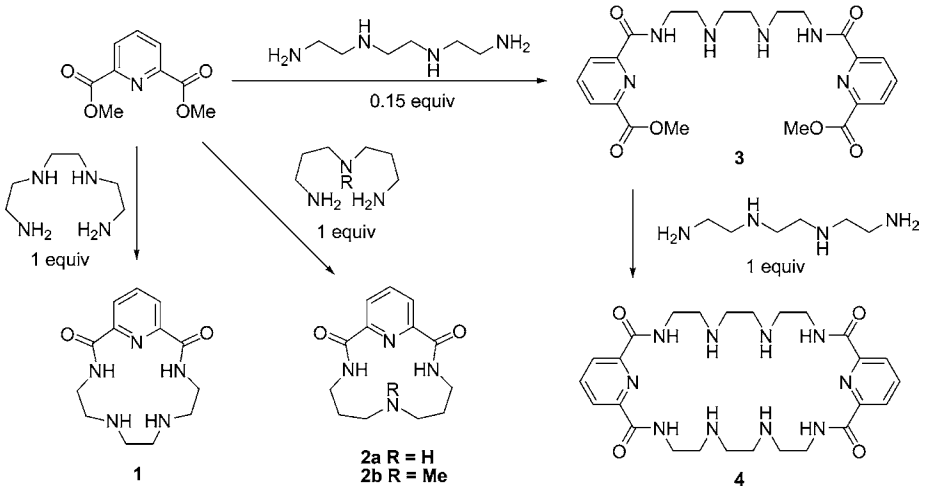
(1) Martinez-Manez, R.; Sancenon, F. *Chem. Rev.* **2003**, *103*, 4419−4476.
(2) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609−1646.
(3) *Supramolecular Chemistry of Anions*; Wiley-VCH: New York, 1997.
(4) Bowman-James, K. *Acc. Chem. Res.* **2005**, *38*, 671−678.
(5) Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17−55.
(6) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; Wiley-VCH: New York, 1995.
(7) Choi, K.; Hamilton, A. D. *Coord. Chem. Rev.* **2003**, *240*, 101−110.
(8) Chmielewski, M. J.; Jurczak, J. *Chem.—Eur. J.* **2005**, *11*, 6080−6094.
(9) Kang, S. O.; Powell, D.; Bowman-James, K. *J. Am. Chem. Soc.* **2005**, *127*, 13478−13479.
(10) Ghosh, S.; Choudhury, A. R.; Row, T. N. G.; Maitra, U. *Org. Lett.* **2005**, *7*, 1441−1444.
(11) Hossain, M. A.; Kang, S. O.; Powell, D.; Bowman-James, K. *Inorg. Chem.* **2003**, *42*, 1397−1399.

10.1021/ol060786r CCC: $33.50
Published on Web 06/24/2006

Scheme 1



In this report, we examine topicity and affinity of anion binding by introducing large, yet controllable, changes in the macrocyclic hosts and by comparing small monomeric and corresponding large dimeric rings. Smaller rings have only one likely anion binding site, while larger rings have two structural fragments suitable for hydrogen bonding with guests, thus providing the possibility for encapsulating two guest molecules or ions. To our knowledge, this is the first study that compares the anion binding properties of products from [1 + 1] and [2 + 2] cyclizations, thus preserving the same type and arrangement of the donor atoms and limiting variables only to the size and shape of the macrocyclic ring. The only studies published to date that pursued a similar approach compared solid state adducts of chloride ions with a tetralactam and an octalactam host formed by the condensation of 2,6-pyridinedicarboxylic acid ester and ethylenediamine in a [2 + 2] and [4 + 4] fashion, respectively,[8,12] but no data for host−guest association in solution have been reported.

We have designed 14-, 15-, and 30-membered macrocycles containing both amide and amino groups (**1**, **2a**, **2b**, and **4**), which are capable of binding small molecules and anions. The 2,6-bis(carbamoyl)pyridine fragment was chosen because of its well-established anion recognition properties.[7,13] Having two distinct sites in one molecule, one of which could be used for other purposes (e.g., serve as a metal binding site[14,15]), can eventually lead to the design of functional systems with selectivity toward specific substrates.

We have probed the guest binding properties of our macrocyclic hosts with several kinds of guests: a neutral H-bond acceptor (DMSO), a neutral H-bond donor and acceptor (MeOH), the smallest anion (F^-), and monofunctional and difunctional carboxylates.

Macrocycle **1** has been synthesized by a simple [1 + 1] condensation of 1,4,7,10-tetraazadecane and 2,6-pyridinedicarboxylic acid ester (Scheme 1).[16] Compounds **2a** and **2b** were obtained using an analogous approach; however for **2b**, an alternative reaction using 2,6-pyridinedicarboxylic acid chloride[17] produced the product in much higher yield. Macrocycle **4** has been synthesized according to the Scheme 1. To make sure that the final product of [2 + 2] condensation was pure and did not contain any of the [1 + 1] product, the product of [2 + 1] condensation, **3**, was isolated and purified, and only then was it allowed to react with an additional 1 equiv of 1,4,7,10-tetraazadecane, giving the final macrocycle **4** in a 10% overall yield.

All synthesized ligands were characterized structurally. These structural data provided us with insight into the binding mode of small molecules to the macrocyclic hosts. Compound **1** did not incorporate solvent molecules in the solid state (crystallization from alcohols, acetonitrile, chloroform, or methylene chloride invariably yielded the same solvent-free structure). The rigid 2,6-bis(carbamoyl)pyridine fragment induced a nearly planar shape for both the 15-membered macrocycle **1**[16] and the 14-membered macrocycles **2a** and **2b** (Figures S1 and S2, Supporting Information).

Compound **4**, which has a large [2 + 2] ring, bound two molecules of either DMSO or methanol, giving rise to two different ring conformations.

In the case of DMSO, each of the two DMSO molecules forms two hydrogen bonds with two of the host's amide groups (Figure 1, Figures S3, S4, Supporting Information). The overall conformation of the macrocyclic cavity resembles the shape of previously described macrocycles with α,ω-diamino linkages.[8] The chains linking the 2,6-bis(carbamoyl) fragments are essentially unstrained, with NCCN torsional angles close to the optimal 180 and 60°. Parameter *h*, introduced by Chmielewski and Jurczak[8] to describe the distance between the planes of the two pyridine rings in related molecules, is 5.79 Å, consistent with the general trend

(12) Szumna, A.; Jurczak, J. *Helv. Chim. Acta* **2001**, *84*, 3760−3765.
(13) Bondy, C. R.; Loeb, S. J. *Coord. Chem. Rev.* **2003**, *240*, 77−99.
(14) Mascharak, P.; Marlin, D. *Chem. Soc. Rev.* **2000**, *29*, 69−74.
(15) Korendovych, I. V.; Rybak-Akimova, E. V. Manuscript in preparation.
(16) Korendovych, I. V.; Staples, R. J.; Reiff, W. M.; Rybak-Akimova, E. V. *Inorg. Chem.* **2004**, *43*, 3930−3941.
(17) Voegtle, F.; Weber, E.; Wehner, W.; Naetscher, R.; Gruetze, J. *Chem. Z.* **1974**, *98*, 562−563.

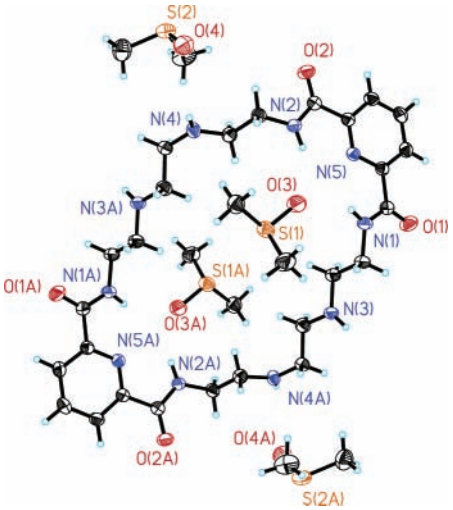


Figure 1. ORTEP plot of **4·2DMSO**.

for macrocycles with aliphatic linkers (Figure S5, Supporting Information). NH groups of the linker in **4·2DMSO** form intermolecular hydrogen bonds with amide groups, resulting in a sheet-like structure (Figure S6, Supporting Information).

Binding of methanol by **4** is different because of the ability of MeOH to form three hydrogen bonds. The presence of additional hydrogen-bonding sites (NH groups) leads to a completely different conformation (Figure 2). The linkers

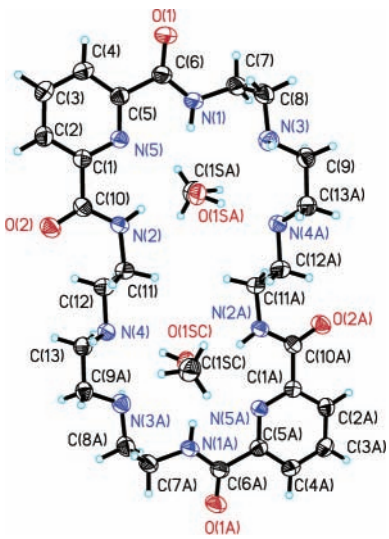


Figure 2. ORTEP plot of **4·2MeOH**.

are still almost unstrained, but the macrocycle adopts a bicompartmental structure with three hydrogen-bonding sites for each methanol molecule. The guest oxygen atom is in a nearly tetrahedral environment provided by the hydrogen bonds. The two pyridine rings are nearly coplanar and separated by 0.65 Å. We call the resulting structure the "Z-conformation" (Figure S7, Supporting Information).

Methanol binding in the solid state was reversible: upon standing in chloroform solution, **4·2MeOH** lost methanol and precipitated as pure **4**, as evidenced by NMR data.

Anions can be expected to bind with hosts **1**−**4** more strongly than neutral molecules. The smallest anion, F^-, was used to probe the effects of the size of the macrocyclic ring. The 15-membered [1 + 1] macrocycle **1** is capable of binding F^- ions, as determined by the NMR titration with NBu_4F. Nonlinear least-squares fit of the resulting titration curve with the program Wineqnmr[18] yielded an association constant of $K = 5.8(7) \times 10^2\ M^{-1}$ (Figure S8, Supporting Information). The 1:1 stoichiometry of the reaction was unambiguously established using a Job's plot (Figures S9 and S10, Supporting Information).

A large excess of fluoride ions leads to deprotonation of the macrocycle to form HF_2^- and DF_2^- ions, as evidenced by a doublet (−143.4 ppm, $^1J_{HF} = 119$ Hz) and a triplet (−143.8 ppm, $^1J_{DF} = 18$ Hz), respectively, in the ^{19}F spectrum. Similar observations were reported by Chmielewski and Jurczak for their hosts.[8] After several days, the HF_2^- signal completely disappears and only the DF_2^- peak is present, due to the fluoride-facilitated deuterium exchange between DMSO-d_6 and the ligand.

The fluoride-binding properties of the 14-membered macrocycles **2a** and **2b** differed drastically from those of **1**: **2a** and **2b** did not bind fluoride. It can be concluded that at least a 15-membered macrocycle is needed for encapsulating the fluoride anion in 2,6-bis(carbamoyl)-containing hosts.

For the larger cavity macrocycle **4**, the corresponding Job's plot has a maximum at a 1:2 ratio of host to fluoride (Figure S11, Supporting Information). To clarify the stoichiometry of the binding of fluoride ion to **4**, we have also performed NMR titrations in solution. The titration curve of **4** with NBu_4F has a sigmoidal shape, in agreement with previously reported results for similar hosts,[8] which may be indicative of the formation of two species. Extracting quantitative binding affinities for the 1:1 and 1:2 complexes of **4** with fluoride, however, was hampered by the experimentally observed dependence of the data (in terms of both the shape of the curve and the values of the fitting parameters) on initial concentration of reagents. Additional experiments showed that variable concentration of water is the reason for such inconsistency. For example, the position of the amide peak at [**4**]:[F^-] = 1:2 shifts by 1 ppm upon increasing the water content from 20 to 110 equiv! The same effect was observed for binding of fluoride to **1** in the presence of water. Water is inherently present in all tetrabutylammonium fluoride solutions prepared from commercially available aqueous NBu_4F, and different amounts of water are added in standard titrations of the macrocyclic host with fluoride solutions. This "water effect" might explain why, in many cases,[8,11] binding of fluoride to the receptor could not be modeled adequately.

The pronounced influence of water on fluoride binding to amidopyridine macrocycles suggested that further studies of fluoride binding to macrocyclic hosts have to be done under carefully controlled conditions. Since anhydrous NBu_4F is

(18) Hynes, M. J. *J. Chem. Soc., Dalton Trans.* **1993**, 311−312.

unstable,[19] water could not be completely excluded from the system. Instead, we decided to perform titrations at a constant water concentration (ca. 250 mM). Qualitatively, the observed sigmoidal shape can be explained by competitive binding of fluoride and water. Quantitative modeling of the multiple equilibria in this system required extensive systematic variations of both H_2O and F^- concentrations and was beyond the scope of the present work. However, fitting of the region where fluoride binding dominates can provide us with an estimate of the binding constants. This region of the curve (Figure S12, Supporting Information) can be fit with both 1:1 and 1:2 models; however, a 1:2 model provides a better fit [$K_1 = 4(7) \times 10^3\ M^{-1}$, $K_2 = 3(5) \times 10^2\ M^{-1}$, $R = 0.31\%$] than a 1:1 model [$K = 3.7(3) \times 10^2\ M^{-1}$, $R = 0.44\%$]. The F^- binding occurs under fast exchange conditions, so no splitting in either ^1H or ^{19}F NMR spectra was observed.

To establish unambiguously the ditopicity of **4**, we have studied binding of tetraethylammonium salts of mono- and dicarboxylic acids. Monocarboxylates are only weakly bound by **4** [$K = 31.9(9)\ M^{-1}$, chemical shift of the adduct 10.17(1) ppm for tetraethylammonium benzoate; $K = 67(3)\ M^{-1}$, chemical shift of the adduct 9.89(1) ppm for tetrabutylammonium acetate, Figures S13 and S14, Supporting Information]. However, going from a monocarboxylate to a dicarboxylate (tetraethylammonium fumarate) improves binding affinities by almost 2 orders of magnitude [$K = 1.1(1) \times 10^3\ M^{-1}$, chemical shift of the adduct 10.95(2) ppm, Figure S15, Supporting Information]. The Job's plot unambiguously establishes a 1:1 stoichiometry of fumarate binding to the macrocycle (Figure S16, Supporting Information). This suggests ditopic binding of the dicarboxylate to **4** in solution. We have also observed that **1**, **2a**, and **2b** do not bind benzoate or fumarate, suggesting that higher flexibility and the presence of additional secondary amino groups and/or an additional amidopyridine moiety in the larger ring are essential for binding of carboxylates. Studies of the binding of dicarboxylates as a function of chain length are in progress.

In conclusion, we have designed and synthesized four macrocyclic compounds that contain amide and amino groups and studied the effects of the ring size on topicity of anion binding. We have applied a novel approach to study topicity of anion binding in macrocyclic structures by comparing the properties of the macrocycles from [1 + 1] versus [2 +2] condensations, thereby examining the effect of cavities of different sizes. We have established that the minimum ring size of the 2,6-bis(carbamoyl)pyridine-containing macrocycle to bind fluoride is 15. Complexation of fluoride has a significant water dependence, suggesting competitive binding of water and fluoride. Preliminary studies suggest a 2:1 binding mode of F^- to **4**. We have obtained indirect evidence of ditopic complexation of dicarboxylate ions in solution: the newly synthesized macrocyclic ligand **4** possesses at least 20-fold higher affinity to dicarboxylates compared to that of monocarboxylates.

Acknowledgment. This research was supported by the NSF (CHE 0111202) and by Tufts University (Faculty Research Award). The NMR and the mass spectroscopy facilities in the Chemistry Department at Tufts University were supported by NSF Grants CHE-9723772 and CHE-0320783.

Supporting Information Available: Synthetic procedures, details of characterization of **2a**, **2b**, **3**, and **4**, crystallographic files in cif format, ^1H NMR spectra, and fit of the binding curves. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060786R

(19) Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050−2051.