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Cation Selectivity of a Folded Ditopic Crown Receptor

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The synthesis and cation binding properties of a folded ditopic crown receptor, 3, are described. Intramolecular hydrogen-bonding interactions preorganize ditopic crown 3 into a helical conformation that positions the crown moieties in a manner that favors the formation of an intramolecular sandwich cation complex. Alkali-metal picrate extraction studies demonstrate that ditopic crown 3 exhibits a significantly different cation

The Future of Supramolecular Chemistry

Proteins derive function through their highly organized, three-dimensional structure, and the reversible interconversion between different conformational states is often the means by which function is modulated or changed. In these molecules, conformational cooperativity that occurs over long distances causes small energetic differences relating conformational states to be dramatically magnified leading to highly stable folded materials. This phenomenon is commonly observed in biomacromolecules; however, there are relatively few synthetic materials that exhibit this cooperativity. Nevertheless, the remarkable efficacy exhibited by functional proteins suggests that synthetic macromolecules capable of adopting high levels of structural self-organization provide tremendous potential to develop materials with novel capabilities and properties not present in natural biomacromolecules. We have recently developed the first example of a well-defined monomolecular dendrimeric system with conformational properties consistent with such cooperativity. However, several important questions remain to be answered by further research in the area of dendrimer structure and stereochemistry. Can this cooperative conformational equilibrium be exploited in synthetic polymers and dendrimers to enhance the selectivity of a molecular recognition event or catalytic process? Can the folded dendron structures be induced to reversibly interconvert between different conformations through the action of an external stimulus in a manner that alters function? Such capabilities may provide the basis for development of catalysts, molecular switches, optical storage devices and drug-delivery vehicles among other functional devices. The work described in this manuscript represents a first step in trying to develop an understanding of how the conformational cooperativity present in folded dendrimer systems can control selectivity in a molecular recognition event. Progress in the development of functional materials will certainly be driven by a better understanding of how conformational equilibria can be controlled over relatively long distances in a manner reminiscent of biological macromolecules.

Jon R. Parquette (born 1966) received a BS degree in chemistry from the University of California, Berkeley in 1988, and his PhD in 1994 from Stanford University working with Barry M. Trost. At Stanford, he was an American Chemical Society, Division of Organic Chemistry Fellow. After completing postdoctoral work at Caltech in 1996, working with Peter Dervan as an American Cancer Society Postdoctoral Fellow, he became a faculty member at The Ohio State University and was promoted to the rank of Associate Professor in 2002. His research interests revolve around the theme of synthetic macromolecular and supramolecular organic chemistry.

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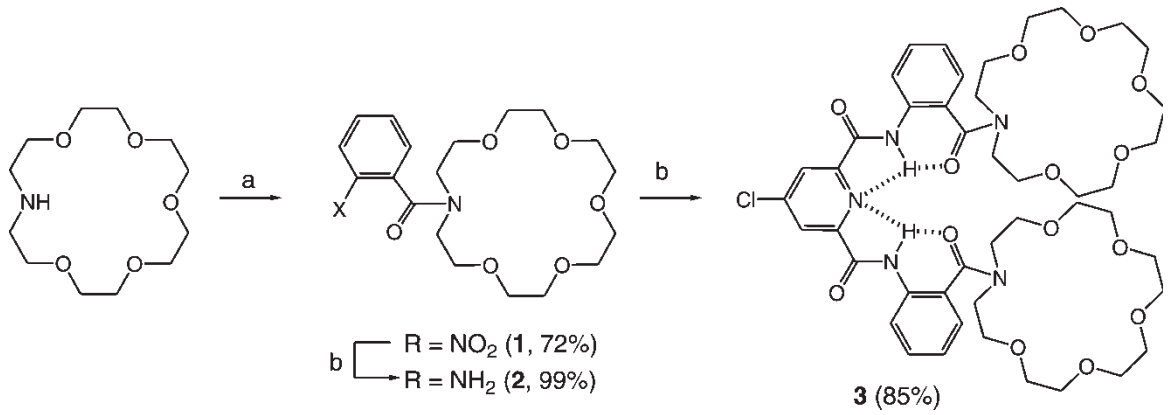

SCHEME 1 (a) 2-Nitrobenzoyl chloride, CH_2Cl_2, pyr. (b) $NaBH_4$, $Cu(OAc)_2 \cdot H_2O$, C_2H_5OH. (c) 4-Chloropyridine-2,6-dicarbonylchloride, pyridine–CH_2Cl_2.

selectivity than mono-crown congener 2. A crystal structure of 3·2KClO$_4$ indicates that two molecules of the complex are assembled into a molecular square in the solid state.

Keywords: Dendrimer; Cation binding; Crown macrocycle; Hydrogen bonding

INTRODUCTION

The cooperative action of adjacent crowns in oligocrown ether compounds often leads to enhanced affinity and selectivity for certain cations [1–5]. Covalently linking together multiple crown moieties imparts an entropic advantage in the formation of sandwich complexes, which accommodate metal ions that are too large for a single crown macrocycle [6–8]. In conjunction with a program directed at exploring the potential for cooperative cation recognition at the periphery of folded dendrimer structures [9–15] based on pyridine-2,6-dicarboxamide [16,17], we report herein the synthesis and cation complexing properties of ditopic crown **3** (Scheme 1).

Pyridine-2,6-dicarboxamides exist primarily in a *syn–syn* conformation because this conformation places the amide NH groups in close proximity to the pyridine-*N*, which permits intramolecular hydrogen bonding interactions to occur and minimizes the repulsive electrostatic interactions between the amide oxygens [18]. Accordingly, two aza-18-crown-6 macrocycles were placed at the periphery of a first-generation dendron previously shown to fold into a helical conformation as a consequence of the *syn–syn* conformation of the pyridine-2,6-dicarboxamide branch unit [16,17]. Bis-crown dendron **3** may potentially bind metal cations either as a 1:1 complex (**A**) or as an intramolecular 2:1 sandwich complex **B**, as shown in Fig. 1. However, the helical conformational preference of the dendron juxtaposes the crown moieties in an orientation ideally suited to complex cations via an intramolecular sandwich complex **B** and should lead to enhanced affinity for larger cations such as Cs^+ and Rb^+.

RESULTS AND DISCUSSION

Synthesis of Bis-crown Macrocycle

First-generation bis[aza-18-C-6] dendron, **3**, was prepared in three steps from aza-18-crown-6 in an overall yield of 60%. Accordingly, acylation of aza-18-crown-6 [19], with 2-nitrobenzoyl chloride

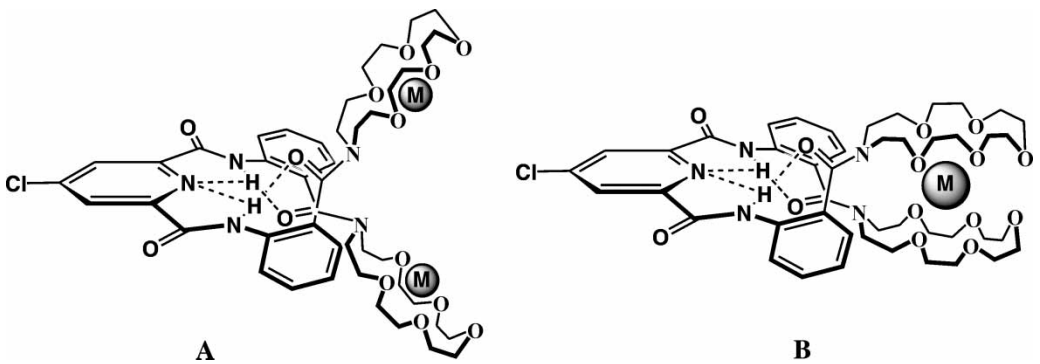

FIGURE 1 Potential binding modes for bis-crown **3**.

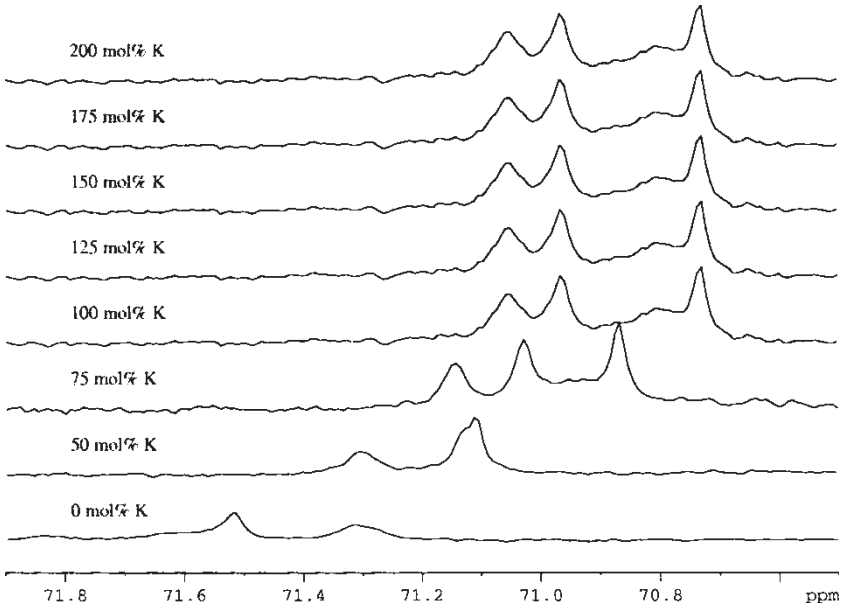

FIGURE 2 ^{13}C NMR spectra of **3** as a function of mol% $KClO_4$ in 95/5 CD_3CN/CD_3OD indicated 1:1 binding.

yielded *N*-[1-oxo-1-(2-nitrophenyl)methyl]aza-18-crown-6, **1**. Initial attempts to reduce the nitro function by hydrogenating over Pd–C were unsuccessful due to catalyst poisoning by the crown moieties. However, reduction with $NaBH_4$-$Cu(OAc)_2$ [20] reproducibly provided amine **2** in near quantitative yields. Subsequent acylation of the 2-aminobenzamide linkage with 4-chloropyridine-2,6-dicarbonylchloride provided ditopic crown receptor **3** in an 85% yield.

Binding Stoichiometry

The metal cation complexing properties of bis-crown **3** were compared with monocrown **2** to ascertain the effect of preorganizing the crown moieties via the pyridine-2,6-dicarboxamide linkage. Since bis-crown **3** can potentially interact with cations via 1:1 complex **A** or an intramolecular 2:1 sandwich complex **B**, the stoichiometry of cation binding was determined by titrating **2** and **3** with alkali metal perchlorates (Li^+, Na^+, K^+, Rb^+, Cs^+) in 95:5 CD_3CN/CD_3OD and monitoring changes in the ^{13}C NMR spectrum in the region corresponding to the carbons of the crown macrocycle [21]. As expected, monocrown **2** bound all cations via 1:1 crown/cation complex **A**. However, these experiments indicated that whereas Li^+ and Na^+ interact with **3** as a 1:1 complex (**A**), K^+, Rb^+ and Cs^+ bind in a 2:1 manner involving both crown moieties as in complex **B**. The stacked plot of the ^{13}C NMR spectra of **3** as a function of the amount of $KClO_4$ is shown in Fig. 2 as a representative example of intramolecular 2:1 complexation.

Binding Constants

The binding constants were measured by solvent extraction of alkali metal picrates from aqueous solutions into chloroform and are plotted as a function of cation in Fig. 3 [22]. Several points are noteworthy. First, the binding selectivity of monocrown **2** and bis-crown **3** displayed opposing trends as a function of cation. For example, monocrown **2** exhibited cation affinity in the order: $Na^+ > Li^+ > K^+ > Rb^+ > Cs^+$, whereas bis-crown **3** demonstrated cation selectivity in approximately the reverse order: $K^+ \cong Rb^+ > Cs^+ > Na^+ > Li^+$. This behavior is consistent with the increased capability of **3** to bind cations with larger ionic radii than the hole size of the crown ring. Second, in contrast to mono- [23] and bis-*N*-alkyl-monoaza-18-C-6 macrocycles [24], which have been reported

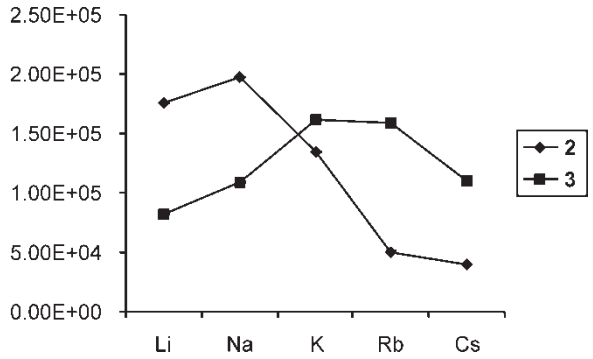

FIGURE 3 Complexation constants for monocrown **2** and bis-crown **3** as a function of cation. Binding constants reflect the average of five independent measurements and are normalized to the binding stoichiometry.

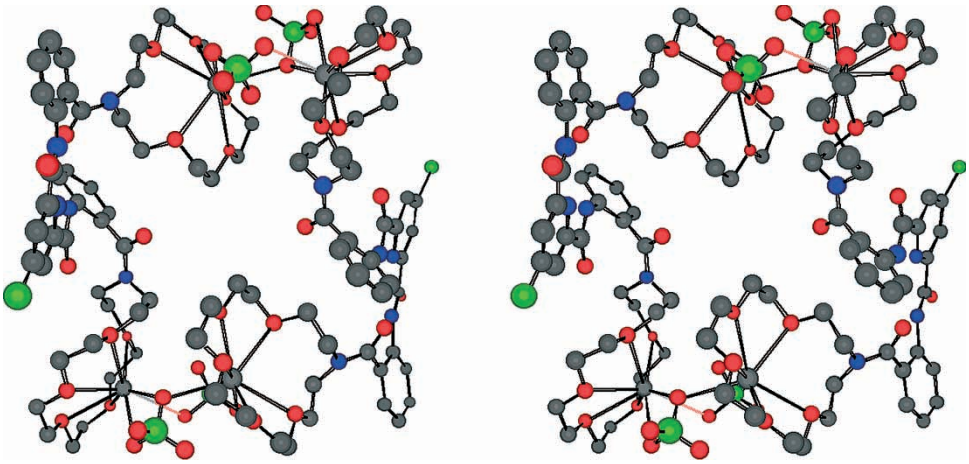

FIGURE 4 Stereodepiction of X-ray crystal structure of **3**·2$KClO_4$. (See colour plate 2 at the end of this issue.)

to exhibit the selectivity $K^+ > Rb^+ > Na^+ > Cs^+ > Li^+$, as would be anticipated based on the match between the cation and ligand cavity diameters, binding of cations by monocrown **2** generally shows an unexpected selectivity for Na^+/Li^+ over K^+. This may be caused by the lack of an interaction between the amide nitrogen of the macrocycle and the cation that is suggested by the crystal structure shown in Fig. 4. Third, bis-crown **3** shows a lower affinity for Li^+ and Na^+ relative to the monocrown **2**. This is likely due to the presence of negative cooperativity relating binding by the adjacent crown ethers that occurs because of charge–charge repulsion that develops upon simultaneous binding to two cations via 1:1 complex **A**. Consequently, the preorganization of the two crown moieties in **3** favors complexation of larger cations via sandwich complex **B**.

Solid-state Structure

A clear, triclinic crystal in space group $P\bar{1}$ was obtained from a solution of **3** and $KClO_4$ (200 mol%) in 95:5 CD_3CN/CH_3OD.[†] In contrast to the 2:1 intramolecular sandwich complex observed in solution by ^{13}C NMR, the solid-state structure indicated a potassium ion bound to each of the two crown macrocycles (Fig. 4). Each potassium ion coordinates to the five oxygen atoms of the crown moieties slightly above the plane of the macrocycle. However, the amide nitrogen atom does not participate in coordination to the potassium cation, presumably due to the reduced basicity of the nitrogen as part of the amide function [24]. The lack of participation by nitrogen may also be the source of the decreased affinity for K^+ in monocrown **2** relative to Na^+ and Li^+ [23]. Further, two molecules of **3**·2$KClO_4$ assembled in the solid state into a molecular square [25] via a dimerization process wherein two perchlorate counterions bridge two K^+ ions contained within crowns on different molecules. Bifurcated coordination of an oxygen atom of a perchlorate counterion to two K^+-crown complexes serves to bridge the two complexes together into the molecular square. The disparity between the solid-state structure and the intramolecular 2:1 sandwich binding in solution most likely derives from the particular crystallinity of the dimerized 1:1 complex. Exposing **3** to 200 mol% $KClO_4$ in 95/5 CD_3CN/CD_3OD for several days did not change the appearance of the ^{13}C NMR spectrum relative to 100 mol% $KClO_4$, indicating that the sandwich complex is stable in solution. Further, repeated attempts to crystallize **3** in the presence of 100 mol% $KClO_4$, $RbClO_4$ or $CsClO_4$ did not lead to crystallization of the corresponding complexes. These observations suggest that the intramolecular 2:1 binding of **3** by $KClO_4$ in solution is not kinetically controlled. Rather, crystallization of the 1:1 complex is responsible for shifting the position of equilibrium towards this binding mode in the solid state.

CONCLUSION

The preorganization of crown macrocycles at the periphery of a folded dendron into an orientation favoring the formation of intramolecular 2:1 sandwich complexes induces cation-binding

[†]Crystallographic information: $C_{45}H_{60}Cl_{11}N_5O_{14}$·2$KClO_4$·$H_2O$, $T = 200(2)$ *K*; $P\bar{1}$, $a = 11.0714$ (1) Å, $b = 15.4689$ (2) Å, $c = 18.0162$ (2) Å. $\alpha = 68.413$ (1)°, $\beta = 77.512$ (1)°, $\gamma = 88.199$ (1)°; $V = 2797.26$ (5) Å^3; $Z = 2$; 9822 unique data; $R1(F) = 0.0516$, $wR2(F^2) = 0.1391$; GOF = 1.051 for $I > 2\sigma(I)$. The CIF file has been deposited with the Cambridge Crystallographic Data Centre and given the reference number CCDC 201180.

selectivities differing significantly from that of the corresponding monomeric congener. The crystal structure of **3**·2$KClO_4$ indicated that incorporating the nitrogen atom of the crown into an amide linkage prevents this atom from participating in recognition of the cation and may be responsible for the decreased selectivity for K^+ in monocrown **2**. Further efforts directed at exploring the binding properties of crown-functionalized, folded dendritic structures at higher generations are currently under way.

EXPERIMENTAL

N-[1-Oxo-1-(2-nitrophenyl)methyl]aza-18-crown-6 (1)

2-Nitrobenzoyl chloride (19.0 g, 102.7 mmol) was added to a solution of aza-18-crown-6 (21.7 g; 82.50 mmol) in a mixture of 2:1 CH_2Cl_2/pyridine (750 mL). After stirring at room temperature for 4 h, the solvent was removed *in vacuo* (~40 mm Hg). The residue was dissolved in CH_2Cl_2 (400 mL) and washed with 1 M H_3PO_4 (400 mL). The 1 M H_3PO_4 solution was back-extracted with CH_2Cl_2 (3 × 200 mL). The volume of the CH_2Cl_2 solution was reduced *in vacuo* to 300 mL and washed with sat. sodium bicarbonate (300 mL). The $NaHCO_3$ solution was then back-extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure (~40 mm Hg), yielding a red oil that was further purified via flash column chromatography (Al_2O_3, 2% MeOH in EtOAc) to give **1** (24.39 g, 59.2 mmol, 72%) as a yellow oil: ^{1}H-NMR (400 MHz, $CDCl_3$), 8.19 (dd, 1H, $J = 0.8$ Hz, 8.3 Hz), 7.68 (td, 1H, $J = 1.1$ Hz, 7.5 Hz), 7.54 (td, 1H, $J = 1.4$ Hz, 7.9 Hz), 7.43 (dd, 1H, $J = 1.3$ Hz, 7.6 Hz), 3.84 (s, 4H), 3.60–3.40 (m, 20H); ^{13}C-NMR (100 MHz, $CDCl_3$), 168.1, 145.0, 134.2, 133.3, 129.5, 128.5, 124.7, 70.7, 70.6, 70.5, 70.4, 70.3, 70.2, 69.2, 68.7 ppm; HRMS for $C_{19}H_{28}N_2O_8Na^+$ (ES) (M + Na). Calcd.: 435.1737. Obsd.: 435.1738.

N-[1-Oxo-1-(2-aminophenyl)methyl]aza-18-crown-6 (2)

$NaBH_4$ (0.90 g; 23.7 mmol) was added in five portions over 10 min to a solution of $Cu(OAc)_2 \cdot H_2O$ (0.13 g; 0.65 mmol) in ethanol (120 mL). *N*-[1-Oxo-1-(2-nitrophenyl)methyl]aza-18-crown-6 (**1**) (2.01 g; 4.9 mmol) was added to the mixture in ethanol (60 mL). After 30 min, an additional portion of $NaBH_4$ (0.30 g, 7.89 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.06 g, 0.30 mmol) was added. After two additional hours, 100 mL of H_2O were added to the mixture, the ethanol was removed under reduced pressure (~40 mm Hg), and the resulting aqueous mixture was extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure yielding **2** (1.85 g; 4.8 mmol; 99%) as a yellow oil: ^{1}H-NMR (400 MHz, $CDCl_3$), 7.13 (m, 2H), 6.71 (m, 2H), 3.70 (bs, 7H), 3.64 (m, 11H), 3.59 (bs, 8H); ^{13}C-NMR (100 MHz, $CDCl_3$), 171.4, 144.2, 130.1, 127.5, 121.7, 117.8, 116.6, 70.7, 70.6, 70.3, 69.3 ppm; HRMS for $C_{19}H_{30}N_2O_6Na^+$ (ES) (M+Na) Calcd.: 405.1996. Obsd.: 405.197.

4-Chloro-2,6-bis[(*N*-aza-18-crown-6)-carbamoylphenyl)carbamoyl]pyridine (3)

To a solution of *N*-[1-oxo-1-(2-aminophenyl)-methyl]aza-18-crown-6 (**2**) (20.10 g; 52.61 mmol) in dry CH_2Cl_2 (450 mL) and pyridine (225 mL) was added 4-chloropyridine-2,6-dicarbonylchloride (6.88 g; 28.90 mmol). After stirring at room temperature for 18 h, the solvent was removed under reduced pressure (~ 40 mm Hg), and residue was dissolved in CH_2Cl_2 (300 mL), washed with 1 M H_3PO_4 (300 mL), sat. sodium bicarbonate (200 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (Al_2O_3, EtOAc) yielding **3** as a pale yellow glass (20.78 g; 22.23 mol; 85%): ^{1}H-NMR (400 MHz, $CDCl_3$), 11.2 (s, 2H), 8.35 (s, 2H), 8.12 (d, 2H, $J = 8.0$ Hz), 7.45 (m, 4H), 7.20 (td, $J = 0.8$ Hz, 7.5 Hz, 2H), 3.63 (m, 30H), 3.56 (bs, 8H), 3.47 (bs, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$), 170.8, 160.5, 150.2, 135.6, 130.2, 128.5, 128.1, 125.1, 124.5, 123.6, 70.9, 70.8, 70.5 ppm; HRMS for $C_{45}H_{60}N_5O_{14}ClNa^+$ (ES) (M + Na) Calcd.: 952.3718; Obsd.: 952.3745.

Acknowledgements

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