An 18-Crown-6 Derivative with Only One Conformation

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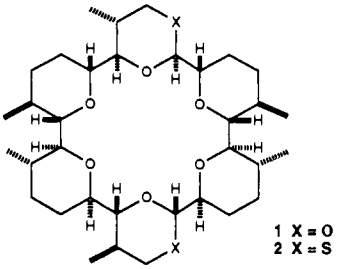
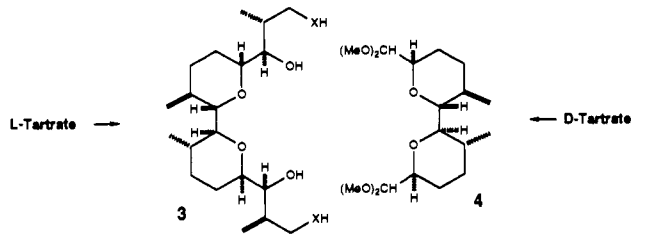
18-crown-6 is a remarkable ionophore.[1] It has a simple structure and yet binds potassium tightly and with ~100-fold selectivity over other alkali metal ions. While it is conformationally preorganized for binding relative to its acyclic analog, it is nevertheless a highly flexible structure with a vast array of distinct low-energy forms.[2] Previous workers have described derivatives[3] with appended rings which reduce flexibility in a limited way, but no derivatives have been reported in which the conformation is really controlled.[4] In this communication, we push 18-crown-6 rigidity to the limit and describe two derivatives (**1** and **2**) which appear to be conformationally homogeneous and



resemble the D_{3d} crystal structure of 18-crown-6·potassium.[5] As we will show, **1** and **2** have novel ion-binding properties which reflect more than just conformational rigidification of a macrocyclic ligand.

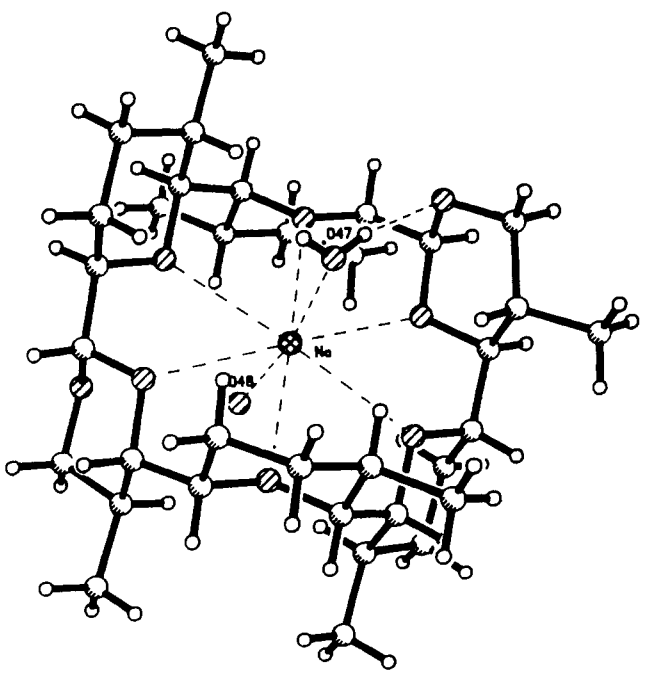
The three-dimensional structures of our new receptors are based on the conformational locking mechanisms we described previously.[6] Thus we use equatorial substitution to favor chairlike six-membered rings and methyl substitution to fix four of the six inter-ring torsional angles. The remaining two unfixed inter-ring bonds (originating from the two acetal centers) are, however, constrained to single conformations by the requirement of macrocyclic ring closure. The stereochemistry chosen enforces a D_{3d} conformation of the 18-crown-6-like core whose best plane is perpendicular to the planes of the surrounding 6-membered rings. There appear to be no low-energy alternatives to this structure as a 1000-step SUMM conformational search[8] using the MacroModel MM2* force field found no other conformer within the first 5 kcal/mol.

The syntheses of **1** and **2** involve macrocyclic acetal formation as shown below. Starting with L- and D-diethyl tartrate, we prepared **3** and **4**, respectively, along lines described previously.[6,7]



In the case of **1**, we treated an equimolar mixture of **3** (X = O), and **4** with BF_3·Et_2O in CH_2Cl_2 (10 mM). The major macrocyclic product (**1**, 40% yield) was diequatorial at the newly formed acetal centers, but diastereomers **1aa** (diaxial, 10%) and **1ae** (axial-equatorial, 15%) were also produced. When **1aa** and **1ae** were treated with *p*-toluenesulfonic acid in $CDCl_3$, they cleanly isomerized to the more stable **1**. Hemithioacetal **2** (40% yield) was prepared by a similar macroacetalization using **3** (X = S) at 7.0 mM concentration, which gave only the diequatorial stereochemistry.

While the ^1H NMR and HRMS of **1** and **2** are fully compatible with the structures proposed, completely unambiguous structures are available only from X-ray crystallography. In the case of **1**, we were able to crystallize its NaSCN complex, and its X-ray structure[9] is shown below. Interestingly, only the 18-crown-6-



like oxygens (not the other acetal oxygens) appear to be involved in ligating the Na^+ which is oriented axially with respect to each chairlike tetrahydropyran ring. Water molecules can be seen to fill the open ends of the cylinder-like ligand and cap the bound Na^+ guest. These waters appear to be hydrogen-bonded to the acetal oxygens not directly associated with Na^+ as indicated for

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(9) We thank Dr. Frank Clark of Ciba Geigy, Summit, NJ, for carrying out the X-ray crystallographic analysis of **1**·NaSCN.

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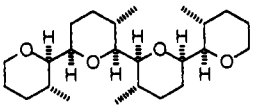
Table I. Alkali Metal Picrate Binding by 18-Crown-6 and Its Derivatives

receptor	Li^+	Na^+	K^+
1(ee)	2.5×10^6	1.9×10^9	4.7×10^8
2(ee)	1.4×10^6	2.5×10^7	9.3×10^7
1ae	6.1×10^4	4.5×10^4	3.2×10^7
1aa	4.9×10^4	4.0×10^4	8.9×10^6
18-crown-6	1.9×10^5	2.3×10^6	2.0×10^8

O47 in the diagram. The macrocyclic ligand is in the same conformation found by the conformational search of unbound **1**.

As expected for analogs of 18-crown-6, standard picrate extraction experiments[10] showed **1** and **2** to be very good hosts for K^+. The results are shown in Table I and are compared with the binding properties of 18-crown-6 and diastereomers of **1**. The reinforced crown ether acetal **1** is particularly ionophoric. Not only does it bind K^+ twice as well as does 18-crown-6, but it binds Na^+ even more tightly than it does K^+. This sodium-selectivity is remarkable considering the fact[11] that Na^+ is ~18 kcal/mol more heavily solvated in water than is K^+, and our binding measurements reflect extraction of the metal ions out of water.

The diastereomers of **1** are significantly less ionophoric than diequatorial **1** itself. According to MM2*, the transannular O–O distance in unbound **1** is ~0.1 Å smaller than in 18-crown-6. Thus the 1000-fold increase in Na^+ binding by **1** over 18-crown-6 is only partially rationalized by its smaller ion-binding site.[12] The second heteroatom in the dioxolane-like rings must play a significant role because hemithioacetal **2** binds Na^+ 100-fold less tightly than does **1**. It may, for example, help to bind the water molecules which cap the bound ion as found in the **1**·NaSCN crystal structure. While the effect of sulfur substitution in ionophores is difficult to predict,[7b] the less ionophoric nature of **2** may reflect the weaker hydrogen-bond-accepting ability of S vs O. Whatever the nature of these secondary heteroatom interactions, the remarkable sodium-binding properties of **1** are not so apparent in other acetal-containing ionophores. Thus, in comparison with podand **5**, podand acetals **6** and **7** are ~2-fold



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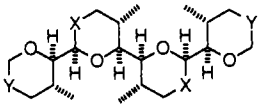

6 X = O, Y = CH_2 **7** X = S, Y = CH_2
8 X = CH_2, Y = O **9** X = CH_2, Y = S

less ionophoric for Na^+ and K^+ while podand acetals **8** and **9** are equally ionophoric with **5** for K^+ and only ~2-fold more ionophoric than **5** for Na^+.[7]

These results demonstrate that adding conformation-restricting networks to 18-crown-6 can have a significant effect on its ion-binding properties. The differences between the properties of **1** and **2** imply that there is more to the effect than simply freezing the 18-crown-6 core in its D_{3d} conformation or slightly diminishing the binding site diameter. The THP-like network itself also significantly influences binding by modifying the microenvironment of the bound ion: thus it buries the ion-binding site with displacement of solvent and may contain functionality which interacts directly or indirectly (e.g., via water) with the bound guest. This study suggests new ways to control ionophoric properties by structural modifications which are remote from the binding site.[13]

Supplementary Material Available: Full experimental procedures and spectral data (6 pages). Ordering information is given on any current masthead page.

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(13) This work was supported by NIH Grant HL25634.