Complexation of Hexosammonium Ions: Evidence for Contributions from OH···OH Hydrogen Bonds in a Hydroxylic Medium

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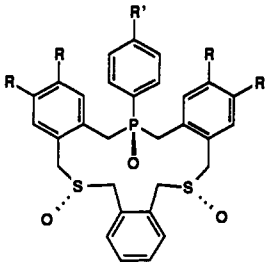
We recently reported that macrocycle **1** is an effective complexing agent for primary ammonium cations in organic solvents.[1] In the solid state, **1** adopts a bowl-shaped conformation in which the P=O and S=O groups appear to be aligned for a three-point hydrogen-bonding interaction with the three ammonium protons (Figure 1). This proposed binding mode, supported by ^{1}H NMR studies of complexation in solution, led us to suspect that a derivative of **1** bearing additional hydrogen-bonding functionality on its periphery might be capable of binding protonated amino sugars via interaction with both ammonium and hydroxyl groups. We now report the verification of this hypothesis and the surprising observation that intermolecular hydroxyl–hydroxyl interactions can contribute to binding affinity in the presence of a hydroxylic cosolvent.



1, R = R' = H
2, R = CH_2OH, R' = H
3, R = CH_2OH, R' = $(CH_2)_3CH_3$

Scheme I shows the preparation of the peripherally functionalized macrocycle **3**; macrocycle **2** was prepared by the analogous route, using commercially available phenylphosphine instead of (*p*-*n*-butylphenyl)phosphine.[2] The positioning of the hydroxymethyl substituents was intended to preclude intramolecular hydrogen bond donation to a sulfoxide or phosphine oxide group. Oxidation to the trioxide level was a crucial step, because four stereoisomeric products (two meso and a *dl*-pair) may result. As previously observed for **1**,[1] the oxidation provided largely one meso isomer of the protected forms of **2** and **3**. The crystal structure of **2** (Figure 1) shows that the predominant meso product in this case was analogous to that observed for **1**; the configuration of **3** was assigned by extrapolation. The solubility of **2** proved to be too low for quantitative solution studies, but the peripheral *n*-butyl group of **3** conferred the required solubility.

Complexation in 10 vol % CD_3OD in $CDCl_3$ was evaluated via ^{1}H NMR spectroscopy. Addition of cyclohexylammonium chloride (**4**) to solutions of either **1** or **3** induced qualitatively similar changes in the macrocycles' spectra, suggesting that the resulting complexes had similar structures. We previously determined the K_a for **1** + **4** to be 1700 M^{-1};[1] the K_a for **3** + **4**, derived as before by monitoring three distinct macrocycle resonances, is 570 M^{-1}.[3] The fact that macrocycle **3** binds **4** 3-fold less strongly than macrocycle **1** suggests that the peripheral substituents of **3** provide a modest hindrance to interaction between the ammonium group and the S=O/P=O/S=O array.

(1) Savage, P. B.; Holmgren, S. K.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 7900.
(2) Synthetic details may be found in the supplementary material.
(3) Each K_a value reported here is the result of two or more determinations, and each determination involved analysis of the movements of two or three distinct macrocycle resonances; the uncertainty of the K_a values is ≤25%.

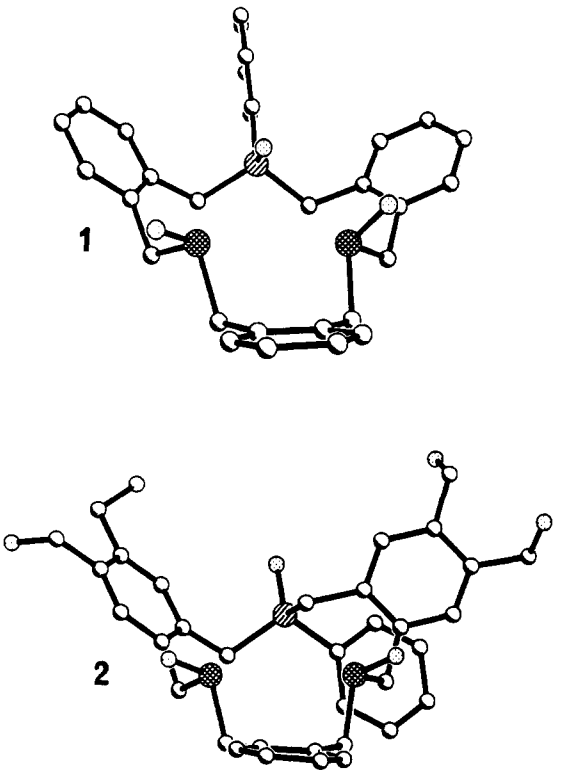
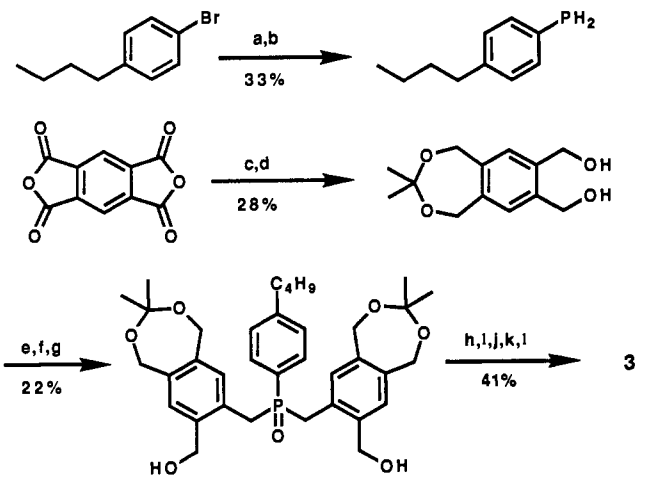


Figure 1. Ball-and-stick representations of macrocycles **1** (ref 1) and **2** in the solid state. Hydrogen atoms have been omitted for clarity. Oxygen atoms are speckled, and sulfur atoms are cross-hatched.

Scheme I[a]



[a] Key: (a) Mg^0, THF; $PCl(OiPr)_2$; (b) $LiAlH_4$. (c) EtOH, H_2SO_4; (d) $LiAlH_4$; $Me_2C(OMe)_2$, *p*-TsOH; $LiAlH_4$; (e) NaH; Me_2-*t*-BuSiCl; (f) $MeSO_2Cl$, Et_3N; (g) (*p*-*n*-Bu-phenyl)phosphine, *n*-BuLi; H_2O_2; *n*-Bu_4NF; (h) $MeSO_2Cl$, Et_3N; (i) LiCl; (j) *o*-$(HSCH_2)_2C_6H_4$, K_2CO_3; (k) mCPBA; (l) CF_3CO_2H.

p-*tert*-Butylbenzyl thioglycoside derivatives **5**–**9**[2] were used to evaluate the binding of hexosammonium ions by **3** in 10 vol % CD_3OD in $CDCl_3$. For each pairing, comlexation was signaled by the same general pattern of changes in the macrocycle's ^{1}H NMR resonances as had been observed for **3** + **4** (Figure 2; the spectra of the fully bound macrocycle differed somewhat from monosaccharide to monosaccharide). ^{1}H NMR titration data obtained with macrocycle **3** indicated K_a values of 3000 M^{-1} for β-glucosammonium derivative **5**, 2800 M^{-1} for α-glucosammonium derivative **6**, 1400 M^{-1} for β-galactosammonium derivative **7**, 1000 M^{-1} for β-mannosammonium derivative **8**, and 2200 M^{-1} for α-mannosammonium derivative **9**.[3] Although the differences

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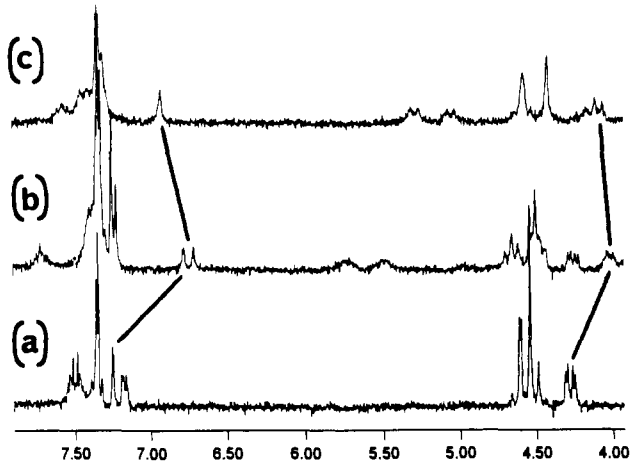
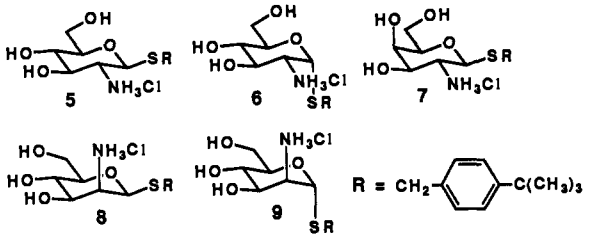


Figure 2. ^{1}H NMR shifts (ppm) induced upon addition of β-glucosammonium derivative **5** and cyclohexylammonium chloride to a solution of **3** in 10 vol % CD_3OD in $CDCl_3$. (a) 2 mM **3**; (b) 2 mM **3** + 6 mM **5**; (c) 2 mM **3** + 6 mM cyclohexylammonium chloride. All resonances from the cations fall outside the spectral window shown. Correlation of those macrocycle resonances used to determine the binding constant is indicated.



among these K_a values are not large, it is clear that in the β-anomer series macrocycle **3** can discriminate between epimers at the 2-position (**5** vs **8**) and, even more interestingly, at the 4-position (**5** vs **7**). The fact that anomers **5** and **6** are not distinguished suggests that the observed discrimination does not result from simple steric effects.[4,5]

β-Glucosammonium derivative **5** was complexed by unadorned macrocycle **1** with a K_a of 810 M^{-1}. The decreased affinity of **1** for **5** relative to cyclohexylammonium implies that some or all of the additional substituents on the six-membered ring of **5** interact unfavorably with the macrocycle in the bound state or that binding of **5** by **1** involves an unfavorable desolvation of the carbohydrate. The fact that the binding preference of macrocycle **1** between cyclohexylammonium and β-glucosammonium is reversed relative to macrocycle **3** suggests that hydroxyl–hydroxyl interactions (presumably hydrogen bonds) between the carbohydrate and the hydroxymethyl groups on **3** stabilize the **3** + **5** complex. This stabilization may result directly from hydrogen bond formation, from the release of methanol molecules that were hydrogen-bonded to **3** and **5** before complex formation, or from a combination of these effects. (CPK models indicate that when the ammonium group of **5** engages in a three-point interaction with the S=O/P=O/S=O array of **3**, the carbohydrate's hydroxyls can easily reach one pair of the macrocycle's hydroxymethyl groups.) Taking into account both the 2-fold favorability of **1** + **4** over **1** + **5** and the 3-fold favorability of **3** + **5** over **3** + **4**, we conclude that the hydroxyl–hydroxyl interactions could stabilize the **3** + **5** bound state by nearly 1 kcal/mol in free energy. This energetic contribution is noteworthy in a solvent that contains 2.5 M CD_3OD.

Carbohydrate complexation by naturally occurring and by artificial receptors is a topic of considerable current interest. The relative contributions of hydrogen bonding, dispersion forces, and the hydrophobic effect to protein–carbohydrate affinity have been the subject of spirited debate.[6] Most synthetic systems reported to date have involved solvents that do not engage in strong hydrogen bonds, media in which carbohydrate–receptor hydrogen bonding is likely to be a dominant source of attraction.[7] In the few reported cases of noncovalent carbohydrate complexation by low molecular weight receptors in water,[8] the hydrophobic effect is expected to be the principal driving force, and it is difficult to evaluate the contribution of polar–polar interactions in these cases. Our results, obtained in a hydroxylic medium in which the hydrophobic effect is inoperative, indicate that interactions between hydroxyls on a carbohydrate and its receptor can stabilize the bound state even when the solvent itself provides competing hydrogen-bonding sites.

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Supplementary Material Available: Full synthetic details for macrocycles **2** and **3** and monosaccharides **5**–**9**, and selected ^{1}H NMR titration data (31 pages). Ordering information is given on any current masthead page.

(4) As previously observed for the binding of simple ammonium ions by macrocycle **1** (ref 1), the affinity of macrocycle **3** for the hexosammonium ions is affected by the nature of the counterion. Thus, K_a for **3** plus the *p-tert*-butylbenzyl thioglycoside of β-glucosammonium hexafluoroantimonate is 12 000 M^{-1}, roughly 4 times larger than that for chloride salt **5**.

(5) The hexosammonium binding order observed for **3** is not observed for simpler macrocycle **1**: β-glucosammonium derivative **5** and β-galactosammonium derivative **7** are bound by **1** with nearly identical strength.

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