Cyclic Hydropyran Oligolides as Preorganized Ligand Arrays: Cumulative Effects of Structural Elements on Shape and Cation Binding

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Substituted hydropyrans are important structural elements in numerous natural ionophores.[1] Synthetic methods developed in our laboratories provide access to hydropyrans varying widely in substitution and stereochemistry.[2] In order to exploit this diversity, a program to design, synthesize, and study cyclic oligolides of hydropyran modules has begun.[3,4] These unnatural ionophores differ in substitution type, relative stereochemistry, or ring size. This paper focuses on the structural features that define the shape and binding efficacy of the 18-membered triolides **1**−**8** (Figure 1).[4]

Preorganization,[5a] binding-site convergence and complementarity,[5b] and cumulative noncovalent interactions[5c] are important in the design of effective host molecules. Several types of local conformational control elements (**A**−**E**, Figure 2) were expected to contribute to the overall shape and degree of rigidity of **1**−**8** (Figure 1) by restricting rotation about every σ-bond of the macrocycle periphery. In **A**, the C1−C2−O3−C6−C7 region is spatially oriented because of the *cis*-2,6-diequatorial hydropyran substitution.[6] The pronounced preference for the syn (*Z*) ester conformation (**B**) confers rigidity about the C1−O2 bonds.[7] Secondary carbinol esters are known to exist preferentially in conformations wherein the carbinyl hydrogen is close to the plane of the ester carbonyl (**C**),[8] in this case restricting O2−C7 rotation. The gauche (or synclinal) preference in vicinal dialkoxyethanes is shown in **D**,[9] suggesting an increment of conformational preference about the C7−C6 bonds. Finally, although less predictable than the preceding effects, it was anticipated that the α-alkoxy ester residue comprising the C1−C2 bonds (**E**) would reflect electronic and/or steric effects in a conformational bias.

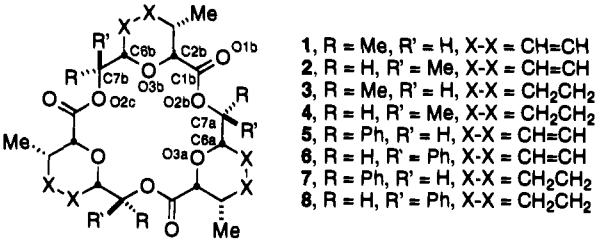

Figure 1.

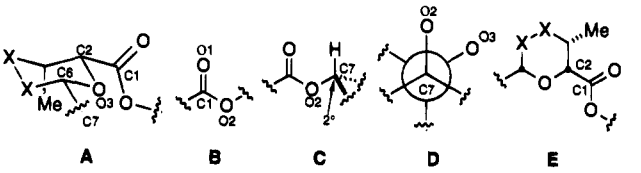

Figure 2.

At issue was whether these various conformational control elements could be manifested in concert. If all incremental preferences could be simultaneously satisfied, a single low-energy conformation of C_3-symmetry could be expected. In contrast to this "harmonious" situation, satisfaction of some conformational preferences at the expense of others (a "discordant" circumstance) was expected to result in a macrocycle of degraded preorganization. Examples of each of these scenarios and related consequences on structure and binding are presented below.

Association constants (K_a) for several of the macrotriolides in Figure 1 and representative cation guests were determined by Cram's picrate extraction method.[10] For comparison, these data and calculated binding free energies are listed in Table 1. Macrocycle **1** has an association constant for K^+ over 2 orders of magnitude higher than its diastereomer **2**. Moreover, **1** exhibits significantly greater selectivity for K^+ over Na^+ ($[\Delta\Delta G]$ = 2.4 kcal/mol) than does **2** ($[\Delta\Delta G]$ = 0.6 kcal/mol). Analogous structure/function relationships are apparent for diastereomeric pairs **5** vs **6** and **7** vs **8**; in each case the superior K^+ ionophore has the same relative stereochemistry as **1**. Of the six atoms in each of **1**, **3**, **5**, and **7** that are involved in K^+ binding (*vide infra*), three (O3a,b,c) are ether oxygens and three (O2a,b,c) are non-carbonyl ester oxygens. Although the ester linkages are synthetically expedient and conformationally defining, they are intrinsically less basic at O2a,b,c than ether oxygens. The consequence of this is illustrated by comparison to the K^+ association constant of dicyclohexano-18-crown-6 (Table 1).[11]

Variable temperature ^1H NMR data for **1** and **2** provide support for the hypothesis that the former is preorganized in a conformation suitable for K^+ binding and the latter is not. Spectra labeled a and a′ in Figure 3 are for macrotriolides **1** and **2**, respectively, in $CDCl_3$ at ambient temperature.[12] These similar spectra both suggest an element of symmetry whereby the three hydropyrans in each macrocycle are magnetically equivalent. Such data can be accommodated by either a single, 3-fold-symmetric solution conformation or an ensemble of equilibrating conformations averaged on the NMR time scale.[13] Lowering the sample temperature of triolide **1** to 0, −25, and −50 °C (spectrum b, Figure 3) affords spectra essentially unchanged from a. These data are consistent with a single C_3-

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Table 1. Comparative Association Constants (K_a, M^{-1}) and Association Free Energies ($-\Delta G°$, kcal·mol^{-1}) of Macrocyclic Hosts for Picrate Salt Guests in $CDCl_3$ Saturated with H_2O at 23–25 °C

macrocyclic hosts	Li^+	Na^+	K^+	$CH_3NH_3^+$
1	$<5.0 \times 10^3$; <5	4.6×10^4; 6.3	2.4×10^6; 8.7	$<5.0 \times 10^3$; <5
2	$<5.0 \times 10^3$; <5	6.6×10^3; 5.2	1.8×10^4; 5.8	$<5.0 \times 10^3$; <5
5	$<5.0 \times 10^3$; <5	$<5.0 \times 10^3$; <5	6.5×10^4; 6.5	$<5.0 \times 10^3$; <5
6	$<5.0 \times 10^3$; <5	$<5.0 \times 10^3$; <5	$<5.0 \times 10^3$; <5	$<5.0 \times 10^3$; <5
7	$<5.0 \times 10^3$; <5	$<5.0 \times 10^3$; <5	1.4×10^4; 5.7	$<5.0 \times 10^3$; <5
8	$<5.0 \times 10^3$; <5	$<5.0 \times 10^3$; <5	$<5.0 \times 10^3$; <5	$<5.0 \times 10^3$; <5
dicyclohexano-18-crown-6[a]			2.0×10^8; 11	

[a] Reference 11.

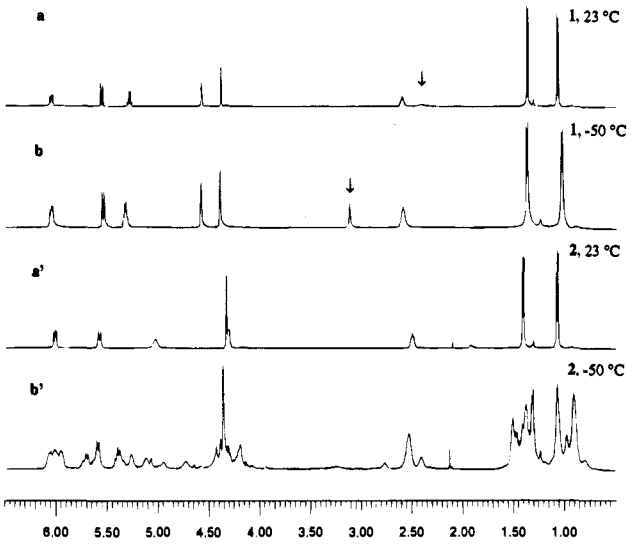

Figure 3. VT ^1H NMR spectra for **1** and **2**. Downward arrow (↓) indicates signal resulting from H_2O.

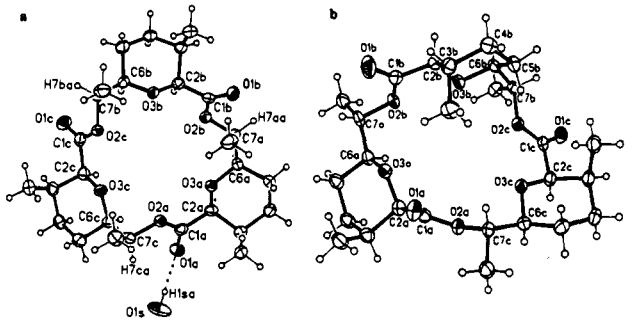

Figure 4. X-ray crystal structures of (a) **3** and (b) **4** showing the atom-labeling scheme.

symmetric, preorganized conformation for **1**. Triolide **2**, however, exhibits a "freezing out" of conformations at 0, −25, and −50 °C (spectrum b′, Figure 3). At room temperature triolide **2** clearly exists as a mixture of several equilibrating conformations of similar energy; i.e., it is not preorganized.

Further support for these conclusions is available from the X-ray crystal structure data depicted for saturated derivatives **3** (Figure 4a) and **4** (Figure 4b), derived from **1** and **2**, respectively.[14] Macrotriolide **3** has pseudo-C_3-symmetry with a well-defined cavity, lined with six oxygens with convergent lone pairs. The associated torsion angles for **3** reveal a harmonious, concerted accommodation of conformational preferences **A**–**D** in Figure 2, plus an antiparallel preference (**E**) for carbonyl and hydropyran C–O dipoles about the three C1–C2 type bonds. Noting that diastereomers **3** and **4** (Figure 1) have inverted relative stereochemistry at the C7a, C7b, and C7c secondary carbinol centers, it is obvious that triolide **4** could not have a conformation similar to **3** and simultaneously satisfy preferences **A**–**E**. The solid state conformation adopted by **4** (Figure 4b) is folded and dissymmetric, with an ill-defined cavity. Although conformational preferences **A**, **B**, and **D** are accommodated, preference **E** is compromised. Preference **C**, involving the C7–O2 type σ-bond, turns out to be a powerful structural determinant. Thus, most of the conformational distortion in **4** is to allow the C7a, C7b, and C7c C–H bonds to be nearly synperiplanar with the proximal ester carbonyl,[8] similar to the orientations in diastereomer **3**. Two obvious consequences of this are seen in the atypical conformation about the C1a–C2a bond in **4** (Figure 4b) and in the twisting of one hydropyran out of the macrocycle mean plane. The analogous mandelate-derived macrotriolide diastereomers **5** and **6** have solid-state conformations nearly identical to **3** and **4**, respectively.[14,15]

An X-ray crystal structure for the complex between host **3** and K^+SCN^- has also been obtained.[14,15] The pyran oxygen (O3a,b,c) and carbinol ester oxygen (O2a,b,c) to K^+ distances are all close to the sum of the van der Waals radii of oxygen (1.40 Å) and K^+ (1.38 Å).[16] Comparison of the solid-state conformations of host **3** and the **3**·K^+ complex reveals a nearly perfect overlap of the macrocycles in the free and complexed states.[17] This further supports the contention that **3** and **1** are preorganized in conformations suitable for binding by summation of the preferences outlined in Figure 2.

It is clear that cumulative conformational preferences can define structure and affect properties in these modular cyclic oligolides. Computational molecular modeling renders the control elements in Figure 2 predictive of macrocycle conformation.[18] Pendant substituent groups at C7a,b,c in **1**, **3**, **5**, and **7** are oriented normal to the macrocycle mean plane, suggesting applications to ion channel mimics.[19] Design, synthesis, and study of new systems based upon the observations above are under way.[20]

Supporting Information Available: Details of the determination of association constants and a depiction of the crystal structures for **3** and **3**·K^+ complex superimposed (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(14) We thank Dr. Douglas R. Powell of the UW–Madison Chemistry Instrumentation Center for these X-ray crystallographic analyses.

(15) Details of these X-ray crystallographic analyses and observed formation of clathrate and coordination polymer structures will be described separately.

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(17) A depiction of these crystal structures superimposed is included in the supporting information.

(18) Molecular modeling using the MM2 or Tripos force fields (MacroModel and Sybyl, respectively) yields minimized structures for **3** and **5** nearly identical to those observed by X-ray crystallography.

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