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Lithium Ion-Selective Binding Properties of a Conformationally Constrained Tris(spirotetrahydrofuran) Secured to an Inositol Orthoformate Platform

Jinsung Tae, Robin D. Rogers,† and Leo A. Paquette*

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210, and the Department of Chemistry, The University of Alabama, Tuscaloosa, Alabama 35487

paquette.1@osu.edu

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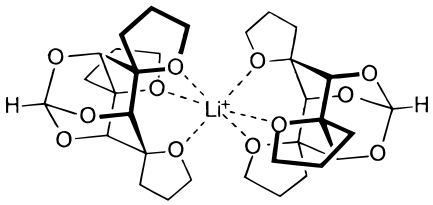
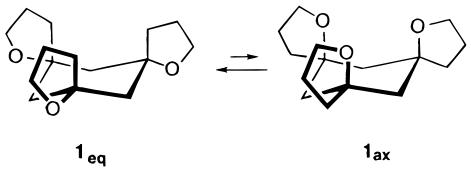
ABSTRACT



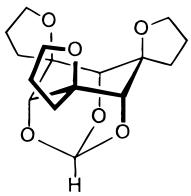
The C_{3v}-symmetric triaxially locked trispirotetrahydrofuran 2 binds Li^+ ions strongly and Na^+ ions much less effectively. The observed discrimination factor is attributed to greater structural preorganiztion and lower solvation prior to selective complexation, and particularly to the formation of a 2:1 sandwich complex involving lithium. ^{13}C NMR studies have defined a reluctance to form a 1:1 species when excess Li^+ is present.

Despite the fact that the all-cis trispirocyclic ether **1** prefers the **1eq** spatial arrangement having its three C−O bonds projected equatorially, the **1ax** conformation can be readily populated and is capable of binding Li^+ and Na^+ ions without difficulty.[1] The ($K_a(Li^+)/K_a(Na^+)$)selectivity ratio of 32 exhibited by **1** is much better than that exhibited by [12]-crown-4 (1.0), but not sufficiently elevated to function as the ligand in a lithium ion selective electrode.[2] The latter have been developed to monitor Li^+ levels in the blood of patients being administered doses of lithium carbonate for the control of manic depressive behavior.[3]

In contrast, ionophore **2** is a significantly more rigid, highly preorganized structure that can presumably enter into binding without wholesale conformational change. The trioxaadamantane scaffold upon which the three spirotetrahydrofuran rings reside can be expected to constrain and reduce somewhat the available cavity flexibility relative to **1**. We have sought to prepare **2** and are now pleased to report on its capacity for binding Li^+ cations in a selective manner.



1_{eq} 1_{ax}



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† Author to whom queries regarding the crystallographic studies should be directed at The University of Alabama.

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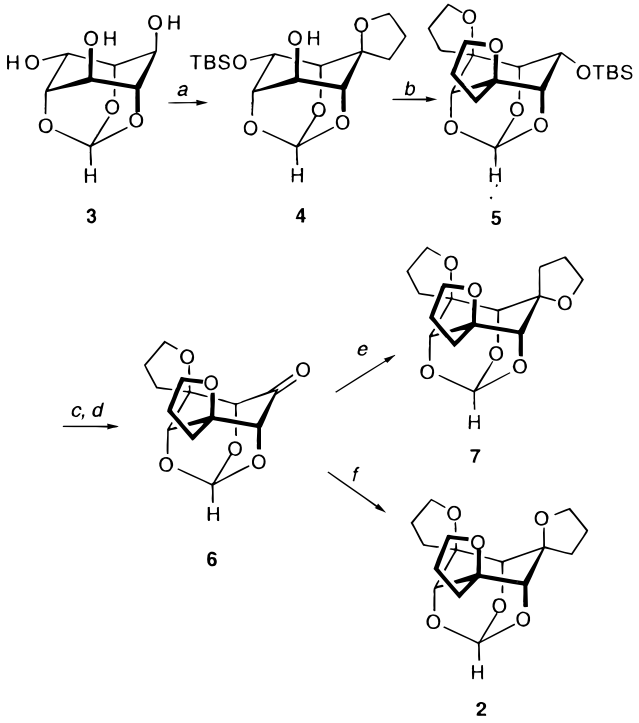
The synthesis of **2** originates from the known *myo*-inositol orthoformate **3**.[4] Since the obvious oxidation of **3** to the triketone in a single operation proved not to be feasible, a stepwise oxidation and capping sequence[5] was adopted (Scheme 1). By means of a sequence of steps that involved

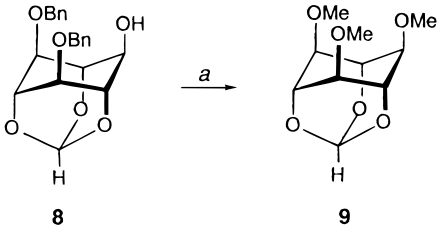
Scheme 1. Synthesis of the *syn*,*syn*-Trispiro Ligand **2**



[a] Reference 7. [b] Dess−Martin periodinane, CH_2Cl_2; $ClMg(CH_2)_3OMgCl$, THF; TsCl, Et_3N (87% over three steps). [c] TBAF, THF, 20 °C (100%). [d] $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N (97%). [e] $ClMg(CH_2)_3OMgCl$, THF; TsCl, Et_3N (45%). [f] $LiClO_4$, THF, rt, 2 h; $ClMg(CH_2)_3OMgCl$, THF; TsCl, Et_3N, CH_2Cl_2; $KN(SiMe_3)_2$, C_6H_6, rt (73% over three steps).

regioselective silylation of the equatorial hydroxyl in **3**, monobenzylation, oxidation to the monoketone, and installation of the first spiroheterocyclic subunit by means of the Normant reagent,[6] convenient access was gained to **4**.[7] Advancement to the C_s-symmetric dispiro intermediate **5** was based reliably on sequential oxidation of **4** to the cyclohexanone and nucleophilic addition to its carbonyl group from the sterically unencumbered exo surface. On subsequent arrival at **6**, we found it striking that the same capping sequence in this instance led very predominantly to **7**. Only when **6** was pretreated with 5 equiv of lithium perchlorate could chelation to the incoming Grignard reagent be totally impeded and nucleophilic attack relegated entirely to the equatorial π-surface.[8] The C_{3v} nature of **2** is very apparent from its six-line ^{13}C NMR spectrum.

Scheme 2. Synthesis of the Trimethoxy Derivative **9**



[a] NaH, MeI, THF; H_2, 10% Pd/C, C_2H_5OH, 1 atm; NaH, MeI, THF (76% over three steps).

For comparison purposes, the trimethoxy derivative **9** was prepared from the known compound **8**[4] in three steps (Scheme 2). While an X-ray crystal analysis of **9** (Figure 1) was achieved without complication, a similar structural view of **2** was not realized despite its tendency to crystallize well. Fortunately, an analogue of **2** subsequently yielded to a comparative solid-state analysis.[9]

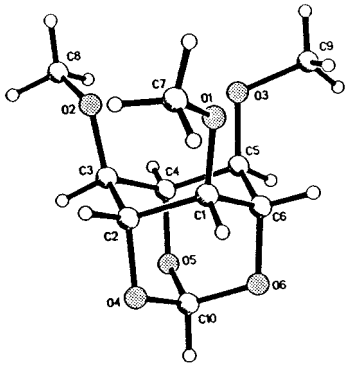


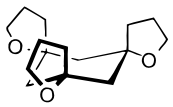
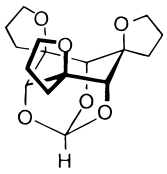
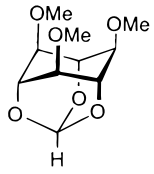
Figure 1. Perspective plot of **9** in the solid state.

The association constants (K_a) for the complexation of **1**, **2**, and **9** to Li^+, Na^+, and K^+, determined as usual in H_2O/$CDCl_3$,[10] are compiled in Table 1. To allow proper comparison, all binding constants have been calculated for 1:1 complexation. Such measurements are recognized to provide *relative* numerical data only, particularly when the stoichiometry of the complexation of **2** under these experimental conditions is not known with certainty. While assumptions have therefore necessarily been made, the triaxial trispiro host ionophore **2** is seen to show very similar overall binding capability for Li^+ but appreciably reduced ligation capacity for Na^+ ion compared to **1**. The consequence of these changes is the very significant improvement in selective ligation capability ($K_a(Li^+)/K_a(Na^+) = 440$) exhibited by **2**. In contrast, **9** does not extract any picrate salt whatsoever, thereby providing telling indication that the arrangement of three *syn*-methoxy groups is not conducive to binding, even of the small Li^+ ion.

(4) Lee, H. W.; Kishi, Y. *J. Org. Chem.* **1985**, *50*, 4402.
(5) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3947.
(6) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, 3013.
(7) Tae, J. Ph.D. Dissertation, The Ohio State University, 1999.
(8) Paquette, L. A.; Tae, J. *Tetrahedron Lett.* **1999**, *40*, 5971.
(9) Paquette, L. A.; Tae, J.; Gallucci, J. C. *Org. Lett.* **2000**, *2*, 143.
(10) Cram, D. J.; Lein, G. M. *J. Am. Chem. Soc.* **1985**, *107*, 3657.

Table 1. Association Constants (K_a, M^{-1}) Determined by Picrate Extraction into Chloroform at 20 °C[a]

$[M^+]_{aq} + [Pic^-]_{aq} + [host]_{org} \rightleftharpoons [M^+Pic^- host]_{org}$ (K_a)

	Li^+	Na^+	K^+
12-crown-4	9.8×10^4	1.1×10^5	8.7×10^4 [b]
 **1**	7.9×10^7 $K_a(Li^+)/K_a(Na^+) = 32$ $K_a(Na^+)/K_a(K^+) = 76$ $K_a(Li^+)/K_a(K^+) = 2400$	2.5×10^6	3.3×10^4
 **2**	1.1×10^7 $K_a(Li^+)/K_a(Na^+) = 440$ $K_a(Na^+)/K_a(K^+) = 4.9$ $K_a(Li^+)/K_a(K^+) = 2157$	2.5×10^4	5.1×10^3
 **9**	no extraction	no extraction	no extraction

[a] The method utilized was developed by Koenig et al.: Koenig, K. E.; Lein, G. M.; Struckler, P.; Kaneda, T.; Cram, D. *J. Am. Chem. Soc.* **1979**, *101*, 3553. [b] We thank Dr. J. T. Negri for this measurement.

Although the K_a values for **2** must necessarily be regarded as approximate, the dramatic difference in the responses of **2** and **9** points out the sensitive relationship between the reduction in binding free energy and the constraints placed on the orbitals of the unshared electron pairs associated with the triad of oxygens. Steric effects are held responsible for the latter phenomenon. Thus, the relevant distances between the oxygen atoms in ionophore **9** are O1−O2 = 2.961(4), O2−O3 = 2.885(4), and O3−O1 = 2.910(4) Å. In contrast, there is only one unique distance exhibited by a trispirotetrahydrofuran related to **2** because of the existence of a 3-fold rotation axis through the molecule.[9] At 2.830(1) Å, this distance is shorter than all three resident in **9**. During coordination to Li^+, the three oxygens must each orient one of their lone electron pairs toward the central core, a rotational process more easily accomplished without steric disadvantages by tetrahydrofuran subunits.

In a solvent system consisting of 1:1 $CH_3CN/CDCl_3$, the conformationally fixed host **2** forms the 2:1 sandwich complex **10** (ORTEP diagram, Figure 2) upon addition of 0.5 equiv of $LiClO_4$ more readily than does **1**. In contrast, a further aliquot of this salt did not transform the 2:1 complex into the 1:1 complex **11**. Only slight line broadening and minor chemical shift changes were observed by ^{13}C NMR spectroscopy (Figure 3).[11] These effects, which begin to materialize above 0.5 equiv of added $LiClO_4$, likely result

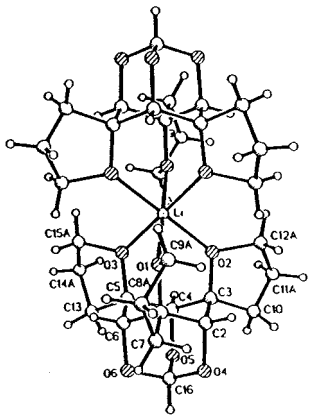


Figure 2. Perspective plot of **10** in the solid state.

from the onset of Li^+ coordination to one or more of the orthoester oxygen centers.

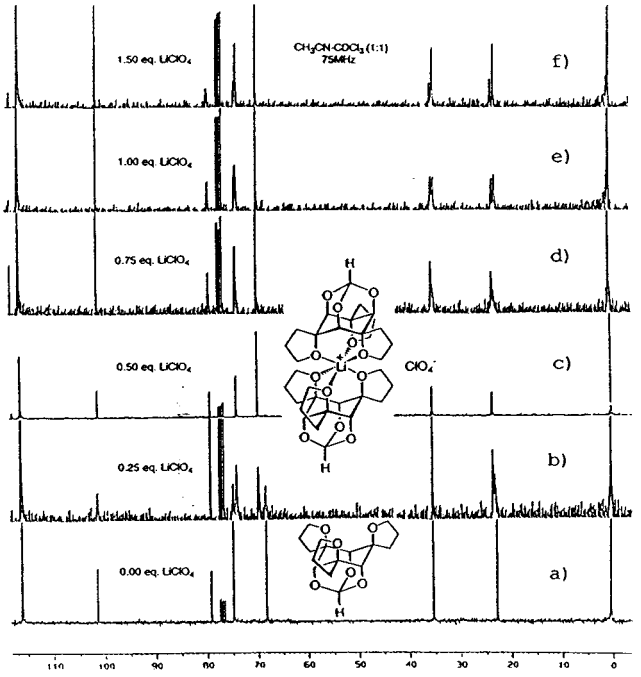
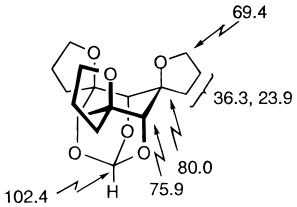
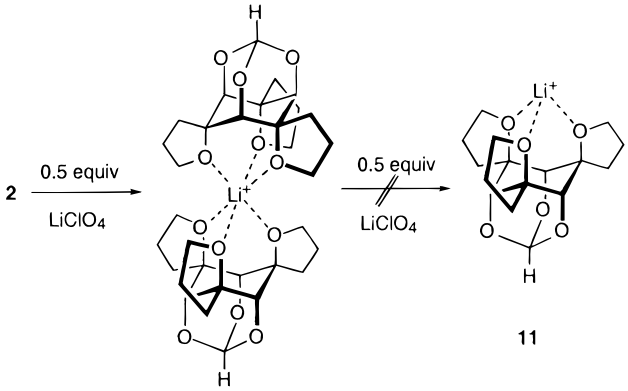


Figure 3. ^{13}C NMR spectra (75 MHz) for the incremental titration of **2** with $LiClO_4$ in $CH_3CN/CDCl_3$ (1/1). Equivalents of $LiClO_4$ added: (a) 0.00; (b) 0.25; (c) 0.50; (d) 0.75; (e) 1.00; (f) 1.50.

As is shown in the companion paper,[9] the facility with which **2** forms the 2:1 complex **10** with Li^+ foreshadows

(11) Pertinent chemical shifts are as shown:





the highly desirable capacity of "dimers" derived therefrom to utilize their two exotopic binding sites for unprecedented polymer formation. It is clear from the behavior of **2** and **9** that spirotetrahydrofuran binding sites are particularly conducive to strong coordination and hold great advantage over simple methoxyl groups.

Acknowledgment. This work was financially supported by the Paquette Research Fund.

Supporting Information Available: Full characterization data for the late-stage products in Scheme 1 and X-ray crystallographic data for **9** and **10**. This information is available free of charge via the Internet at http://pubs.acs.org.

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