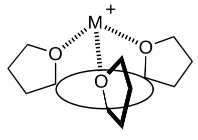
A Belted Monofacial Ionophore Featuring High Selectivity for Lithium Ion Complexation**

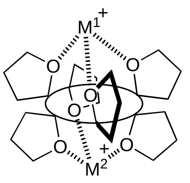
Leo A. Paquette,* Jinsung Tae, Eugene R. Hickey, and Robin D. Rogers

The search for new ligands capable of exhibiting selectivity for binding to specific metal ions continues to grow at an unabated pace.[1, 2] The observed variations in complex stability have been rationalized principally in terms of the shape, cavity size, and conformational flexibility characteristics of a given macrocyclic ether.[3] In select cases, interaction energies have been computed by molecular mechanics[4] and molecular dynamics methods.[5] Despite this, quantitative means for predicting the relationship of binding stability to the three-dimensional characteristics of a crown ether have only recently been reported.[6]

Several years ago, we suggested that the enhanced binding efficiency of tetrahydrofurans might be very suitably exploited by proper assimilation of these building blocks into belted spirocyclic networks.[7] With level of substitution, locus of the oxygen atoms, and relative stereochemistry serving as the relevant principles of rational design, it was anticipated that heightened levels of structural preorganization could be achieved with resultant enhancement of selective metal ion binding. Moreover, such novel structures offer the unique potential of being specifically tailored to serve as monofacial (as in **A**)[8] or bifacial ionophores (see **B**).[9] The latter compound class offers the added attractive option of incorporating two different metal ions (because of a cavity size dependency relating the two faces) and of elaborating ladder polymers of alternating ligand and M$^+$ components. We now report the synthesis and crystallographic characterization of *cis,cis*-1,8,14-trioxatrispiro[4.1.4.1]octadecane (**9**), define the extraordinary selectivity of its binding to alkali metal ions, and quantify computationally the structural requirements of each metal ion–donor interaction.

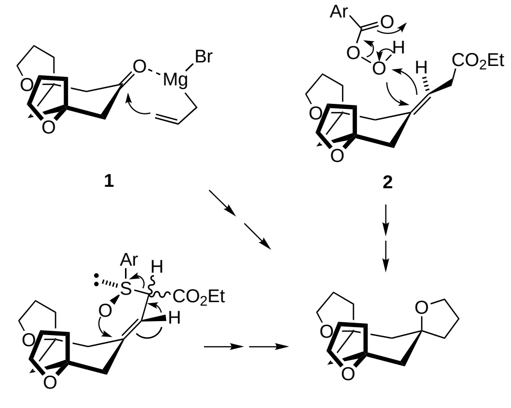


A

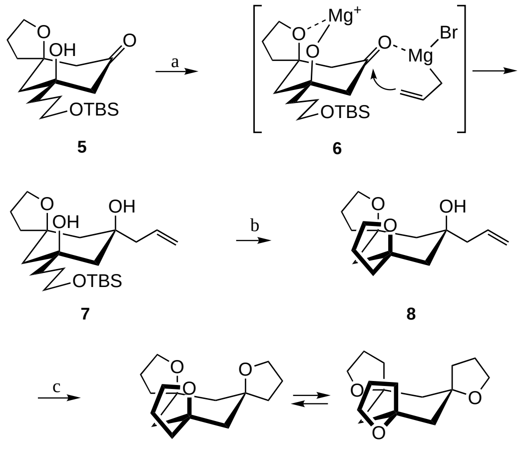


B

With the discovery that *cis*-dispirocyclohexanone **1**[10] undergoes nucleophilic attack exclusively from the equatorial direction, and that its *exo*-methylene derivatives **2** and **3** react cleanly from the opposite π surface (Scheme 1), came the realization that the formation of *cis,trans* trispiro product **4** had to be skirted by making recourse to a superior stereocontrol element. The silyl-protected 3-hydroxypropyl substituent in **5** proved well suited to this task. As expected, the bulkiness of this side chain guaranteed its equatorial occupancy and opened the way to rapid deprotonation with formation of chelate **6** upon treatment with Grignard reagents such as allylmagnesium bromide (see **6**, Scheme 2). The C–O bonds, which are oriented axially in **6**, provide adequate steric shielding to deter syn approach to the carbonyl group. As a consequence, the triad array of oxygen atoms resident in **7** is fixed in an all-*syn* relationship. The C_{3v} symmetry of **9** (m.p. 111–113 °C) is quite apparent spectroscopically (five ^{13}C signals; see Table 1). The crystal structure (Figure 1)



Scheme 1. π-Facial stereoselectivity of attack on *cis*-dispirocyclohexanone **1** and its *exo*-methylene congeners **2** and **3**.



Scheme 2. Synthesis of the *syn,syn* trispiro ligand **9**: a) allylmagnesium bromide, Et_2O/THF (1/1), 20 °C, 15 h, 77%; b) TBAF, THF, 20 °C, 4 h; TsCl, Et_3N, DMAP, CH_2Cl_2, 20 °C, 12 h (88% over 2 steps); c) BH_3, THF, 0 °C, 1 h; TsCl, Et_3N, DMAP, CH_2Cl_2, 20 °C for 6 h, then reflux for 15 h (81% over 2 steps). TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TsCl = *p*-toluenesulfonyl chloride, DMAP = dimethylaminopyridine.

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Table 1. Selected spectroscopic data for compounds **4**, **9**, and **10**.[a]

4: IR (film): $\tilde{\nu}$ = 1448, 1349, 1177, 1047 cm^{-1}; ^{1}H NMR (C_6D_6): δ = 3.75–3.60 (m, 4H), 3.60–3.48 (m, 2H), 2.15–1.95 (m, 3H), 1.75–1.40 (series of m, 15H); ^{13}C NMR (C_6D_6): δ = 82.9, 82.5, 66.7, 65.9, 48.0, 45.9, 38.9, 36.7, 26.4, 25.2; HR-MS: *m/z* calcd: 252.1725 [M^+]; found: 252.1730.

9: IR (film): $\tilde{\nu}$ = 1454, 1222, 1044 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 3.80 (t, J = 6.9 Hz, 6H), 1.95–1.80 (m, 9H), 1.70–1.65 (m, 6H), 1.57 (d, J = 13.6 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 81.5, 66.0, 45.5, 37.5, 25.3; HR-MS: *m/z* calcd: 252.1725 [M^+]; found: 252.1712.

10: ^{1}H NMR ($CDCl_3$): δ = 3.76 (t, J = 6.2 Hz, 6H), 1.95–1.70 (m, 15H), 1.55 (d, J = 14.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 81.6, 68.1, 45.3, 39.7, 25.0; positive-ion FAB-MS: *m/z* (%) calcd for **9** · Li^+: 259; found: 259.15 (100), *m/z* (%) calcd for (**9**)$_2Li^+$: 511; found: 511.42 (13.5).

[a] NMR spectra recorded at 300 (^{1}H) and 75 MHz (^{13}C). Correct elemental analyses were obtained for all compounds.

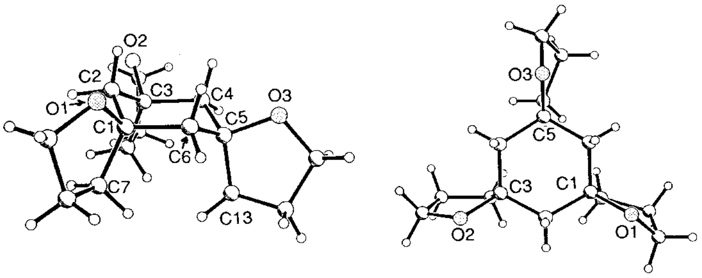
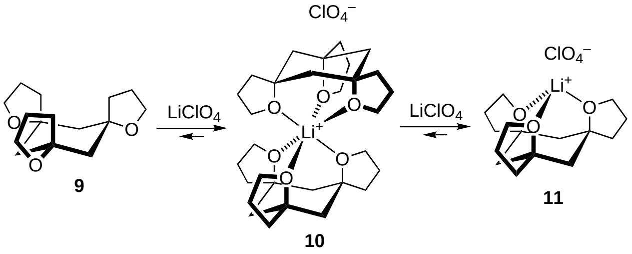


Figure 1. Side (left) and top views (right) of the molecular structure of **9** in the solid state. Selected bond lengths [Å] and angles [°]: O1–C1 1.465(4), O2–C3 1.459(4), O3–C5 1.453(4), C1–C6 1.520(5), C1–C2 1.527(4), C2–C3 1.522(4), C3–C4 1.514(4), C4–C5 1.534(5), C5–C6 1.527(4); C1-C2-C3 114.4(3), C2-C3-C4 109.7(3), C3-C4-C5 116.1(3), C4-C5-C6 109.7(3), C5-C6-C1 116.6(3), C6-C1-C2 110.3(2).

shows that the conformation with all oxygen atoms in equatorial positions is adopted in the solid state.[11] This is rather remarkable in that MM3-based molecular mechanics (MacroModel 5.0) indicates **9-eq** to be 3.93 kcal mol^{-1} less stable than **9-ax**. Although intermolecular stacking interactions may be held responsible here, this conformational preference appears to persist as well in solution (see below), a likely consequence of more favorable dipole–dipole interactions.

The association constants (K_a) for the complexation of **9** to Li^+, Na^+, and K^+ picrates were determined in $H_2O/CDCl_3$.[12] These data reveal **9** to exhibit high selectivity for the lithium ion ($K_a(Li^+)/K_a(Na^+) = 7.9 \times 10^7/2.5 \times 10^6 = 32$, $K_a(Li^+)/K_a(K^+) = 7.9 \times 10^7/3.3 \times 10^4 = 2400$) in a manner comparable to the behavior of highly preorganized spherands[13] and smaller cryptands.[14] The corresponding values for [15]crown-5 are $K_a(Li^+)/K_a(Na^+) = 0.94 \times 10^5/6.3 \times 10^6 = 0.015$ and $K_a(Li^+)/K_a(K^+) = 0.94 \times 10^5/1.1 \times 10^6 = 0.085$. Although the consequences of belting as in **9** are clearly quite special, there exists a strict requirement that placement of the three heteroatoms be precisely defined. This point is reflected in the inability of **4** to extract any of the picrate salts at measurable levels.

The independent preparation of 2:1 sandwich complexes of **9** to $LiBF_4$ and $NaBF_4$ provided compounds of type **10** (see Scheme 3), for which crystals amenable to X-ray analysis were obtained.[15] The major difference in the two structures is the increased distance of Na^+ (1.554 Å) relative to Li^+ (1.279 Å) above the plane defined by the three oxygen centers. Molecular mechanics calculations[16] indicate the level of distortion experienced by **9** in accommodating Na^+ to be approximately 3.4 kcal mol^{-1} more than for Li^+. Upon going from Na^+ to K^+, the energy increment rises by an additional 11 kcal mol^{-1}. Consequently, the concordance with size–match selectivity is excellent. ^{13}C NMR titration experiments involving **9** and $LiClO_4$ in CH_3CN/C_6D_6 (4/1) clearly defined the generation of the 2:1 complex **10** (up to 0.50 equiv of salt). The latter is cleanly transformed into the 1:1 complex **11** as this amount of additive is exceeded (Scheme 3, Figure 2). The replacement of the set of signals due to **10** by those attributable to **11** is very clearly demarcated, thereby requiring slow exchange between the free ligand, **10**, and **11** under the conditions of measurement. The differences in the chemical shifts observed for the three species suggest that a conformational change is likely occurring upon metal ion complexation.[16] If so, the present data suggest that the **9-ax** ⇌ **9-eq** equilibrium is defined by a barrier high enough to show a single conformation (**9-eq**) on the NMR time scale, but of sufficiently low energy to allow for facile complexation to the smaller alkali metal ions via **9-ax**.



Scheme 3. Formation of **10** upon addition of 0.5 equivalents of $LiClO_4$ to **9**, and its transformation to **11** upon addition of 1.00 equivalent of $LiClO_4$.

Significantly, the readiness with which **9** forms 2:1 complexes such as **10** with Li^+ and Na^+ may well foreshadow the highly desirable capacity of its bifacial homologues to engage in unprecedented ladder complex formation. It is clear from the behavior of **9** that the presence of a belt provides positive inducement for selective ion complexation, most notably when the stereochemical and spatial arrangements satisfy those structural requirements conducive to strong coordination.

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[1] The Sci-Finder program of the Chemical Abstracts Service currently (September 20, 1998) lists 38709 references to papers that contain the word "ionophore", 12215 reference citations for "crown ether", and 1778 references to papers dealing with "cryptands". Specific attention is called to studies involving the conformational control of cation binding by the research groups of W. C. Still (tetrahydropyrans; M. T. Burger, A. Armstrong, G. Guarneri, D. Q. McDonald, W. C. Still *J. Am. Chem. Soc.* **1994**, *116*, 3593) and U. Koert (tetrahydrofurans; U. Koert, M. Stein, H. Wagner, *Chem. Eur. J.* **1997**, *3*, 1170).

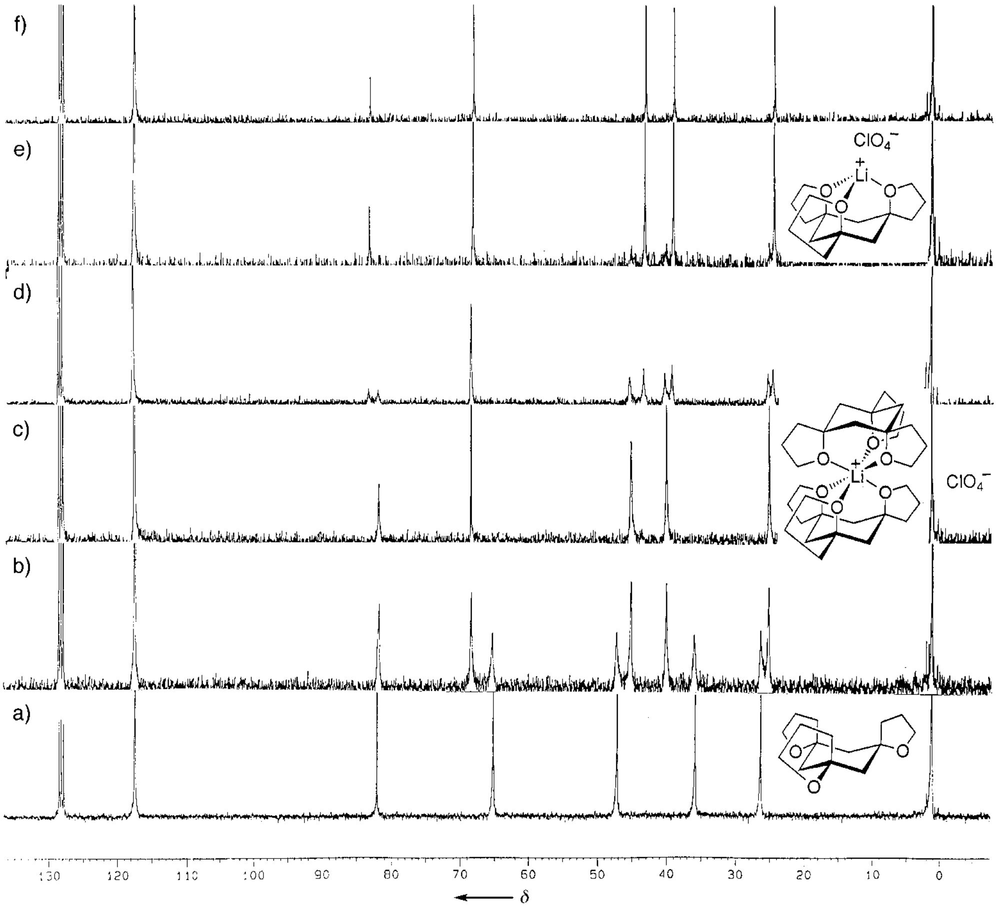

Figure 2. ^{13}C NMR spectra (75 MHz) for the incremental titration of **9** with $LiClO_4$ in CH_3CN/C_6D_6 (4/1). Equivalents of $LiClO_4$ added: a) 0.00, b) 0.25, c) 0.50, d) 0.75, e) 1.00, f) 1.50.

[2] Reviews: a) G. Gokel, *Crown Ethers and Cryptands*, The Royal Society of Chemistry, Cambridge, UK, **1991**; b) *Crown Compounds: Toward Future Applications* (Ed.: S. R. Cooper), VCH, New York, **1992**; c) F. Vögtle, *Supramolecular Chemistry*, Wiley, Chichester, **1991**; d) Y. Inoue, G. W. Gokel, *Cation Binding by Macrocycles*, Marcel Dekker, New York, **1990**; e) *Polyether Antibiotics, Vols. I and II* (Ed.: W. J. Westlay), Marcel Dekker, New York, **1983**; f) M. Dobler, *Ionophores and Their Structures*, Wiley, New York, **1981**; g) R. M. Izatt, J. J. Christensen, *Synthetic Multidentate Macrocyclic Compounds*, Academic Press, New York, **1978**; h) L. F. Lindoy, *The Chemistry of Macrocyclic Ligand Complexes*, Cambridge University Press, Cambridge, UK **1989**.

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[8] The presence of three *syn* axial oxygen centers on a six-membered ring is quite uncommon. This arrangement is not present in sugars and has been evaluated only in *cis*-inositol (S. J. Angyal, R. J. Hickman, *Aust. J. Chem.* **1975**, *28*, 1279), muellitol (S. J. Angyal, D. Greeves, L. Littlemore, *Aust. J. Chem.* **1975**, *38*, 1561), and 2-deoxy-2-methyl-*epi*-inositol (S. J. Angyal, D. Greeves, V. A. Pickles, *Carbohydr. Res.* **1974**, *35*, 165).

[9] Bifacial ionophores are virtually unknown; see a) W. Y. Lee, C. H. Park, *J. Org. Chem.* **1993**, *58*, 7149; b) L. A. Paquette, J. Tae, B. M. Branan, S. W. E. Eisenberg, J. E. Hofferberth, *Angew. Chem.* **1999**, *111*, 1505; *Angew. Chem. Int. Ed.* **1999**, *38*, 1412.

[10] This intermediate was prepared by sequential Birch reduction and lithium aluminum hydride reduction of 3,5-dimethoxybenzoic acid followed by O-benzylation, treatment with a catalytic quantity of sulfuric acid in isobutanol, coupling to the Normant reagent ($ClMg(CH_2)_3$-$OMgCl$), hydrolysis with TsOH (4-methylbenzenesulfonic acid) in CH_2Cl_2, more advanced capping with the Normant reagent, and chromatographic separation of the diastereomers.

[11] Crystal data for **9**: $C_{15}H_{24}O_3$, $M_r = 252.34$, monoclinic, space group $P2_1/n$, $a = 5.9063(6)$, $b = 16.716(2)$, $c = 13.8555(14)$ Å, $\beta = 96.378(2)°$, $V = 1359.5(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.233$ Mg m^{-3}, $F(000) = 552$, $\mu(Mo_{K\alpha}) = 0.084$ mm^{-1}, $T = 173(2)$ K. A total of 8504 reflections were collected of which 3517 were unique ($R(int) = 0.056$) and 1623 were observed $[I > 2\sigma(I)]$. The refinement converged to $R1 = 0.092$, $wR2 = 0.214$, and $S = 1.045$. Crystallographic data (excluding structure factors) for this structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-111932. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[15] In the case of $(\mathbf{9})_2 \cdot NaBF_4$, a CH_2Cl_2 solvate was examined.

[16] These computations involved the Macintosh-based CHEM-3D PLUS software package, which was found to properly orient the lone pairs in both the free ligand (filled orbitals approximately coplanar with the cyclohexane C–C bonds) and the complexes (one pair from each oxygen centrally oriented for binding purposes). The metal cations were removed without disruption of the spatial orientation of the now "distorted" ligands, which were then examined in CHEM-3D and MODEL for their MM2 energies without further processing. The cited values may be higher than warranted because the X-ray structures show that the lone pairs on oxygen are not actually pointing toward the metal ion. Rather, a line drawn from an oxygen atom to the metal center nearly bisects the lone pair-oxygen-lone pair angle with resultant reduction in ligand strain. Such adjustments lower the value from 3.4 kcal mol^{-1} to only 0.57 kcal mol^{-1}.

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