Structural Criteria for the Rational Design of Selective Ligands. 2. Effect of Alkyl Substitution on Metal Ion Complex Stability with Ligands Bearing Ethylene-Bridged Ether Donors

Benjamin P. Hay,* Delong Zhang, and Jim R. Rustad

Pacific Northwest National Laboratory, Richland, Washington 99352

Received November 16, 1995[⊗]

A novel approach is presented for the application and interpretation of molecular mechanics calculations in ligand structural design. The methodology yields strain energies that (i) provide a yardstick for the measurement of ligand binding site organization for metal ion complexation and (ii) allow the comparison of any two ligands independent of either the number and type of donor atoms or the identity of the metal ion. Application of this methodology is demonstrated in a detailed examination of the influence of alkyl substitution on the structural organization of ethylene-bridged, bidentate, ether donor ligands for the alkali and alkaline earth cations. Nine cases are examined, including the unsubstituted ethylene bridge (dimethoxyethane), all possible arrangements of individual alkyl groups (monoalkylation, *gem*-dialkylation, *meso*-dialkylation, *d,l*-dialkylation, trialkylation, and tetraalkylation), and both *cis* and *trans* attachments of the cyclohexyl group. The calculated degree of binding site organization for metal ion complexation afforded by these connecting structures is shown to correlate with known changes in complex stability caused by alkyl substitution of crown ether macrocycles.

I. Introduction

Designing multidentate ligands for selective metal ion complexation is a two-step process: (1) choosing donor groups and (2) choosing the structure that ties them together. Criteria for the first step are fairly well understood; the choices are dictated by known affinities for the target metal ion and lack of affinities for nontarget metal ions through studies of unidentate ligands.[1] The number of donor groups is usually selected to achieve coordinative saturation in the target metal ion.[2] Reliable criteria for the second step are often lacking. The effect of ligand structure on metal ion complexation is often discussed and rationalized in qualitative terms, e.g., complementarity and preorganization.[1,3−7] These principles are easily understood but difficult to apply. For example, how is it determined whether one ligand is structurally more or less organized for binding than another? We present a general molecular mechanics (MM) approach to quantitatively assess the influence of connecting structure on complex stability, and apply the methodology in an examination of the influence of alkyl substituents on the binding site organization of ethylene-bridged ether donors for complexation with alkali and alkaline earth cations.

1. Interpretation of MM Calculations. The majority of MM applications to coordination compounds have focused on the conformational analysis of metal complexes and the prediction of structure in isolated complexes.[8] This work has demonstrated that MM is an accurate tool for predicting structure and providing insight into the nature and magnitude of steric interactions in metal complexes. A second, much smaller group of MM studies yielded quantitative relationships between ligand structure and thermodynamic quantities. Linear correlations among structure and complexation enthalpies, redox potentials, and complexation free energies have been obtained for series of octahedral nickel amine complexes,[9] octahedral cobalt amine complexes,[10] and potassium hexadentate ether complexes,[11] respectively. These studies have demonstrated that MM calculations provide a quantitative basis for understanding the effect of connecting structure on ligand−metal ion interaction and suggest that MM calculations could be used to provide criteria for the second step in ligand design. The key lies in appropriate interpretation of the MM results.

MM calculations yield structures and steric energies. The absolute value of a steric energy has little significance,[12] and direct comparisons of steric energies are valid only when the structures are conformational or configurational isomers, i.e., when the number and type of potential energy terms are identical for each structure. In such cases, the difference in calculated steric energy is known as the strain energy[12] and corresponds to experimentally observable quantities such as a difference in energy between two conformers. Strain energies pertaining to one molecule can be compared with those of another; steric energies do not correspond to experimental observables and, in general, should not be compared.

When performing MM calculations on ligands and their metal complexes, which steric energies should be determined and how should they be interpreted? The correlation obtained for the series of cobalt amine complexes was based on the difference in steric energy between Co(2+) and Co(3+) structures.[10]

[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1996.

(1) Hancock, R. D.; Martell, A. E. *Chem. Rev.* **1989**, *89*, 1875.
(2) Huheey, J. E. In *Inorganic Chemistry*; Harper and Row: New York, 1978.
(3) Cram, D. J.; Lein, G. M. *J. Am. Chem. Soc.* **1985**, *107*, 3657.
(4) Cram, D. J. *Angew. Chem., Int. Engl. Ed.* **1986**, *25*, 1039.
(5) (a) Potvin, P. G.; Lehn, J.-M. *Prog. Macrocycl. Chem.* **1987**, *3*, 167. (b) Lehn, J.-M. *Angew. Chem., Int. Engl. Ed.* **1988**, *27*, 89.
(6) Hancock, R. D.; Martell, A. E. *Comments Inorg. Chem.* **1988**, *6*, 237.
(7) Busch, D. H. In *Transition Metals in Supramolecular Chemistry*; Fabbrizzi, L., Poggi, A., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1994.
(8) (a) Brubaker, G. R.; Johnson, D. W. *Coord. Chem. Rev.* **1984**, 53, 1. (b) Hancock, R. D. *Prog. Inorg. Chem.* **1989**, 37, 187. (c) Comba, P. *Coord. Chem. Rev.* **1993**, *123*, 1. (d) Hay, B. P. *Coord. Chem. Rev.* **1993**, *126*, 177.
(9) (a) Thom, V. J.; Boeyens, J. C. A.; McDougall, G. J.; Hancock, R. D. *J. Am. Chem. Soc.* **1984**, *106*, 3198. (b) Hancock, R. D.; McDougall, G. J.; Marsicano, F. *Inorg. Chem.* **1979**, *18*, 2847.
(10) Hambley, T. W. *Inorg. Chem.* **1988**, *27*, 2496.
(11) Hay, B. P.; Rustad, J. R.; Hostetler, C. J. *J. Am. Chem. Soc.* **1993**, *115*, 11158.
(12) Burkert, U.; Allinger, N. L In *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982.

0020-1669/96/1335-2650$12.00/0

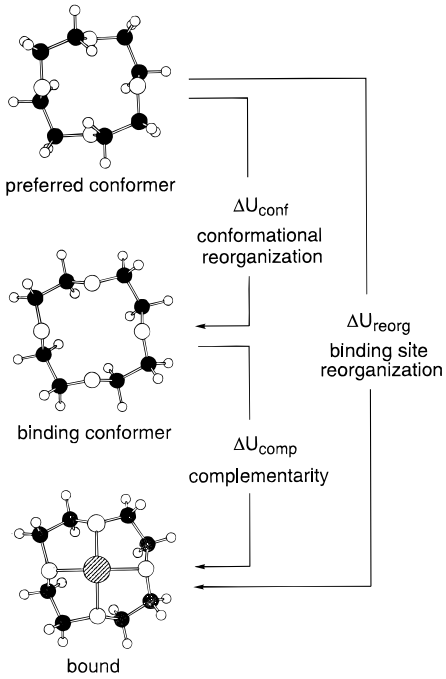


Figure 1. The three structural states of a ligand used to define steric and strain energies as illustrated for 12-crown-4.

These differences were not strain energies because the two structures were not conformational or configurational isomers. The correlations involving series of nickel amine complexes[9] and potassium ether complexes[11] were based on the difference in the steric energy of the free ligand and that of the metal complex. Again, these differences were not strain energies, because the two structures were not conformational or configurational isomers.

The correlations obtained in these studies[9−11] were due to the difference in steric energies giving the strain energy for the ligand plus a residual steric energy component for the metal ion interactions. Because the metal ion and number and type of donor atoms were constants, many of the metal-dependent potential energy terms (M−L bond stretches, M−L−X and L−M−L bond angles, M−L−X−X torsion angles) remained constant. Thus, using MM steric energies in these studies requires that the identity of the metal ion and the number and type of donor atoms are constant.

We propose a new formalism for applying and interpreting MM calculations in the structural design of ligands (Figure 1). This formalism yields strain energies that provide a measurement of the degree of binding site organization for metal ion complexation and allow the comparison of the degree of binding site organization in any two ligands independent of the number and type of donor atoms or the identity of the metal ion. We define the degree of binding site organization in terms of steric energies obtained from MM calculations; this involves the preferred conformation of the free ligand, the binding conformation of the free ligand, and the bound ligand, as shown in Figure 1.

Coordination of a metal ion to a ligand often changes the ligand's structure. The magnitude of these changes, i.e., the extent of ligand *structural reorganization* associated with metal ion complexation, is an indicator of the *binding site organization*. Ligand structural reorganization is a two-step process: that which occurs prior to binding and that which occurs during binding. The magnitude of each step can be quantified by applying MM. The coordination of a metal ion to a ligand that contains a highly organized set of binding sites will require little to no change.

Many ligands are flexible and can adopt multiple conformations. When the preferred conformation differs from the binding conformation, the ligand must undergo a conformational change. This *conformational reorganization* costs energy that can be quantified with MM calculations. The change in ligand steric energy going from the preferred free ligand conformation to the binding conformation, ΔU_{conf}, yields a strain energy that provides a quantitative measure of the structural reorganization that occurs prior to complexation.

Structural reorganization during complexation is a measure of the *complementarity* in the ligand. As originally stated, "to complex, hosts must have binding sites which cooperatively contact and attract binding sites of guests without generating strong nonbonded repulsions".[3] Taken to the logical extreme, a ligand with perfectly complementary binding sites will not experience unfavorable steric interactions (*neither* strong nonbonded repulsions *nor* distortions from preferred bond lengths, bond angles, and torsion angles) as a result of complexation.

Although the gross conformation of a free ligand in its binding conformation does not change on complexation, metal ion coordination to noncomplementary binding sites will change the ligand structure that generates steric strain. The change in ligand steric energy going from the binding conformation of the free ligand to the bound ligand structure, ΔU_{comp}, provides a quantitative measure of the degree of complementarity offered by the ligand cavity. ΔU_{comp} is a strain energy because it is the change in steric energy within the ligand and does not contain any contributions from metal-dependent potential energy terms. Therefore, it can be used to compare the degree of complementarity in any ligand for complexation to any metal ion.

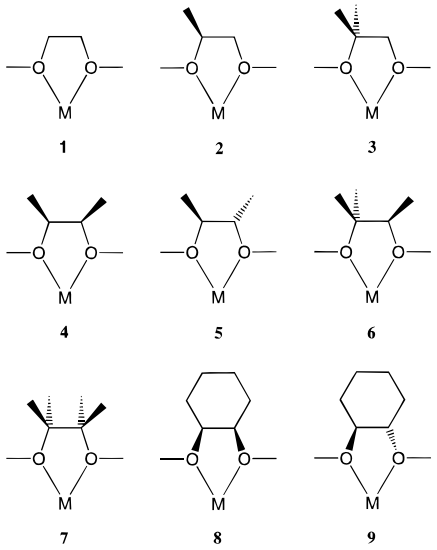
We designate the sum of the two structural reorganization components as the ligand's structural *reorganization energy*, $\Delta U_{reorg} = \Delta U_{conf} + \Delta U_{comp}$. This quantity is an MM strain energy that provides a quantitative measurement of the degree of a ligand's binding site organization for metal ion complexation. Ligands that are poorly organized for binding will exhibit large ΔU_{reorg} values; ligands highly organized for binding will exhibit low ΔU_{reorg} values. A ligand which is perfectly *preorganized* for binding, i.e., locked in a binding conformation with complementary sites, would exhibit a ΔU_{reorg} of zero.

2. Analysis of Connecting Structure. A bidentate ligand is the simplest case in which the issue of binding site organization arises. Here the ability of the two donor atoms to achieve optimum orientation relative to the metal ion is restricted by the connecting structure. Because the same restrictions are present when the connecting structure occurs in a multidentate ligand, bidentate ligands can be used to model connecting structure effects in multidentate ligands.

The influence of connecting structure on the metal ion selectivity of multidentate amine ligands has been explained in terms of steric effects in simple bidentate amines.[13] In these studies, steric energies for metal complexes of ethylene- and propylene-bridged diamine ligands were determined as a function of M−N bond length. Plots of metal complex steric energy vs M−N bond length revealed that the ethylene bridge (five-member chelate ring) provided binding sites that were most complementary for larger (ionic radii ≥2.3 Å) metal ions, while the propylene bridge (six-member chelate ring) provided binding sites that were most complementary for smaller (ionic radii ≤2.3 Å) metal ions. These results explain why replacing ethylene-

(13) (a) Hancock, R. D. *Acc. Chem. Res.* **1990**, *23*, 253. (b) Hancock, R. D.; Wade, P. W.; Ngwenya, M. P.; de Sousa, A. S.; Damu, K. V. *Inorg. Chem.* **1990**, *29*, 1968. (c) Hancock, R. D. *J. Chem. Educ.* **1992**, *69*, 615.

Chart 1



bridged amine donors with propylene-bridged amine donors in multidentate ligands frequently results in an increased selectivity for smaller metal ions.

Our MM modeling has focused on ligands containing ether donors. In the first paper of this series, we examined geometric requirements for optimal ether coordination with the alkali and alkaline earth cations.[14] We showed that, unlike amine donors that prefer tetrahedral geometry when bound to a metal ion, coordinated ether donors prefer trigonal planar geometry. The effect of donor atom geometry on the metal ion size preference of ethylene-bridged bidentate ligands was examined in a subsequent study.[15] ΔU_{comp} values were determined as a function of M−O bond length for dimethoxyethane and as a function of M−N bond length for the analogous bidentate amine, *N*,*N*′-dimethylethylenediamine. Plots of ΔU_{comp} vs metal ionic radius revealed that while both types of five-member chelate rings exhibit maximum complementarity for the largest metal ions (ionic radii ≥ 3.0 Å), those formed by the diether are significantly more strained than those of the diamine for all metal ion sizes; i.e., the ethylene connecting structure is a more complementary arrangement for tetrahedral donor atoms than for trigonal planar donor atoms. The preference for macrocycles that contain only ethylene-bridged ether donors such as 12-crown-4, 15-crown-5, and 18-crown-6 to selectively bind larger metal ions (K^+, Rb^+, Cs^+, and Ba^{2+}) rather than smaller metal ions (Li^+, Na^+, and Ca^{2+}) was rationalized in terms of these findings.[15]

Ethylene bridges are the most prevalent connecting structures in multidentate ethers. Many of these ligands have been prepared with alkyl-substituted ethylene bridges.[16,17] Experimental data reveal that the alkylation of ethylene bridges in crown ether macrocycles almost always results in a drop in metal complex stability.[17] We applied the MM formalism described above to study this effect. Nine bidentate ethers were examined for binding site organization for the alkali and alkaline earth cations (see Chart 1), including the unsubstituted ligand, **1**, all possible arrangements of individual alkyl groups **2**−**7**, and two diastereomeric attachments of the cyclohexyl group, **8** and **9**. We found that the calculated degree of binding site organization in **1**−**9** correlates with changes in complex stability that result from alkyl substitution of crown ether macrocycles.

II. Methods

1. Software and Hardware. MM calculations were performed with a modified version of the MM3 program[18] on a Hewlett Packard 735 workstation. The program was modified to add 1,3 van der Waals interactions between two oxygen donor atoms attached to the same metal ion (details in supplemental material). In addition, the Saunders' stochastic search subroutine,[19] provided with the MM3 program, was modified to accept ether−metal ion complexes and to perform extensive conformational searches on each ligand and its complex with the alkali cations (Li^+−Cs^+) and the alkaline earth cations (Mg^{2+}−Ba^{2+}). These searches yielded the global minimum conformation for each structure.

The treatment of metal complexes and the MM3 parameters for ethers and their metal complexes was described in our previous work.[14] The ability of this model to accurately reproduce structural and conformational energies of crown ethers[20] and their complexes[14] has been documented. In our prior MM3 calculations[14] the metal ions were coordinatively saturated, and the donor atoms in the primary coordination sphere prevented contact between the metal ion and other atoms in the ligand. It is not necessary to include van der Waals interactions with the metal ion in such situations,[8d] and they were not used in our previous work. But in this study metal ions are coordinatively unsaturated, and in a few instances it was necessary to add van der Waals interactions with the metal ion to prevent alkyl substituents on the ethylene bridge moving too close to the metal ion during conformational searches. We assigned MM3 van der Waals parameters for the noble gas with the same electronic configuration to each metal ion, including the calculations reported here:[21] metal ion, r (Å), ϵ (kcal/mol); Li^+, 1.53, 0.026; Na^+ and Mg^{2+}, 1.60, 0.090; K^+ and Ca^{2+}, 1.99, 0.268; Rb^+ and Sr^{2+}, 2.15, 0.358; Cs^+ and Ba^{2+}, 2.28, 0.495.

The molecular graphics program Chem3D Plus[22] was used on a Macintosh IIci computer to build initial sets of molecular coordinates for MM3 and to view and plot the molecular structures obtained from the energy minimization by the MM3 program.

2. Steric Energy and Strain Energy Definitions. Steric energies from the MM calculations are defined with respect to three structural states of the ligand illustrated in Figure 1. The steric energy of the preferred conformation of the free ligand is designated U_{free}, that of the binding conformation of the free ligand U_{bind}, and that of the bound ligand U_{bound}. The latter quantity is calculated by determining the lowest energy structure for the ligand metal complex, optimizing its geometry through MM3 calculation, removing the metal ion, and performing an initial energy calculation in which no atoms are allowed to move on the remaining ligand structure.

The strain energy ΔU_{conf} is the difference in steric energy between the preferred free ligand conformation and its binding conformation, $U_{bind} - U_{free}$. The strain energy ΔU_{comp} is the steric energy difference between the binding conformation of the free ligand and the bound

(14) Hay, B. P.; Rustad, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 6316.
(15) Hay, B. P.; Rustad, J. R. *Supramol. Chem.*, in press.
(16) (a) Bajaj, A. V.; Poonia, N. S. *Coord. Chem. Rev.* **1988**, *87*, 55. (b) Vogtle, R; Weber, E. In *Crown Ethers and Analogues*; Papai, S., Rappaport, Z., Eds.; Wiley: New York, 1989.
(17) (a) Christensen, J. J.; Eatough, D. J.; Izatt, R. M. *Chem. Rev.* **1974**, *74*, 351. (b) Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J. *Chem. Rev.* **1985**, *85*, 271. (c) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721.
(18) (a) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551. (b) MM3 (1992 version) was obtained from the Technical Utilization Corp., Inc., 235 Glen Village Court, Powell, OH 43065.
(19) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150.
(20) Hay, B. P.; Rustad, J. R.; Zipperer, J.; Wester, D. W. *THEOCHEM, J. Mol. Struct.* 1995, *337*, 39.
(21) Including van der Waals interactions in these calculations prevents generation of unrealistic structures during the conformational searches. While sufficient for this purpose, the van der Waals parameters used here are only approximate and have not in any way been optimized for performance. In the majority of cases examined in this study, metal ion van der Waals interactions make a negligible contribution to the steric energy, and the use of these approximate parameters in no way alters the conclusions presented in this paper. The trends presented in Figure 5 are insensitive to large variations in the van der Waals parameters. In addition, equally good correlations between $\Delta \log K$ and $\Delta\Delta U_{reorg}$ are obtained when van der Waals interactions with the metal are excluded from the calculations altogether.
(22) Rubenstein, M.; Rubenstein S. Cambridge Scientific Computing Inc., Cambridge, MA 1989.

Table 1. Summary of Conformational Analysis Results for **1**−**9**[a]

ligand	conformers found	first [U_{free}]	second [$U - U_{free}$]	third [$U - U_{free}$]	fourth [$U - U_{free}$]	fifth [$U - U_{free}$]
1	10	0+0	000	0+−	0++	00+
		[5.49]	[+0.54]	[+1.40]	[+1.94]	[+2.33]
2	20	0+−,eq(−)	0+0,eq	0−0,ax	000	0−−,ax(+)
		[8.49]	[+0.01]	[+0.73]	[+1.02]	[+1.15]
3	7	0+−(−)	0+0	0++(+)	000	00+(+)
		[12.62]	[+0.22]	[+0.75]	[+1.06]	[+1.27]
4	11	000	0+0,ax,eq	0+−,ax(0),eq(−)	++−,ax(+),eq(−)	0++,ax(+),eq(0)
		[13.18]	[+0.17]	[+0.21]	[+0.43]	[+0.59]
5	18	0+0,ax,ax	0−0,eq,eq	0−+,eq,eq	+−+,eq,eq	00+
		[13.09]	[+0.03]	[+0.31]	[+0.99]	[+1.42]
6	20	0+0,ax	0+−,ax(0)	000	0−+,eq(0)	00+(0)
		[18.07]	[+0.06]	[+0.62]	[+0.72]	[+0.82]
7	13	000	0+−	0+0	++−	0++
		[24.81]	[+0.42]	[+0.67]	[+3.08]	[+3.42]
8	22	0+0,ax,eq	0++,ax(+),eq(0)	0+−,ax(0),eq(−)	++−,ax(+),eq(−)	0+−,ax(−),eq(0)
		[18.28]	[+0.26]	[+0.35]	[+0.40]	[+2.28]
9	26	0+0,eq,eq	0+−,eq,eq	+−+,eq,eq	000	00+
		[16.59]	[+0.35]	[+1.21]	[+2.37]	[+2.54]

[a] Each entry gives the ligand number, total number of conformers located, the structures of the five lowest energy conformers (see text for explanation of nomenclature), the steric energy for the lowest energy conformer of the free ligand (U_{free}), and the relative strain energies for the next four conformers ($U - U_{free}$). All energies are given in kcal/mol.

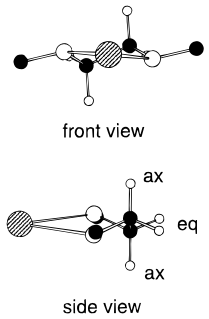


Figure 2. Hydrogen atoms on the ethylene bridge have two distinguishable positions when the O−C−C−O group has a *gauche* conformation. The two hydrogens closest to the plane defined by the two oxygen atoms and the midpoint of C−C bond are equatorial (eq). The remaining two hydrogens, with C−H bonds that are roughly perpendicular to this plane, are axial (ax).

ligand, $U_{bound} - U_{bind}$. The strain energy ΔU_{reorg} is the steric energy difference between the preferred free ligand conformation and the bound ligand, $U_{bound} - U_{free}$. This quantity is also given by $\Delta U_{conf} + \Delta U_{comp}$.

3. Conformer Nomenclature. The three dihedral angles of the C−O−C−C−O−C backbone in each ligand are indicated by a group of three symbols (+ for angles from 0 to $^2/_3\pi$, − for angles from 0 to $-^2/_3\pi$, and 0 for angles between $^2/_3\pi$ and $^4/_3\pi$). Axial and equatorial sites exist on the ethylene group when the 0−C−C−O dihedral angle of this backbone is gauche (+ or −). These sites are illustrated in Figure 2. In such cases, the substituent position is indicated by adding *ax* (axial) or *eq* (equatorial). When the backbone conformation is asymmetric, e.g., 0++ or ++−, the substitution may occur on either side of the ethylene group. To distinguish between these two, (+) or (−) is used to indicate placement nearest the corresponding *gauche* C−C−O−C group, and (0) is used to indicate placement nearest the *anti* C−C−O−C group.

III. Results and Discussion

1. Conformational Analysis of the Free Ligands. The results of conformational searches on ligands **1**−**9** are presented in Figure 3, which shows the lowest energy conformation for each ligand, and in Table 1, which gives the total number of conformers located, the structures of the five lowest energy conformers, the strain energy for the lowest energy conformer (U_{free}), and the relative strain energies for the next four conformers ($U - U_{free}$).

Ligand **1** prefers to adopt the 0+0 conformation. The low energy forms for **2**−**9** (see Table 1) reveal that alkylation on

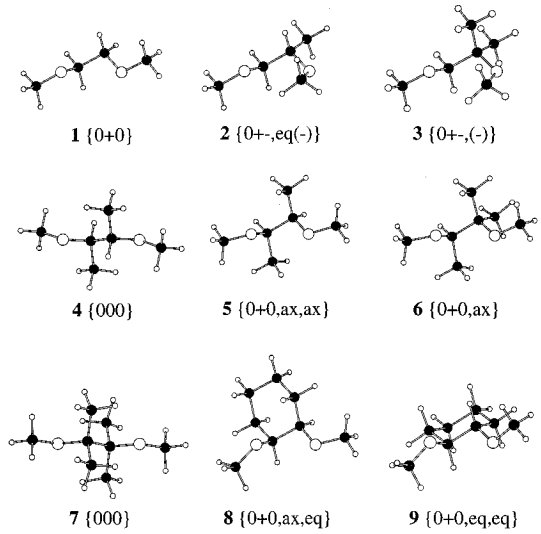


Figure 3. Most stable conformers for **1**−**9**.

the ethylene bridge alters the relative stability of the various C−O−C−C−O−C backbone conformations. For some substitution patterns, ligands **5**, **6**, **8**, and **9**, 0+0 remains the lowest energy form. But monoalkylation, **2**, and gem-dialkylation, **3**, cause a slight preference (0.01 and 0.22 kcal/mol, respectively) for the 0+− form. *Cis*-dialkylation, **4**, and tetraalkylation, **7**, stabilize the 000 over the 0+0 form (0.17 and 0.67 kcal/mol, respectively).

Alkyl substituents may take either axial or equatorial positions on the ethylene bridge in ligands **2**, **4**, **5**, **6**, **8**, and **9** when these ligands have a gauche O−C−C−O torsion angle. The methyl substituent in **2** prefers an equatorial position. This is expected, because equatorial substitution gives an *anti* O−C−C−C dihedral angle, while axial substitution yields the less stable *gauche* form. The stereochemistry of *meso*-dimethyl substitution, **4**, requires one substituent to be axial and the other equatorial. The *d*,*l*-dimethyl groups, as occur in **5** and **6**, adopt axial positions to avoid the unfavorable van der Waals interactions that would occur between adjacent equatorial substituents. In ligands **8** and **9** the cyclohexyl rings adopt the stable chair conformation. As with **4**, the stereochemistry of *cis*-cyclohexyl substitution, **8**, requires one substituent to be axial and the other equatorial in the C−O−C−C−O−C group. The stereochemistry of *trans*-cyclohexyl substitution, **9**, allows either a diequa-

torial or a diaxial arrangement of the cyclohexane ring. The first is much more stable. Therefore, unlike the *trans*-dimethyl-substituted ligand, **5**, which adopts a diaxial arrangement, the *trans*-cyclohexyl-substituted ligand, **9**, adopts the diequatorial form.

Attempts have been made to determine the identity and relative stability of the various conformations of **1**; conclusions from a review of this work[23] are summarized here. The data indicate a predominance of the 0+0 and 000 conformers, with lesser contributions of several higher energy forms, including 0+−, 0++, 00+, +0+, and +++. The 0+0 conformer is the only form observed in the crystal and the predominant conformer in the liquid and gas phases by 0.5−1.5 and 0.3−0.4 kcal/mol, respectively. In good agreement with these data, we obtain the 0+0 and 000 conformers as the lowest energy forms, with 0+0 more stable than 000 by 0.54 kcal/mol.

The conformational preferences of the isolated C−O−C−C−O−C group will, to a large extent, control conformation in molecules that contain multiple C−O−C−C−O−C groups. This effect can be observed in crystalline poly(ethyleneoxide), where the C−O−C−C−O−C groups exclusively adopt a 0+0 conformation, and in spectroscopic studies of the solution structure of poly(ethylene oxide), which indicate that 0+0 is the predominant form.[24]

The proclivity for the 0+0 conformation is also evident in the structures of crown ethers. Using the Cambridge Crystallographic Database,[25] we analyzed the C−O−C−C−O−C conformation in 12-crown-4, 15-crown-5, and 18-crown-6 rings for all structures that do not contain a metal ion to ether oxygen bond. Only five of 10 possible conformers of **1** were observed in the 823 groups that were examined. The identity and frequency of occurrence were 0+0 (86.6%), 000 (1.6%), 0+− (1.7%), 0++ (9.6%), and +++ (0.5%). The most frequently observed conformers correspond to the four calculated lowest energy forms of **1**, with 0+0 clearly predominating. The population of the 0++ form is higher than would be expected from the relative energies given in Table 1 because cyclic structures such as 12-crown-4 necessitate a sharper folding of the C−O−C−C−O−C chain that can be achieved by forming the *gauche* C−O dihedral angle found in the 0++ form.[24]

As with the unsubstituted ligand, **1**, the conformational preferences of the substituted ligands, **2**−**9**, are expected to influence conformation in molecules containing alkyl substituted C−O−C−C−O−C groups. However, the Cambridge Crystallographic Database contained structural data only on the uncomplexed, alkyl-substituted, crown ether patterns of **2** and **8**.

The crystal structure of tetramethyldibenzo-18-crown-6,[26] the only metal-free crown ether to compare with **2**, contains four monoalkylated ethylene bridges. Two exhibit the predicted lowest energy conformer for **2**, 0+−,eq(−); the other two adopt the 000 conformation. This is consistent with results from our conformational analysis, because the macrocyclic ring prevents all four subunits from adopting the lowest energy conformer of **2.** The stereochemistry of methyl substitution (7R, 9R, 18S, 20S) prevents all four methyl groups from simultaneously adopting equatorial positions; thus the presence of two 0+−, eq(−) groups does not allow the remaining two to adopt the second lowest energy form, 0+0,eq.

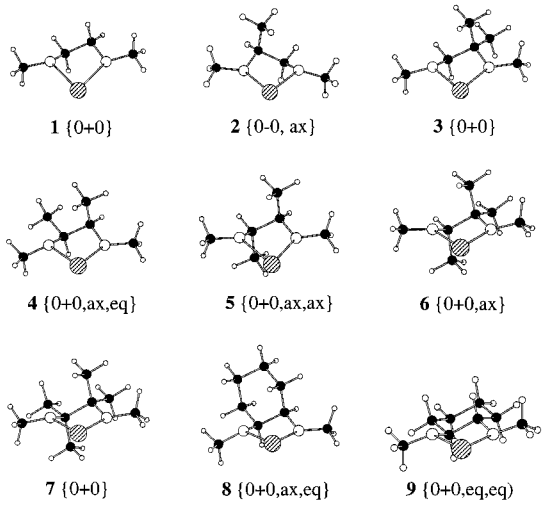


Figure 4. Most stable conformers for alkali and alkaline earth cation complexes of **1**−**9**.

Eleven *cis*-cyclohexyl-substituted crown ether structures were located that did not contain a metal ion to ether oxygen bond. Only three of the 22 possible conformers of **8** were observed for these *cis*-cyclohexyl substituted C−O−C−C−O−C groups. The identity and frequency of occurrence were 0+0,ax,eq (55%), 0++,ax(+),eq(0) (50%), and ++−,ax(+),eq(−) (5%). In good agreement with our results, these three conformers correspond to the low energy forms calculated for **8**, with the two lowest predominating (see Table 1).

2. Conformational Analysis of Metal Complexes. The results of conformational searches alkali and alkaline earth metal ion complexes with ligands **1**−**9** are presented in Figure 4, which shows the lowest energy conformation for each complex. Table 2 gives the ligand number and steric energy of the bound ligand (U_{bound}) for each cation. The results are discussed below and, where possible, compared with experimental data to verify the accuracy of the model.

The searches reveal that metal ion coordination restricts the possible arrangements of the C−O−C−C−O−C backbone. The 0+0 form occurs in all of the lowest energy conformations. With the exception of the monoalkylated ligand **2,** alkyl positions in the bound ligand correspond to the preferred alkyl positions in the free ligand. The methyl group prefers the equatorial position in the free ligand but an axial position in the bound ligand because in metal complexes, equatorial substitution gives rise to unfavorable van der Waals interactions between the substituent and the terminal O−CH_3 groups (*vide infra*). The switch in position does not occur in the other ligands because equatorial alkyl group position is demanded by stereochemistry, e.g., **4** and **8**; or a strong preference exists for equatorial substitution on the cyclohexane ring, e.g., **9**; or the axial position is already the most stable form of the free ligand, e.g., **5** and **6**.

As with free ligands, it is reasonable to expect the conformational preference in the metal complexes of **1**−**9** to influence ligand conformation in those containing the C−O−C−C−O−C groups. Calculations on **1** and experimental data support this expectation. We examined C−O−C−C−O−C conformation in alkali and alkaline earth metal complexes of acyclic polyethers 15-crown-5 and 18-crown-6 with the Cambridge Crystallographic Database; only three conformers were observed out of the 680 groups examined. The identity and frequency of occurrence were 0+0 (87.1%), 0++ (12.2%), and +++ (0.7%), consistent with the results for **1** that indicate 0+0 to be the most stable conformer for all metal ions; 0++ to be the next most

(23) Senderowitz, H.; Golender, L.; Fuchs, B. *Tetrahedron* **1994**, *50*, 9707.
(24) Dale, J. *Isr. J. Chem.* **1980**, *20*, 3.
(25) Cambridge Crystallographic Database (1994 version). Allen, F. H.; Bellard, S. A.; Brice, M. D.; Cartwright, B. A.; Doubleday, A.; Higgs, H.; Hummelink, T.; Hummelink-Peters, B. G.; Kennard, O.; Motherwell, W. D. S.; Rodgers, J. R.; Watson, D. G. *Acta Crystallogr.* **1979**, *B35*, 2331.
(26) Mallinson, P. R. *J. Chem.Soc., Perkin Trans. 2* **1975**, 266.

Table 2. Values of U_{bound} for Complexes of **1**−**9** with the Alkali and Alkaline Earth Cation Complexes[a]

ligand	Li	Na	K	Rb	Cs	Mg	Ca	Sr	Ba
1	8.95	7.54	6.79	6.66	6.55	10.92	9.26	8.40	8.07
2	11.84	10.80	10.13	10.03	9.96	13.48	11.96	11.36	11.07
3	15.75	14.61	14.06	13.98	13.92	17.70	16.15	15.44	15.20
4	16.45	15.30	14.74	14.68	14.60	18.32	16.76	16.19	15.90
5	14.92	14.04	13.63	13.58	13.54	16.35	14.97	14.53	14.27
6	20.22	19.30	18.89	18.84	18.79	21.81	20.33	19.86	19.62
7	27.78	27.02	26.73	26.72	26.70	29.43	28.26	27.85	27.78
8	20.88	19.88	19.50	19.44	19.40	22.67	21.21	20.69	20.47
9	21.07	19.83	19.31	19.22	19.18	23.81	22.32	21.50	21.37

[a] Each entry gives the ligand number and the steric energy for the bound ligand, U_{bound}, as a function of cation. Energies are given in kcal/mol.

stable (higher in energy by 1.0−1.5 kcal/mol), and +++ to be significantly higher in energy (≥3 kcal/mol). Structural data on metal-complexed, alkyl-substituted crown ethers were available only for the patterns of **2**, **5**, and **8**.

Monoalkylated ethylene bridges, e.g., **2**, occur in a potassium complex of dimethyl-18-crown-6[27] and two tetramethyldibenzo-18-crown-6 complexes of cesium.[28] In all cases, the C−O−C−C−O−C groups adopt the 0+0 conformation, but due to the stereochemistry of the alkyl group attachments, half are in an axial position and half in an equatorial position. Thus, while these data neither confirm nor rule out the predicted preference for axial alkyl position for metal complexes of **2**, they are consistent with the conformational analysis results obtained for **2**.

The *d,l*-dialkylated bridges (**5**) occur in a calcium complex, tetramethyl-18-crown-6.[29] The two calcium-coordinated C−O−C−C−O−C groups adopt a 0+0 conformation with both methyl substituents in axial position, the lowest energy conformation predicted for metal complexes of **5**.

The *cis*-cyclohexyl-substituted ethylene bridges, e.g., **8**, occur in three potassium complexes, two strontium complexes, and one barium complex of dicyclohexano-18-crown-6.[30−33] In all cases, the experimental structures contained either the predicted low-energy 0+0 form (**8** in Figure 4) or a slightly higher energy (0.1−0.2 kcal/mol) 0++ form.

3. Analysis of Binding Site Organization. The steric energies given in Tables 1 and 2 allow computation of the reorganization energy, ΔU_{reorg}, for metal ion complexation in **1**−**9**. Values of ΔU_{reorg} ($U_{bound} - U_{free}$), plotted as a function of metal ion size and charge in Figure 5, lead to several general observations. First, regardless of the alkyl substitution, ligands **1**−**9** develop less strain on complexation with the larger of two metal ions. Thus, as demonstrated for **1**,[14,15] all ethylene-bridged ligands examined are structurally most organized for complexation with larger metals. Second, for a metal ion of a given size, complexation by ligands **1**−**9** causes more strain with a +2 cation than with a +1 cation; thus, they are most organized for complexation with the lower valent ion of two metal ions of equal size. Third, alkyl substitution can significantly increase

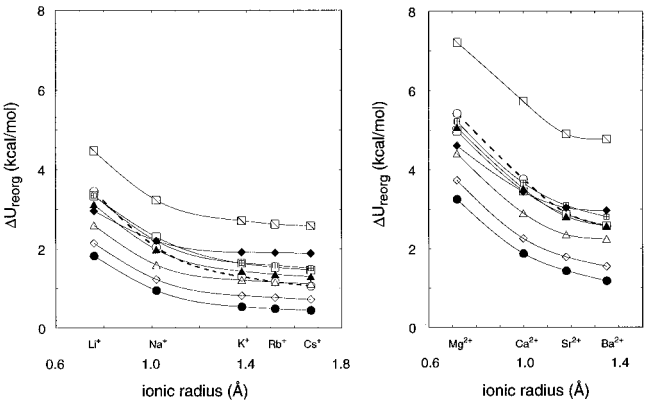


Figure 5. Plots of ΔU_{reorg} vs metal ionic radius[34] (⊙, **1**; ⊡, **2**; ▲, **3**; crossed square, **4**; ●, **5**; ◇, **6**; ◆, **7**; △, **8**; slashed square, **9**). For (a) the alkali +1 cations and (b) the alkaline earth +2 cations: A dashed line is used to indicate the unsubstituted ligand, **1**.

or decrease the degree of binding site organization. For example, with any given metal ion, introducing *trans*-dimethyl substitution, **5**, increases organization, and *trans*-cyclohexyl substitution, **9**, decreases organization. The general organization for large metal ions of low charge and the specific effects of alkyl substitution are easily rationalized with a closer look at the components of ΔU_{reorg}.

Consider the degree of binding site organization afforded by the unsubstituted ethylene bridge in **1**. The lowest energy conformer for the free ligand is $\Delta U_{conf} = 0$. Thus the structural preference for large, low-charged metal ions results from their greater degree of complementarity. Coordinated ether oxygens prefer a trigonal planar geometry; to provide this geometry at both oxygen donors, the O−C−C−O angle in **1** would need to adopt a value of zero, with both oxygens eclipsed. The ethylene bridge, however, prefers a *gauche* O−C−C−O torsion angle and is thus unable to provide the optimum orientation of the trigonal planar oxygen donors. On metal ion coordination, the O−C−C−O torsion angle is decreased, with a concomitant increase in ligand strain as the oxygens attempt to achieve their preferred geometries. The magnitude of this ligand strain is directly correlated to the strength of the trigonal planar geometry preference, which is at maximum for small, high valent ions and at minimum for large, low valent ions.[14,15] The ethylene bridge in **1** thus provides binding sites that are more complementary for the larger, low valent metal ions.

The factors that control the change in complementarity as a function of metal ion size and charge in **1** are also present in **2**−**9** and account for the similar shapes of the ΔU_{reorg} vs ionic radius curves shown in Figure 5. Although the shapes are similar, the curves for different ligands are offset on the *y*-axis; i.e., for a given metal ion, the degree of binding site organization varies as a function of alkyl substitution. These differences are

(27) Dyer, R. B.; Ghirardelli, R. G.; Palmer, R. A.; Holt, E. M. *Inorg.Chem.* **1986**, *25*, 3184.
(28) Mallinson, P. R. *J. Chem. Soc. Perkin Trans. 2* **1975**, 261.
(29) Dyer, R. B.; Metcalf, D. H.; Ghirardelli, R. G.; Palmer, E. M.; Holt, E. M. *J. Am. Chem. Soc.* **1986**, *108*, 3621.
(30) Krasnova, N. F.; Simonov, Yu. A.; Bel'skii, V. K.; Abashkin, V. M.; Yakshin, V. V.; Malinovskii, T. I.; Laskorin, B. N. *Dokl. Akad. Nauk SSSR* **1984**, *276*, 607.
(31) (a) Fraser, M. E.; Fortier, S.; Markiewicz, M. K.; Rodrigue, A.; Bovenkamp, J. W. *Can. J. Chem.* **1987**, *65*, 2558. (b) Rath, N. P.; Holt, E. M. *J. Chem. Soc., Chem. Commun.* **1986**, 311.
(32) Krasnova, N. F.; Dvorkin, A. A.; Simonov, Yu. A.; Abashkin, V. M.; Yakshin, V. V. *Kristallogr.* **1985**, *30*, 86.
(33) Burns, J. H.; Bryan, S. A. *Acta Crystallogr., C* **1988**, *44*, 1742.
(34) Effective ionic radii for coordination number six were taken from Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751.

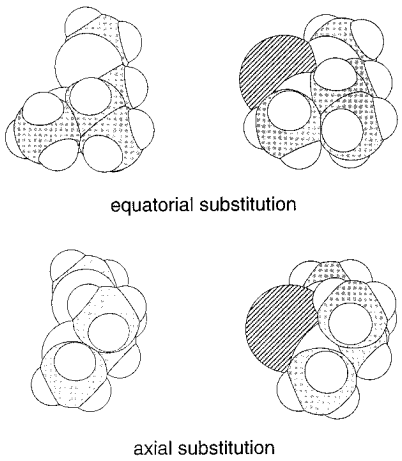


Figure 6. Space filling representations illustrating how metal ion coordination to a ligand with equatorial alkyl substituent (top left) pushes the substituent into closer contact with terminal O−CH_3 group (top right). Metal ion coordination to a ligand with an axial alkyl substituent (bottom left) separates the substituent from the terminal O−CH_3 group (bottom right).

attributable to the effect of alkyl substitution on complementarity, which is moderated, in some cases, by conformational reorganization.

The effect of a given alkylation pattern on complementarity depends to a large extent on whether the alkyl substituents occupy equatorial or axial sites. Equatorial positioning increases ligand strain on metal complexation; axial positioning decreases it (see Figure 6). An alkyl substituent on the ethylene bridge experiences unfavorable van der Waals interactions with the nearest terminal O−CH_3 group. Metal ion coordination causes the O−C−C−O torsion angle to decrease, resulting in a flattened C−O−C−C−O−C backbone. This flattening pushes the equatorial alkyl substituent into the terminal O−CH_3 group, increasing unfavorable van der Waals interactions; axial substituents move away from the terminal O−CH_3 group, reducing unfavorable interactions.

Introducing one alkyl group to the ethylene bridge, **2**, decreases organization for +1 cations and increases it for +2 cations. Examining the ΔU_{reorg} components reveals that **2**, with one axial methyl group, yields binding sites of increased complementarity for all metal ions. Complexation by **2**, however, requires conformational reorganization from the 0+−,eq(−) form to the 0−0,ax form at a cost of 0.73 kcal/mol. In +1 cations, the gain in complementarity is offset by the cost of conformational reorganization, and **2** is less organized than **1**. Gains in complementarity exceed the cost of conformational reorganization in +2 cations, and **2** is more organized than **1**.

The introduction of two methyl groups to the ethylene bridge results in possible isomers **3**, **4**, and **5**. Geminal dialkylation, **3,** and *meso*-dialkylation, **4,** exhibit similar behavior. The ligands each contain one axial and one equatorial substituent; their introduction yields increased complementarity for small +1 cations and all the +2 cations and decreased complementarity for large +1 cations. Complexation by **3** requires a conformer change from 0+−(−) to 0+0 at an expense of 0.22 kcal/mol, and complexation by **4** requires a conformer change from 000 to 0+0,ax,eq at an expense of 0.17 kcal/mol. The combined effects of conformational reorganization and complementarity shift give rise to the observed trends in Figure 5, i.e., increased organization for small cations and decreased organization for large cations compared with **1**.

In **5**, *d*,*l*-dialkylation causes the largest increase in organization of the examined ligands due to the increased complementarity afforded by the two axial substituents plus the fact that the most stable free ligand conformer of **5** is the binding conformation ($\Delta U_{conf} = 0$). The introduction of three methyl groups to the ethylene bridge, **6**, also yields increased organization for all metal ions. As with **5**, this is a result of increased complementarity caused by the two axial substituents. However, the additional equatorial methyl substituent in **6** decreases the gain in complementarity, so the binding conformation of **6** is not as well organized as that of **5**.

The introduction of four methyl groups to the ethylene bridge, **7**, increases organization for small metal ions and decreases organization for larger metal ions. The binding conformer of this ligand contains two axial and two equatorial methyl substituents. As in **3** and **4**, the equal number leads to increased complementarity for the small +1 cations and all the +2 cations and decreased complementarity for large +1 cations. As with **3** and **4**, complexation by **7** entails conformational reorganization from the 000 form to the 0+0 form at an expense of 0.67 kcal/mol.

Introducing a cyclohexyl group to an ethylene bridge results in two possible diastereomers, **8** and **9**. These two isomers exhibit very different behavior that results entirely from differences in complementarity. *Cis* attachment of the cyclohexyl group, **8**, results in increased organization for all metal ions except cesium. The *cis* isomer, like **3**, **4**, and **7**, has an equal number of axial and equatorial substituents on the ethylene bridge, a pattern that gives rise to similar trends in complementarity. Additional impacts on complementarity arise from interactions within the cyclohexyl ring, where the two methoxy groups are constrained by *cis* stereochemistry to occupy axial and equatorial sites. As a result there are unfavorable 1,3-diaxial interactions between the two axial hydrogens and the axial oxygen, and the O−C−C−O torsion angle in the free ligand form of **8** is compressed to 64°, significantly lower than the 72° angle found in **1**. The additional decrease in O−C−C−O torsion angle that occurs on metal ion coordination, e.g., 59° for potassium, further relieves the strain caused by the unfavorable 1,3-diaxial interactions. In contrast, *trans* attachment of the cyclohexyl group, **9**, results in a large decrease in organization for all metal ions, in part from the decrease in complementarity caused by two equatorial substituents on the ethylene bridge. In addition, the decrease in O−C−C−O torsion angle that occurs on metal ion coordination causes distortion and development of strain in the cyclohexyl ring.

4. Changes in Complex Stability vs Changes in Binding Site Organization. Complex stability is typically reported in terms of the logarithm of the association constant, log *K*. These log *K* values are proportional to the free energy of complexation: $\log K = -1/(2.303RT)\Delta G$. This equation can be expressed in terms of enthalpy and entropy: $\log K = -\Delta H/(2.303RT) + \Delta S/(2.303R)$. A proportionality has been observed between ΔH and ΔS for a wide variety of complexation reactions;[35] as a result, log *K* values are often linearly related to ΔH: $\log K = a\Delta H + b$, and it is possible to predict changes in complex stability from changes in the enthalpy of complexation.

The calculated degree of binding site organization, ΔU_{reorg}, is related to ΔH for complexation. The ΔH can be separated into a negative component reflecting the gain in enthalpy from forming metal ion−donor atom bonds and a positive component reflecting a loss of enthalpy due to unfavorable steric interactions: $\Delta H = \Delta H_{bond} + \Delta U_{reorg}$.[9a] The gain in enthalpy should

(35) (a) Searle, M. S.; Westwell, M. S.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 2* **1995**, 141. (b) Inoue, Y.; Hakushi, T.; Liu, Y. In *Cation Binding by Macorcycles*; Inoue, Y., Gokel, G. W., Eds.; Marcel Dekker: New York, 1990. (b)

be approximately constant for a given metal ion interacting with a fixed number and type of donor atoms under constant conditions (temperature, solvent, ionic strength). Under such conditions, log K should be proportional to ΔU_{reorg}.

It follows that, for a series of ligands with a fixed number and type of donor atoms (**1**−**9**) interacting with a given metal ion, ΔU_{reorg} should be linearly correlated with free energies for metal ion complexation. Stability constant data are not available for metal ion complexes of **1**−**9**, and it is impossible to directly compare theory and experiment**.** But we can demonstrate that calculated differences in binding site organization caused by alkylation of the ethylene bridge correlate closely with measured differences in complex stability caused by alkyl substitution of crown ethers.

The change in logarithm of the association constant going from an unalkylated crown ether to an alkylated analogue, Δ log K, is an experimental measure of the effect of alkylation on complex stability. Compilations of stability constant data for macrocyclic ethers[17] yield Δ log K values for replacing unalkylated ethylene bridges (**1**) in 15-crown-5, benzo-15-crown-5, 18-crown-6, benzo-18-crown-6, and dibenzo-18-crown-6 macrocycles with monoalkyl (**2**), *gem*-dialkyl (**3**), *cis*-cyclohexyl (**8**), and *trans*-cyclohexyl (**9**) substituted ethylene bridges. Enough data are available for Na^+, K^+, Rb^+, and Cs^+ in the same solvent at the same temperature (methanol solvent at 25 °C) to provide consistent thermodynamic data to compare with theory.

On average, introducing monoalkylated ethylene bridges drops log K values by −0.28 (Na), −0.49 (K), −0.45 (Rb), and −0.40 (Cs), and introducing *gem*-dialkylated ethylene bridges drops log K values by −0.26 (Na) and −0.68 (K). Introducing a single *cis*-cyclohexyl group can increase or decrease log K: +0.16 (Na), −0.11 (K), +0.30 (Rb), and −0.38 (Cs). The effect of adding two *cis*-cyclohexyl substituted ethylene bridges depends on stereochemistry. When groups are added in *syn* fashion, the effect is small on log K: −0.24 (Na), −0.10 (K), and +0.03 (Cs); when added in *anti* fashion, the effect is larger: −0.64 (Na), −0.73 (K), and −1.09 (Cs). On average, introducing two *cis*-cyclohexyl substituted ethylene bridges causes a drop in stability: −0.32 (Na), −0.43 (K), −0.46 (Rb), −0.503 (Cs). When two *trans*-cyclohexyl substituents are added, the magnitude of the effect also varies with stereochemistry: *syn* attachment causes a large drop in log K: −1.35 (Na), −1.95 (K), −1.92 (Rb), and −1.70 (Cs); *anti* attachment causes a larger drop: −1.82 (Na), −2.83 (K), −2.61 (Rb), and −2.43 (Cs). On average, introducing two *trans*-cyclohexyl substituted ethylene bridges decreases log K: −1.58 (Na), −2.39 (K), −2.27 (Rb), −2.07 (Cs).

These MM analyses have demonstrated that alkyl substitution on the ethylene bridge alters binding site organization for metal ion complexation. Replacing an unalkylated ethylene bridge in a macrocycle with an alkylated ethylene bridge should correspondingly alter the degree of the macrocycle's organization for metal ion complexation. If we assume that the connecting structure in a macrocyclic ligand behaves like that in the simple bidentate chelates **1**−**9**, a quantitative measure of this change is provided by $\Delta\Delta U_{reorg} = \Delta U_{reorg}$ (alkyl substituted component) − ΔU_{reorg} (**1**). If more than one ethylene bridge is affected, the change in the degree of macrocycle organization is provided by the sum of $\Delta\Delta U_{reorg}$ values over all ethylene bridges that are replaced.

Plots of the average Δ log K vs $\Delta\Delta U_{reorg}$ are shown for Na^+ (Figure 7), K^+ (Figure 8), Rb^+ (Figure 9), and Cs^+ (Figure 10). In each case there is a good correlation between the experimental change in complex stability and the calculated change in

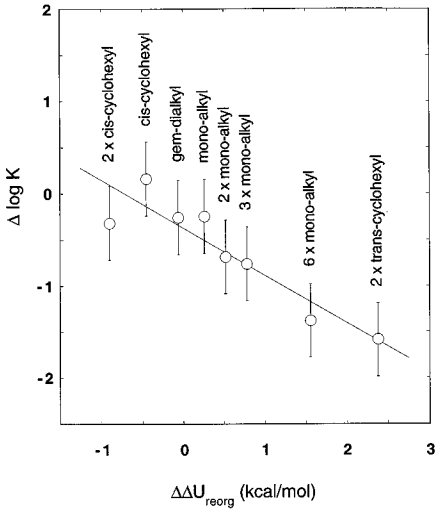


Figure 7. Plot of the change in complex stability, Δ log K, vs the change in binding site organization, $\Delta\Delta U_{reorg}$, for sodium complexes. Error bars reflect a confidence level of $\pm 3\sigma$. Regression line: $\Delta \log K = -0.368 - 0.517\Delta\Delta U_{reorg}$ ($r = 0.922$).

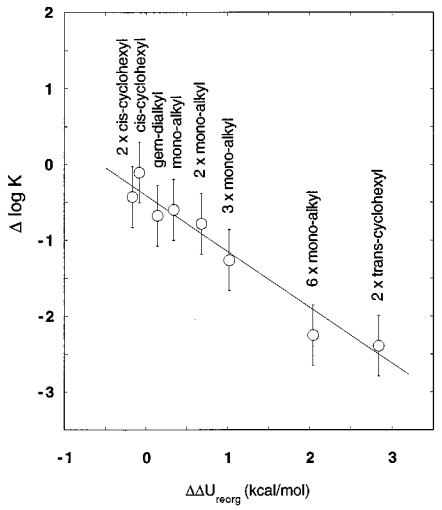


Figure 8. Plot of the change in complex stability, Δ log K, vs the change in binding site organization, $\Delta\Delta U_{reorg}$, for potassium complexes. Error bars reflect a confidence level of $\pm 3\sigma$. Regression line: $\Delta \log K = -0.411 - 0.763\Delta\Delta U_{reorg}$ ($r = 0.974$).

macrocycle organization. Each plot exhibits a near-zero intercept and a negative slope; i.e., the replacement of existing connecting structure with connecting structure of lower binding site organization leads to a decrease in binding constant. These correlations lend further support to the concept that the coordination chemistry of macrocyclic ligands is strongly influenced by the structural requirements of the individual chelate rings within the macrocycle.[13,14] These correlations also demonstrate the utility of the MM approach for predicting the effect of connecting structure on complex stability.

The MM analysis of the binding site organization in simple bidentate chelates provides a fast and convenient method for screening possible connecting structures in multidentate ligand design. There are, however, instances in which this method must be used with caution. The approach assumes that connecting structure in the bidentate chelate will behave similarly when in a multidentate ligand structure. This assumption is most likely to hold with conformationally labile ligands such as acyclic or macrocyclic ligands with larger, more flexible rings. Additional steric constraints in more rigid ligands may invalidate the comparison. The failure of predictions based on the behavior of individual chelate rings has been observed where

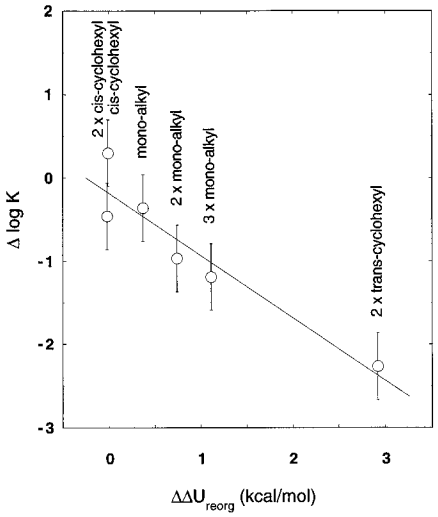


Figure 9. Plot of the change in complex stability, Δ log K, vs the change in binding site organization, $\Delta\Delta U_{reorg}$, for rubidium complexes. Error bars reflect a confidence level of $\pm 3\sigma$. Regression line: $\Delta \log K = -0.184 - 0.750\Delta\Delta U_{reorg}$ ($r = 0.944$).

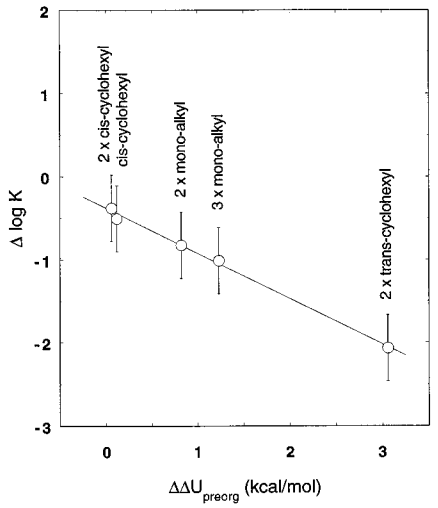


Figure 10. Plot of the change in complex stability, Δ log K, vs the change in binding site organization, $\Delta\Delta U_{reorg}$, for cesium complexes. Error bars reflect a confidence level of $\pm 3\sigma$. Regression line: $\Delta \log K = -0.378 - 0.546\Delta\Delta U_{reorg}$ ($r = 0.998$).

these chelate rings occur in small, conformationally rigid macrocycles.[7,13b,36] And additional steric effects may exist in conformationally labile ligands. For example, although the average influence of *cis* and *trans* dicyclohexyl substitution is correctly predicted (see Figures 7−10), the approach presented here does not predict the differences in complex stability among *syn* and *anti* isomers. It has been demonstrated elsewhere that these differences are correctly accounted for when MM calculations are performed on the entire ligand structure.[11,14]

Given that the organization afforded by a given connecting bridge may vary as a function of overall ligand structure, we can rank the degree of binding site organization (Figure 5) provided by the connecting structures examined in this study as (small +1 cations) **5** > **6** > **8** > **7**, **3** > **4**, **2**, **1** > **9**; (large +1 cations) **5** > **6** > **1**, **8** > **3** > **2**, **4** > **7** > **9**; (small +2 cations) **5** > **6** > **8** > **7** > **2** > **3** > **4** > **1** > **9**; (large +2 cations) **5** > **6** > **8** > **1**, **2**, **3** > **4** > **7** > **9**. The correlations obtained in Figures 7−10 suggest that, to a good approximation, these sequences can be used to predict the effect of alkyl substitution on the relative complex stability for a given metal ion.

Given the relative changes in complex stability for a pair of metal ions, it is also possible to determine the relative change in metal ion selectivity. Comparing the ΔU_{reorg} with ionic radius plots in Figure 5 shows that cases **1**−**9** are structurally more organized to complex larger metal ions. This preference is stronger in some ligands and strongest for **1**; the curve for **1** is steeper than those of the other ligands. This indicates that, for the substitution patterns examined in this study, alkylation of the ethylene bridges in macrocyclic ligands should decrease selectivity for large metal ions. Experimental data are consistent with this prediction. The alkyl substitution of 15- and 18-member rings causes the selectivity (K_M/K_{Na}, methanol, 25 °C) for the larger K^+, Rb^+, and Cs^+ ions over the smaller Na^+ ion to decrease by a factor of 2.4, on average. Alkyl substitution of 18-member rings causes the selectivity (K_{Ba}/K_M, H_2O, 25 °C) for the larger Ba^{2+} ion over the smaller Na^+ and Sr^{2+} ions to decrease, on average, by factors of 3.3 and 2.8, respectively.

IV. Summary

The connecting structure controls the ability of ligand donor atoms to interact with the metal ion. MM calculations on simple bidentate ligands can be used to quantitatively assess the influence of connecting structure on the degree of binding site organization for metal ion complexation. An MM assessment of the effect of alkylation on ethylene-bridged ether donor atoms yields the following criteria for ligand design:

Regardless of alkyl substitution pattern, ethylene-bridged ether donors are structurally organized to bind large, low valent metal ions over small, high valent metal ions. Multidentate ligands that contain ethylene-bridged ether donors thus have an inherent steric preference for complex large, low valent metal ions that results from the geometric requirements of the ethylene connection and will be present independent of cavity size.

Alkyl substitution on the ethylene bridge can significantly change the degree of complementarity for a given metal ion. The magnitude and direction of the change is a function of substituent placement. Axial substitution, as in the *trans*-dialkyl case (**5**), increases complementarity; equatorial substitution, as in the *trans*-cyclohexyl case (**9**), decreases complementarity.

The majority of alkyl substitution patterns decrease binding site organization, causing a drop in complex stability. Exceptions are *d,l*-dialkylation (**5**), trialkylation (**6**), and *cis*-cyclohexyl substitution (**8**). While stability constant data are not available for ligands containing **5** and **6**, ligands containing **8** have been shown to increase complex stability.

Regardless of pattern, alkyl substitution of ethylene bridges decreases selectivity for large cations. Experimental data indicate the decrease is usually less than an order of magnitude.

Acknowledgment. We gratefully acknowledge the support of the Efficient Separations and Processing Integrated Program of the Office of Environmental Restoration and Waste Management's Office of Technology Development of the U.S. Department of Energy. We thank Dr. Brian M. Rapko for a critical review of the manuscript. Pacific Northwest National Laboratory is operated for the U.S. Department of Energy by Battelle under Contract DE-AC06-76RLO 1830.

Supporting Information Available: Modification to MM3 code to add 1,3 van der Waals interactions between two oxygen donor atoms attached to the same metal ion and an example set of MM3 input files (3 pages). Ordering information is given on any current masthead page.

(36) Zhang, D.; Busch, D. H. *Inorg. Chem.* **1994**, *33*, 5138.

IC9514760