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Structural Criteria for the Rational Design of Selective Ligands: Extension of the MM3 Force Field to Aliphatic Ether Complexes of the Alkali and Alkaline Earth Cations

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Abstract: Structural requirements for strain-free metal ion complexation by an aliphatic ether group are investigated through the use of both *ab initio* molecular orbital and molecular mechanics calculations. Hartree–Fock calculations on simple models, M–O(Me)$_2$ and M–O(Me)(Et), reveal a preference for trigonal planar geometry when aliphatic ether oxygens are coordinated to alkali and alkaline earth cations. This preference is found to be strongest in small, high-valent cations and weakest in large, low-valent cations. Results from the Hartree–Fock calculations are used to extend the MM3 force field for calculation on aliphatic ether complexes with the alkali (Li to Cs) and alkaline earth (Mg to Ba) cations. The resulting molecular model (i) reproduces the experimental crystal structures of 51 different complexes of multidentate ethers with alkali and alkaline earth cations, (ii) explains experimental trends in the structure of five-membered chelate rings of aliphatic ethers, (iii) reveals a fundamental difference between the metal ion size selectivity of five-membered chelate rings of ethers versus that of amines, and (iv) rationalizes trends in the stability of four potassium complexes with the diasteriomers of dicyclohexyl-18-crown-6. Two structural requirements for strain-free metal ion complexation, M–O length and oxygen orientation, are identified and quantified. It is demonstrated that the degree to which ligand structure can satisfy the trigonal planar geometry preference of the coordinated ether oxygens can have a greater affect on complex stability than the ability of the ligand to satisfy M–O length preferences.

I. Introduction

The remarkable ability of macrocyclic ethers to selectively complex metal cations is a topic of fundamental interest in coordination chemistry. A large number of macrocyclic ethers have been synthesized, and the stabilities of many of their metal complexes have been determined.[1-8] The structures of such ligands and their complexes have also been studied extensively in the solid state,[3,9] in solution,[10] and through the application of molecular models.[11-13] However, although a large body of data has been accumulated, factors that control metal ion recognition remain incompletely understood. These factors include the solvation of the cation and the ligand, number and type of donor atoms, and the ligand structure.[1-8] In this paper, we focus on the influence of ligand structure on the stability of multidentate, aliphatic ether complexes with the alkali and alkaline earth cations.

A key goal in ligand design is to attain a high degree of metal ion selectivity. To achieve this goal, the ligand must complex the target metal ion more strongly than the other metal ions in the system. From a structural point of view, the highest possible complex stability that can be obtained with any given group of donor atoms will be obtained when each donor atom in the ligand is spatially arranged to perfectly satisfy the structural requirements of metal ion–donor group interactions.[14] Failure to satisfy these requirements destabilizes the complex. Thus, the design

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of selectivity through the manipulation of structure involves tailoring the ligand to achieve a good fit to the target ion and a poor fit to other metal ions. It is obvious that success in the rational *a priori* design of selective multidentate ligands will depend largely on understanding the structural requirements of the metal ion–donor group interactions.

It is widely accepted that the only important structural requirement for the ideal metal ion–ether donor group interaction is attainment of the preferred M–O length. The structural design of multidentate ethers for metal ion discrimination among the alkali and alkaline earth cations has been based on achieving a match between the size of the ligand cavity and the size of the cation.[1–8] This concept is also prevalent in most molecular modeling studies on macrocyclic ether complexes[12] in which metal-dependent potential function parameters have been derived by fitting them only to the M–O lengths and interaction energies in simple models, e.g. M–O(Me)$_2$ or M(OH$_2$)$_6$.

In early studies, crown ether macrocycles were varied to attempt to attain metal ion selectivity on the basis of cavity size. This approach was not entirely successful.[15] Deviations from predicted size-match selectivity behavior for crown ethers have been attributed to differences in cation solvation and/or to flexibility that allows the ligand to achieve optimum M–O lengths with more than one metal ion.[14,16] Observed metal ion selectivities of cryptands, which possess a more conformationally organized spherical cavity than the flexible planar cavities of crown ethers, do show a strong correlation between the size of the cation and the size of the cavity.[7] Further metal ion selectivity enhancements have been obtained for ligands with conformationally rigid cavities, e.g. spherands. This enhanced selectivity has been attributed to the fact that a rigid cavity can accommodate only a very narrow range of M–O lengths.[8]

Thus, the control of cavity size, i.e. M–O length, has served as the main basis for designing metal ion selective multidentate ethers for the past two decades. The current criteria for the structural design of selective ligands for the alkali and alkaline earth cations is a very rigid cavity with the correct radius for the target metal ion. The rationale for these criteria is that size-based selectivity will be obtained because cations that are too small cannot simultaneously contact all the donor atoms, and attempts to bind cations that are too large cause the development of severe steric strain within the complex.

The possibility of additional structural requirements for ideal metal ion–ether interaction has been largely ignored, perhaps because it has often been possible to rationalize observed selectivity patterns in terms of either cavity size alone or some combination of cavity size, conformational flexibility, and solvation. One such additional requirement is the directional preference of the ether coordination sites. It has been noted that the selectivity patterns of some crown ethers are better explained in terms of chelate ring size rather than macrocycle cavity size,[14] implying the presence of a preferred geometry at the oxygen atom. In a survey of crystallographic data,[17] it was observed that ether oxygen donor groups appear to have preferred geometry preferences when coordinated with alkali and alkaline earth cations. While there was a definite tendency for lithium to lie within the C–O–C plane of an aliphatic ether donor (i.e. trigonal planar oxygen), unambiguous assignments of coordinated oxygen geometry preferences were not possible for the other cations. More recently, the geometry preferences of the coordinated ether oxygen and their impact on complex stability have been considered in molecular mechanics studies.

It has been postulated that the sp^3 oxygens of ethers and alcohols prefer a tetrahedral geometry when coordinated to a metal ion; i.e., there is a steric preference for an M–O–C angle of 109.5°.[13b,18] The consequences of a tetrahedral, neutral oxygen donor have been discussed with respect to steric strain and chelate ring size.[18a,b] It was concluded that with tetrahedral M–O–C angles, five-membered aliphatic ether chelate rings would exhibit a steric preference to complex a metal ion roughly the size of sodium (an M–O length of $\sim$2.5 Å), and six-membered aliphatic ether chelate rings would exhibit a steric preference to bind smaller metal ions.[18a] The putative preference for tetrahedral oxygen geometry has been shown to be consistent with the experimental metal ion size selectivity of five- and six-membered chelate rings of aromatic bidentate alcohols.[18b]

The nature of the geometry preference for coordination of the ether oxygen to the potassium ion has been clarified in a more recent study.[19] *Ab initio* molecular orbital calculations on the simple models K–O(Me)$_2$ and K–O(Me)(Et) revealed a significant preference for trigonal planar, rather than tetrahedral, oxygen coordination. The ether oxygen geometry preferences were incorporated in the MM2 force field, which was then used to examine the structure and steric strain in a series of 11 hexadentate aliphatic crown ethers and their potassium complexes. The calculated increase in strain energy on the complexation of potassium (range from 6.6 to 16.8 kcal/mol) correlated well with experimental stability constants (log *K* range from 1.7 to 6.1) to yield the first structure–stability relationship that quantitatively accounts for the affect of alkyl substitution on complex stability. It was concluded that it is necessary to consider both M–O length preference and the oxygen geometry preference to understand the relationship between structure and stability.

In the present study, we have continued to investigate the structural requirements for strain-free metal ion complexation by aliphatic ethers. In what follows, we present the development and validation of an extended MM3 force field for aliphatic ether complexes of the alkali (Li to Cs) and alkaline earth (Mg to Ba) cations. Both oxygen geometry preference and M–O length preference are examined as a function of metal ion size and charge. The relative importance of these structural preferences are discussed with respect to the design of ligand structure.

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II. Development of the Molecular Model

1. Hardware and Software. All molecular mechanics (MM) calculations were carried out using the MM3 program[20] with the augmented force field described in this work. *Ab initio* quantum calculations were performed with the *Gaussian 90* program.[21] Both MM and quantum calculations were performed on a Sun SparcII workstation. The molecular graphics program Chem3D Plus[22] was used on a MacIntosh IIci personal computer to build initial sets of molecular coordinates for MM3 and *Gaussian 90*, to plot energy-minimized molecular coordinates obtained from the calculations, and to plot crystal structure data from the Cambridge Crystallographic Database.[23]

2. Potential Functions. Although originally designed to model organic compounds and transition metal complexes with simple metal geometries, the MM3 program can readily be applied to model the more varied geometries found in ether complexes of the alkali and alkaline earth metal ions. No modification to the code is necessary. This application excludes several potential functions that would otherwise be present in purely organic structures and changes the way the potential functions are assigned at the metal ion center. These changes, which affect the number and type of interactions that are present in the MM calculation, are discussed in this section. Alterations to the organic, or metal-independent, MM3 parameter set are discussed in Section 3, and the development of the additional metal-dependent force field parameters is presented in Sections 4 and 5.

With two exceptions, the default MM3 potential functions are used to describe all interactions. The exceptions are the stretch–bend and bend–bend terms that involve angles subtended at the ether oxygen. When present, these terms yield unrealistically large stretch–bend energies and bend–bend energies due to the high variability in M–O length and M–O–C bond angle. In our previous work with MM2,[19] it was necessary to exclude all stretch–bend terms to remove the few undesirable ones. With MM3, it is possible to selectively remove only those stretch–bend terms that involve angles subtended at oxygen. However, it is necessary to exclude all bend–bend interactions to remove those involving oxygen. Thus, for all calculations described in this work, the input files were altered to zero stretch–bend terms at oxygen and to zero all bend–bend terms.

Interactions involving the metal ion were handled with the points-on-a-sphere approach.[24] This approach entails the replacement of all O–M–O bond angle terms with 1,3 van der Waals interactions between ligated oxygens, the neglect of torsional interactions about M–O bonds, and the neglect of all nonbonded interactions (both van der Waals and electrostatic) that involve the metal ion. With this approach, only five new types of interaction are added to the force field for each metal ion. These are the M–O stretch, M–O–C bend, oxygen out-of-plane bend, M–O–C–H torsion, and M–O–C–C torsion. With one exception, these interactions are treated with the same potential functions that were used for corresponding organic interactions.

The exception is the oxygen out-of-plane bending interaction. The standard MM3 out-of-plane bending function, intended for use with sp^2 carbon and nitrogen atoms, proved to be too stiff for this application. We therefore adopted the following alternative. A dummy atom, D, is attached to each coordinated oxygen atom such that the M–O–D and C–O–D angles are ≤90°. Parameters are chosen for the dummy atom such that the only contribution to the strain energy total comes from M–O–D and C–O–D bending interactions. An energetic preference for the metal ion to lie in the plane defined by the C–O–C group is achieved by assigning a strain-free value of 90° to the M–O–D and C–O–D angles.

All options described above for assigning potential functions to interactions that involve a metal ion were specified in standard MM3 input files using methods reported elsewhere.[25] Example input files are available as supplementary material.

3. Metal-Independent Parameters. As in other applications of molecular mechanics to coordination compounds,[24] we adopted the assumption that force field parameters used for modeling the various interactions in ethers are transferable to the ether portion of a metal complex. Moreover, we assume these parameters to be independent of the identity of the metal ion. In the current application of MM3 (see Section 2 above), the term metal-independent refers to the parameters that are used for interactions that involve C (atom type 1), H (atom type 5), and O (atom type 6). These include C–H, C–C, and C–O stretches; H–C–H, C–C–H, O–C–H, C–C–C, C–C–O, and C–O–C bends; stretch–bends at carbon; H–C–C–H, H–C–C–C, H–C–C–O, H–C–O–C, C–C–C–C, C–C–C–O, and C–C–O–C torsions; C–C and C–O torsion–stretches; C–O dipole–dipole interactions; and H- -H, H- -C, H- -O, C- -C, C- -O, and O- -O van der Waals interactions. With only two exceptions, detailed below, the default MM3 parameters (1992 Version) were applied to all of these interactions.

The first exception is the electronegativity correction that is used to obtain a shorter strain-free length for the C–C bond when an oxygen atom is attached to each carbon atom. In this situation, the default MM3 parameter, $\Delta l_e = -0.007$ Å, gives a strain-free C–C bond length of 1.513 Å. Use of this value yields calculated lengths that are significantly longer than the average experimental value of 1.49 ± 0.03 Å found in metal complexes (see Table 3 below). To compensate for this, we have decreased the value of the parameter Δl_e to −0.020 Å, which gives a strain-free value of 1.493 Å.

The second exception is the set of parameters for the O–C–C–O torsion interaction. The default MM3 parameters, $V_1 = 1.00$, $V_2 = -2.00$, and $V_3 = 0.30$ kcal/mol, gave poor agreement between experimental and calculated O–C–C–O torsion angles. Improved performance was obtained when these parameters were replaced with the values that were used in our earlier work, $V_1 = 3.36$, $V_2 = -4.82$, and $V_3 = 3.84$ kcal/mol.[19] To avoid confusion elsewhere in the text, we will use MM3′ to refer to calculations performed with these modifications to the MM3 force field.

The effect of these two alterations to the organic parameter set, plus the exclusion of stretch–bends at oxygen and bend–bends at all atom centers (see Section 2 above), was evaluated by checking calculated structures and, where data were available, by the conformational equilibria of simple ethers including dimethyl ether, ethyl methyl ether, diethyl ether, methyl isopropyl ether, and diisopropyl ether. Comparison with reported MM3 force field calculations[26] showed that our changes to the force field do not significantly alter the results in these cases. For 1,2-dimethoxyethane, we calculate the *tgt* conformation to be lower in energy than the *ttt* conformation by 0.54 kcal/mol, which is in agreement with experimental data that indicate a gauche preference of 0.4 kcal/mol in the gas phase[27] (default MM3 parameters yield a slight trans preference of 0.05 kcal/mol).[26]

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Table 1. Comparison of Experimental versus Calculated (Parentheses) Structural Features of Metal-Free Aliphatic Crown Ethers[a]

ligand	C–C	C–O	bite[b]	C–O–C	C–C–O	O–C–C–O	C–O–C–C_a	C–O–C–C_g
1	2.50 (2.51)	1.42 (1.43)	2.99 (2.95)	113 (114)	109 (109)	75 (76)	157 (160)	94 (96)
2	2.51 (2.51)	1.43 (1.43)	2.93 (2.91)	112 (114)	111 (110)	66 (70)	167 (170)	85 (86)
3	2.51 (2.51)	1.43 (1.43)	2.94 (2.91)	111 (114)	112 (110)	68 (69)	167 (170)	83 (85)
4	2.52 (2.51)	1.43 (1.43)	2.85 (2.86)	115 (115)	110 (109)	65 (66)	175 (173)	92 (97)
5	2.52 (2.51)	1.43 (1.43)	2.82 (2.83)	115 (115)	110 (109)	57 (60)	167 (168)	64 (64)
6	2.51 (2.50)	1.43 (1.43)	2.93 (2.93)	113 (114)	109 (109)	70 (73)	167 (173)	80 (75)

[a] Values represent average bond lengths (Å), bond angles (deg), and torsion angles (deg) in the macrocyclic rings and do not include contributions from alkyl substituents. The C–O–C–C torsion angles are differentiated with a subscript *a* (anti) or *g* (gauche). [b] Average distance (Å) between oxygens within O–CH_2–CH_2–O groups.

Table 2. Metal-Dependent MM3 Parameter Set[a]

	M–O stretch		M–O–C bend		M–O–D and C–O–D bends		M–O–C–H torsion			M–O–C–C torsion		
metal ion	r_0	K_r	θ_0	K_θ	θ_0	K_θ	V_1	V_2	V_3	V_1	V_2	V_3
Li^+	2.050	0.290	123.5	0.170	90.0	0.183	0.000	0.000	0.127	–2.900	1.100	0.537
Na^+	2.380	0.210	123.5	0.140	90.0	0.118	0.000	0.000	0.075	–1.625	0.950	0.383
K^+	2.750	0.170	123.5	0.120	90.0	0.079	0.000	0.000	0.060	–1.100	0.880	0.200
Rb^+	2.920	0.135	123.5	0.110	90.0	0.074	0.000	0.000	0.049	–1.000	0.720	0.254
Cs^+	3.100	0.125	123.5	0.104	90.0	0.066	0.000	0.000	0.045	–1.000	0.700	0.165
Mg^{2+}	2.047	0.579	123.5	0.246	90.0	0.430	0.000	0.000	0.334	–6.439	1.617	2.204
Ca^{2+}	2.400	0.430	123.5	0.210	90.0	0.294	0.000	0.000	0.194	–4.650	1.375	1.275
Sr^{2+}	2.580	0.340	123.5	0.195	90.0	0.220	0.000	0.000	0.167	–3.327	1.227	1.023
Ba^{2+}	2.830	0.290	123.5	0.181	90.0	0.198	0.000	0.000	0.137	–2.991	1.174	0.764

[a] Parameters are given in standard MM3 units as follows: r_0, Å; K_r, mdyn/Å; θ_0, deg; K_θ, mdyn·Å/rad^2; V_i kcal/mol.

MM3′ was further tested by examining metal-free aliphatic crown ethers for which crystallographic data are available,[28] **1**–**6**. The results are summarized in Table 1. Structural features of these ligands were accurately reproduced (bond length root mean squared deviation = ±0.005 Å, bond angle root mean squared deviation = 1.0°, and torsion angle root mean squared deviation = 2.5°).

4. Parameters for Metal-Dependent Bends and Torsions. After the fact that MM3′ yielded satisfactory results for aliphatic ethers was verified, it was necessary to develop parameters for the interactions that involve the metal ions (atom type 54) and dummy atoms (atom type 11). There are the M–O stretch, the M–O–C bend, the oxygen out-of-plane interaction (M–O–D and C–O–D bends), the M–O–C–H torsion, and the M–O–C–C torsion. These interactions can be divided into two groups, an M–O stretch interaction that establishes a preferred distance from the ether oxygen to the metal ion and the other four interactions that establish the preferred orientation of the ether group relative to the metal ion. These two groups of interactions were parametrized by different methods. Parametrization of the interactions that dictate ether group orientation is described in this section.

Where possible, the parameters for the metal-dependent bends and torsions were determined through the use of *ab initio* calculations. Hartree–Fock calculations with the STO-3G basis set were performed to determine optimized geometries and potential surfaces for selected distortions in the simple molecular fragments M–$O(Me)_2$ and M–O(Me)(Et), where M = Li, Na, K, Rb, Mg, Ca, and Sr. For these calculations, the M–O bond lengths were constrained to the average distance found in crystallographic data (see Table 3 below). We felt this level of theory to be adequate for the current application because the goal was to obtain relative potential energy surfaces rather than absolute energies.[28] Because no electron pairs are disturbed during the distortions, the associated energy error is expected to be approximately constant over the range of the distortion.

Using methods described in detail elsewhere,[19] selected structural distortions of M–$O(Me)_2$ and M–O(Me)(Et) were performed to yield potential energy surfaces. The metal-dependent bend force constants and torsion parameters were then optimized by fitting MM3′-generated potential surfaces to the *ab initio* generated ones. Because of a lack of basis sets, an alternate method was employed to determine the metal-dependent bend and torsion parameters for Cs and Ba. Plots of the parameters already determined for the other metal ions revealed definite trends when plotted against the charge-to-size ratio for the cation.[30] Values for Cs and Ba were interpolated from these plots. The resulting set of parameters is presented in Table 2.

Changes in the experimental structure of the O–CH_2–CH_2–O chelate were used as a basis to check the performance of the metal-dependent bend and torsion parameters. The Cambridge Crystallographic Database was searched to determine the average structural features in the O–CH_2–CH_2–O chelate ring as a function of metal ion for Li to Cs and Mg to Ba. This search, constrained to structures with R-factors of less than 7%, yielded the following results: metal ion (number of fragments located), Li (142), Na (237), K (397), Rb (27), Cs (29), Mg (13), Ca (52), Sr (48), Ba (117). For each metal ion, average values and their root mean squared deviations were determined for M–O, C–O, and C–C lengths, the chelate bite (O- -O distance), the O–M–O, M–O–C, and O–C–C angles, and the M–O–C–C and O–C–C–O torsion angles. These results, summarized in Table 3, reveal the changes in chelate ring structure that occur as the metal ion is varied.

For each metal ion, MM3′ energy minimizations were performed for the simple fragment, M(1,2-dimethoxyethane). During these calculations, M–O lengths were constrained to the average values given in Table 3. Calculated bond lengths, bond angles, and torsional angles for M(1,2-dimethoxyethane) are compared with the average values obtained for the O–CH_2–CH_2–O chelate ring in crystal structures (Table 3).

5. M–O Stretch Parameters. The M–O stretch parameters were developed only after all other parameters had been assigned. This development was accomplished through an iterative process in which the strain-free length, r_0, and the force constant, K_r,

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(28) (a) Schaeffer, H. F. *Modern Theoretical Chemistry*; Plenum: New York, 1977; Vol. 3. (b) Carsky, P.; Urban, M. *Ab initio Calculations. Lecture Notes in Chemistry*; Springer-Verlag: New York, 1980; Vol. 16.

(29) Cambridge Crystallographic Database[23] reference codes for these structures are as follows: **1**, TOXCDP; **2**, FUNTAJ; **3**, JEMWED; **4**, GEFJOQ; **5**, GEFJIK; **6**, HOXOCD.

(30) (a) Charge-to-size ratios calculated using Shannon's ionic radii[30b] for coordination number six were as follows: Li, 1.316 Å^{-1}; Na, 0.980 Å^{-1}; K, 0.725 Å^{-1}; Rb, 0.658 Å^{-1}; Cs, 0.599 Å^{-1}; Mg, 2.788 Å^{-1}; Ca, 2.000 Å^{-1}; Sr, 1.695 Å^{-1}; Ba, 1.481 Å^{-1}; Ra, 1.408 Å^{-1}. (b) Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751.

Table 3. Experimental versus Calculated Structural Features of O–CH_2–CH_2–O Chelate Rings[a]

cation		M–O	O–C	C–C	bite[b]	O–M–O	M–O–C	O–C–C	M–O–C–C	O–C–C–O
Li	exp	2.26(0.05)	1.43(0.02)	1.50(0.03)	2.72(0.05)	74(4)	111(2)	108(1)	42(3)	57(4)
	calc		1.43	1.50	2.68	73	114	108	41	54
Na	exp	2.52(0.13)	1.42(0.02)	1.49(0.04)	2.75(0.05)	66(3)	112(2)	109(2)	45(3)	61(5)
	calc		1.43	1.50	2.76	66	115	109	44	58
K	exp	2.83(0.06)	1.42(0.02)	1.48(0.04)	2.81(0.05)	59(2)	114(3)	109(2)	48(3)	65(4)
	calc		1.43	1.50	2.82	60	116	109	47	62
Rb	exp	2.95(0.05)	1.42(0.02)	1.48(0.02)	2.85(0.05)	59(2)	113(1)	110(2)	48(2)	66(3)
	calc		1.43	1.50	2.84	58	116	110	48	63
Cs	exp	3.19(0.13)	1.42(0.01)	1.48(0.02)	2.87(0.04)	54(3)	113(2)	110(1)	48(2)	68(4)
	calc		1.43	1.50	2.86	53	118	110	49	65
Mg	exp	2.22(0.05)	1.43(0.01)	1.50(0.01)	2.61(0.05)	72(2)	115(1)	106(1)	43(2)	54(4)
	calc		1.43	1.50	2.63	73	115	107	40	51
Ca	exp	2.51(0.05)	1.44(0.02)	1.49(0.05)	2.69(0.04)	65(2)	116(2)	108(3)	44(4)	56(5)
	calc		1.43	1.50	2.72	65	117	109	42	54
Sr	exp	2.68(0.05)	1.43(0.02)	1.48(0.04)	2.75(0.03)	62(2)	116(1)	109(2)	44(5)	57(6)
	calc		1.43	1.50	2.75	62	117	109	44	57
Ba	exp	2.87(0.05)	1.43(0.02)	1.49(0.03)	2.78(0.05)	58(2)	116(2)	109(2)	46(4)	60(6)
	calc		1.43	1.50	2.79	58	118	109	46	59

[a] Average experimental values for selected structural features (root mean squared deviations in parentheses). Calculated values obtained from MM3′ calculations on M(1,2-dimethoxyethane) with M–O lengths fixed at observed values. Lengths are given in Å. Angles are given in degrees. [b] Bite is the distance between oxygen atoms.

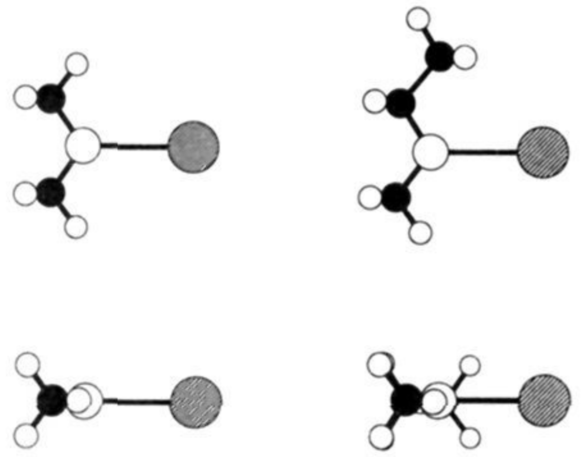

Figure 1. Representative geometry-optimized Hartree–Fock STO-3G structures obtained for M–O$(Me)_2$ and M–O(Me)(Et).

were manually adjusted to give the best overall agreement between MM3′-calculated M–O lengths and the M–O lengths that occur in the crystal structures. Final calculations on these structures served to validate the performance of the entire MM3′ force field. A total of 65 crystal structures,[31] representing 51 different complexes of multidentate aliphatic ethers with the alkali and alkaline earth cations, **7**–**57** (Chart 1), were examined.

In the solid state, many of these complexes have other types of ligands bound to the metal ion in addition to the multidentate aliphatic ether. These extra ligands can influence the ether–metal ion structure by causing steric crowding in the inner coordination sphere. This influence is strongest for small metal ions in which short M–L lengths hold the extra ligands close to the ether but becomes negligible for the larger metal ions. To a good approximation, the effect of the additional ligation can be modeled by simply including the donor atom of each extra ligand. Such ligand donor atoms, where L = O, N, F, or Cl, were attached to the metal ion with fixed bond lengths corresponding to the observed M–L lengths in the crystal structures. These L atoms were allowed to interact with the rest of the complex through van der Waals interactions alone. Default MM3 van der Waals parameters were used for these interactions.

Input coordinates for these calculations were prepared as follows. Atomic coordinates were read into Chem3D Plus from the Cambridge Structural Database. Dummy atoms were added to each coordinated ether oxygen. When absent, hydrogen atoms were added using the "rectify" feature of Chem3D Plus. When present, non-ether ligand types were reduced to ligand donor atoms. For each metal ion, a series of MM3′ calculations was performed on each complex over a range of strain-free lengths, r_o. For each strain-free length, the stretching force constant, k_r, was varied, and the calculated structures were compared with the experimental data. The resulting set of M–O stretch parameters is presented in Table 2.

The structures calculated with the final parameter set (Table 2) were compared with the crystal structures for **7**–**57** to assess the performance of the model. The average experimental and calculated structural features are summarized for each case in Table 4. A measure of the overall accuracy of the model is given by the deviation between average experimental and calculated structural features: feature, root mean squared deviation; M–O, ±0.03 Å; bite, ±0.04 Å; M–O–C, ±2°; O–M–O, ±1°; C–O–C, ±2°; C–C–O, ±2°; M–O–C–C, ±3°; O–C–C–O, ±3°; C–O–C–C_a, ±5°; and C–O–C–C_g, ±6°. Although the calculations were performed on isolated complexes with single-atom representations for non-ether ligands, the overall level of agreement establishes that the model reproduces the solid-state geometries reasonably well and that it can be used to predict the structure of multidentate ether complexes.

III. Results and Discussion

1. Preferred Ether Orientation. Figure 1 illustrates representative geometry-optimized *ab initio* structures obtained for M–O$(Me)_2$ and M–O(Me)(Et). For all metal ions that were investigated, minimum-energy configurations are obtained with the metal ion located in the plane of the C–O–C group. These results establish that, on coordination with an alkali or alkaline earth cation, the ether oxygen prefers to adopt a trigonal planar geometry. Distortion from this planar configuration results in a significant increase in energy or, in molecular mechanics terms, a significant increase in steric strain. The magnitude of this strain is dependent on the size and charge of the metal ion.

The nature of this dependency can be illustrated by comparing potential surfaces for the movement of the different metal ions out of the C–O–C plane in M–O$(Me)_2$. These distortions were constrained such that a projection of the M–O bond onto the

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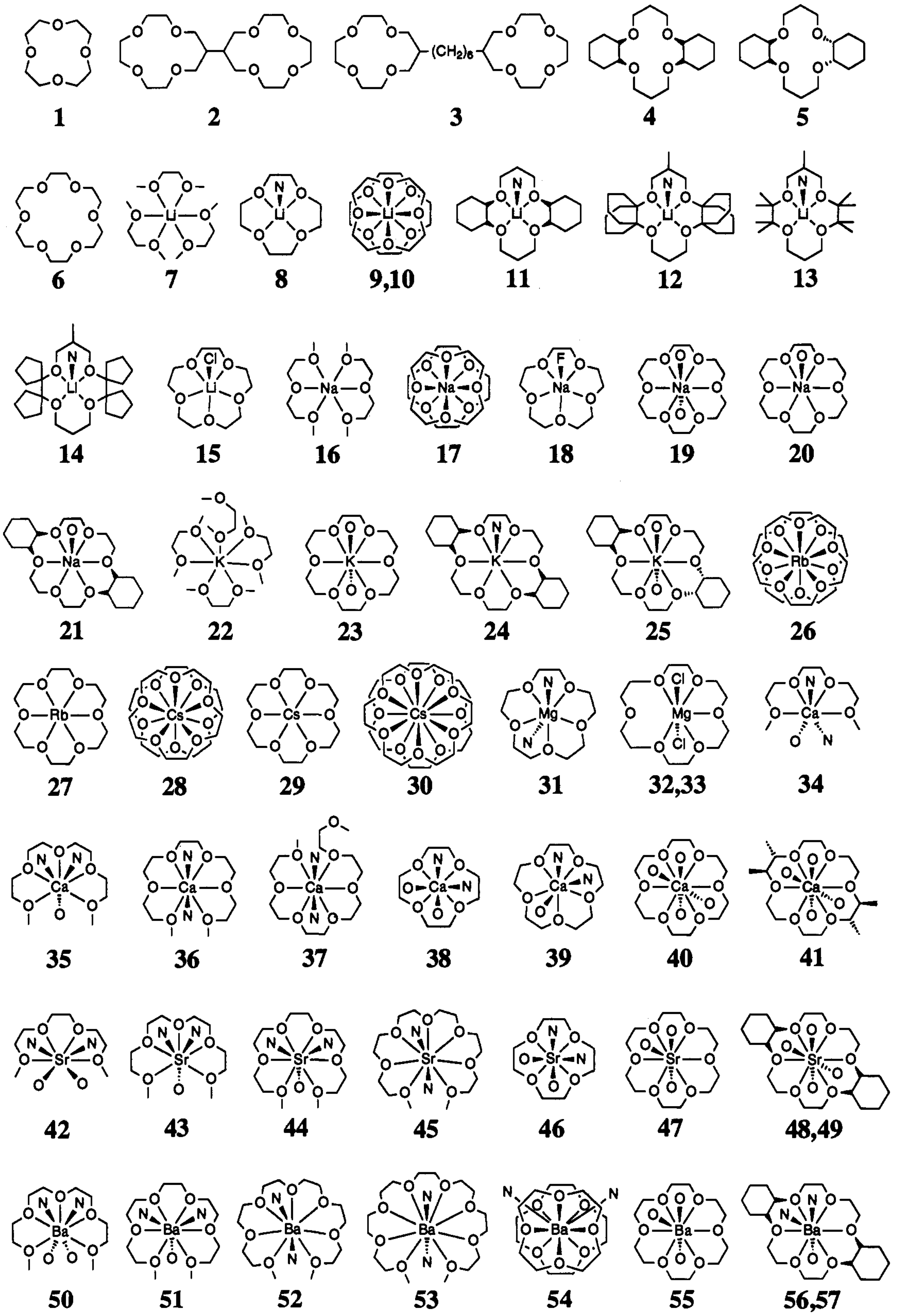
(31) (a) Where available, Chambridge Crystallographic Database[23] reference codes for these structures are as follows: **7**, GIMWEE; **8**, BARVOF, CEMVIZ, DUWYOJ; **9**, DUGYUZ; **10**, CEVMUL, FALGAA; **11**, GEFJUW; **15**, FUVFUX; **16**, VAHWEG; **17**, FOPPOP, GARLIU; **18**, SEHHAO, VAJZAH; **19**, FEJBAX; **20**, NATHOD; **21**, GANZOK; **22**, KIVZOE; **23**, DECDUC, DEJWOE, DIKXEA; **24**, COXCUN; **25**, GANZIE, DIJLAJ (axial ligands I); **26**, **FABMIA**, JEPMIA; **27**, JAPVOL, KIZWAR; **28**, JEPMEW, TAGFEM; **29**, SOJVUI; **30**, FABMAW, FUJCUI; **31**, FUYCOR; **32**, FIYXUG; **33**, KEGXOJ; **34**, FIXKUS; **35**, FIXKEC; **36**, FITFAP; **37**, FUJBAN; **38**, FUYCUX; **39**, FUYCIL; **40**, FEWGAP; **41**, DUJJOH; **42**, FIXLAZ; **43**, FIXKIG; **44**, FITFET; **45**, FUJBER; **46**, FUYDAE; **47**, FIBFUR; **48**, CUBNIW; **49**, VUYXUI; **50**, FIXKOM; **51**, FITFIX; **52**, CIRVII; **53**, FIXKAY; **54**, FUYDEI; **55**, DAZWEZ; **56**, BACYHC; **57**, VUYYAP. (B) Structural data for **12**–**14** were provided by Dr. Richard A. Sachleben and Dr. John H. Burns, Oak Ridge National Laboratory, Oak Ridge, TN.

Chart 1



C–O–C plane bisected the C–O–C angle. The energy for this out-of-plane distortion was obtained (using MM3′) as a function of the angle Ψ formed between the M–O bond and the C–O–C plane (i.e the equilibrium geometry has a Ψ angle of 0°). Plots of energy versus the angle Ψ presented in Figure 2 reveal (i) the divalent cations have a stronger preference to remain in a planar configuration than the monovalent cations and, (ii) for a given charge, the preference becomes progressively weaker as the bond length becomes longer. The amount of distortion required to yield 1 kcal/mol of strain is as follows: metal ion, Ψ (deg); Mg, 23; Ca, 24.5; Sr, 28.5; Ba, 29; Li, 30; Na, 33.5; K, 39; Rb, 39.5; Cs, 41.

Some direct experimental evidence for the preferred planar orientation is available from complexes that have unidentate ether ligands coordinated to the metal ion. For example, in the $(THF)_2$-(18-crown-6) complex of sodium (**19**) the C–O–C planes of the

Table 4. Comparison of Experimental versus Calculated (Parentheses) Structural Features of Aliphatic Ether Complexes with the Alkali and Alkaline Earth Cations[a]

complex	M–O	bite[b]	M–O–C	O–M–O[c]	C–O–C	C–C–O	M–O–C–C	O–C–C–O	C–O–C–C_a	C–O–C–C_g
7	2.12 (2.22)	2.67 (2.67)	120 (120)	78 (74)	112 (113)	111 (108)	37 (41)	50 (53)	177 (164)	
8	2.17 (2.25)	2.70 (2.62)	110 (115)	77 (72)	114 (117)	108 (107)	41 (42)	55 (53)	165 (172)	
9	2.37 (2.36)	2.76 (2.64)	112 (112)	71 (68)	114 (116)	109 (107)	43 (42)	58 (53)	166 (172)	81 (89)
10	2.37 (2.35)	2.77 (2.64)	112 (116)	71 (68)	114 (116)	109 (107)	43 (42)	58 (53)	165 (171)	81 (89)
11	2.02 (1.97)	2.63 (2.62)	115 (117)	86 (90)	115 (119)	107 (108)	42 (42)	55 (54)	174 (172)	
12	2.04 (2.06)	2.56 (2.61)	116 (116)	84 (85)	117 (120)	109 (109)	41 (40)	51 (51)	171 (167)	
13	2.02 (2.05)	2.53 (2.60)	116 (117)	84 (85)	117 (120)	107 (108)	44 (40)	73 (68)	168 (165)	
14	2.03 (2.06)	2.55 (2.60)	115 (116)	84 (85)	119 (121)	105 (108)	44 (40)	74 (72)	167 (165)	
15	2.23 (2.22)	2.59 (2.60)	115 (116)	71 (72)	118 (117)	110 (107)	34 (41)	45 (51)	168 (169)	
16	2.37 (2.41)	2.71 (2.72)	116 (118)	70 (69)	114 (114)	109 (108)	44 (44)	59 (58)	177 (173)	
17	2.49 (2.49)	2.80 (2.72)	112 (115)	59 (57)	114 (116)	110 (108)	43 (44)	59 (57)	164 (169)	80 (84)
18	2.45 (2.37)	2.74 (2.69)	111 (114)	59 (57)	114 (117)	108 (107)	43 (44)	61 (57)	171 (173)	88 (95)
19	2.76 (2.73)	2.78 (2.73)	117 (119)	60 (60)	112 (113)	109 (108)	48 (47)	63 (59)	177 (172)	
20	2.55 (2.58)	2.76 (2.72)	114 (116)	66 (64)	113 (115)	109 (109)	43 (45)	57 (58)	173 (176)	74 (85)
21	2.55 (2.58)	2.76 (2.72)	115 (116)	63 (63)	114 (115)	108 (108)	45 (46)	59 (58)	168 (170)	76 (82)
22	2.76 (2.76)	2.76 (2.81)	117 (119)	60 (61)	114 (112)	112 (109)	49 (48)	64 (62)	172 (169)	
23	2.80 (2.79)	2.82 (2.80)	114 (116)	61 (60)	113 (113)	109 (109)	49 (48)	66 (63)	177 (175)	
24	2.79 (2.80)	2.77 (2.77)	116 (116)	60 (60)	116 (115)	112 (108)	44 (47)	59 (61)	175 (171)	
25	2.81 (2.79)	2.82 (2.80)	114 (116)	60 (60)	113 (115)	108 (108)	49 (48)	66 (63)	172 (173)	
26	3.00 (3.00)	2.86 (2.81)	114 (116)	57 (56)	113 (115)	112 (109)	43 (48)	69 (62)	164 (171)	81 (83)
27	2.98 (2.92)	2.83 (2.82)	113 (115)	57 (58)	112 (113)	109 (109)	48 (48)	66 (64)	176 (174)	
28	3.12 (3.10)	2.87 (2.84)	114 (116)	55 (54)	110 (115)	111 (109)	44 (48)	67 (64)	169 (171)	81 (83)
29	3.13 (3.07)	2.83 (2.84)	111 (115)	54 (55)	112 (114)	109 (109)	47 (48)	66 (64)	176 (172)	
30	3.34 (3.32)	2.87 (2.85)	115 (117)	51 (51)	113 (113)	111 (110)	47 (49)	65 (65)	175 (173)	81 (79)
31	2.18 (2.16)	2.57 (2.54)	117 (118)	72 (73)	118 (118)	110 (106)	34 (39)	43 (46)	168 (164)	
32	2.25 (2.36)	2.61 (2.56)	117 (122)	72 (73)	114 (114)	109 (107)	42 (42)	59 (55)	174 (158)	
33	2.27 (2.30)	2.62 (2.57)	117 (121)	72 (73)	113 (114)	108 (108)	47 (45)	61 (59)	173 (163)	
34	2.45 (2.48)	2.67 (2.67)	118 (120)	66 (65)	114 (114)	110 (108)	40 (42)	51 (53)	168 (165)	
35	2.49 (2.51)	2.71 (2.67)	118 (120)	66 (64)	113 (114)	111 (108)	38 (42)	50 (53)	165 (165)	
36	2.50 (2.52)	2.67 (2.67)	117 (120)	41 (43)	113 (115)	113 (107)	41 (43)	53 (55)	173 (166)	
37	2.46 (2.48)	2.68 (2.67)	118 (119)	66 (65)	115 (115)	110 (108)	39 (42)	52 (56)	175 (169)	108 (109)
38	2.52 (2.50)	2.72 (2.63)	115 (117)	65 (64)	115 (116)	112 (107)	37 (42)	49 (52)	162 (171)	91 (90)
39	2.54 (2.52)	2.69 (2.65)	116 (118)	61 (60)	114 (116)	108 (107)	31 (44)	56 (53)	171 (170)	90 (96)
40	2.61 (2.59)	2.70 (2.66)	116 (119)	62 (62)	115 (115)	107 (108)	48 (43)	61 (53)	171 (167)	98 (102)
41	2.62 (2.64)	2.66 (2.66)	120 (120)	61 (60)	118 (115)	113 (107)	31 (44)	39 (53)	161 (154)	
42	2.66 (2.66)	2.75 (2.71)	118 (119)	62 (62)	113 (115)	110 (108)	43 (44)	57 (56)	172 (169)	81 (89)
43	2.63 (2.65)	2.74 (2.72)	117 (119)	63 (62)	112 (114)	109 (109)	46 (44)	60 (56)	173 (167)	
44	2.73 (2.70)	2.74 (2.72)	118 (119)	60 (61)	115 (114)	111 (108)	45 (45)	59 (56)	176 (167)	
45	2.70 (2.69)	2.73 (2.71)	117 (119)	61 (61)	113 (115)	110 (108)	43 (44)	56 (56)	171 (169)	121 (115)
46	2.64 (2.63)	2.75 (2.69)	116 (117)	63 (61)	113 (116)	114 (108)	34 (43)	45 (55)	158 (170)	94 (87)
47	2.74 (2.70)	2.77 (2.72)	115 (118)	61 (61)	116 (115)	108 (108)	49 (45)	64 (57)	172 (169)	106 (95)
48	2.73 (2.69)	2.77 (2.73)	116 (118)	61 (61)	112 (116)	108 (108)	47 (45)	61 (57)	173 (170)	111 (98)
49	2.73 (2.72)	2.76 (2.73)	115 (118)	61 (60)	116 (116)	110 (108)	42 (46)	55 (58)	168 (167)	
50	2.88 (2.86)	2.79 (2.78)	117 (119)	58 (58)	112 (113)	109 (109)	48 (46)	63 (59)	173 (167)	
51	2.85 (2.86)	2.77 (2.77)	117 (119)	58 (58)	114 (114)	110 (109)	45 (47)	58 (58)	173 (167)	
52	2.91 (2.90)	2.80 (2.77)	117 (119)	57 (57)	113 (114)	109 (109)	48 (46)	63 (60)	172 (168)	
53	2.90 (2.90)	2.76 (2.75)	117 (119)	57 (57)	112 (114)	110 (109)	53 (55)	60 (58)	170 (166)	
54	2.92 (2.89)	2.76 (2.72)	117 (118)	57 (56)	111 (116)	108 (108)	46 (44)	61 (56)	165 (169)	77 (84)
55	2.84 (2.82)	2.81 (2.78)	115 (117)	59 (59)	112 (115)	108 (109)	49 (46)	65 (59)	172 (171)	
56	2.83 (2.82)	2.78 (2.78)	116 (118)	59 (59)	114 (117)	109 (109)	61 (59)	61 (59)	173 (167)	131 (126)
57	2.84 (2.84)	2.79 (2.77)	116 (118)	59 (59)	114 (115)	108 (109)	49 (47)	64 (60)	169 (168)	

[a] Values represent average bond lengths (Å), bond angles (deg), and torsion angles (deg) in the macrocyclic rings and do not include contributrions from alkyl substituents. The C–O–C–C torsion angles are differentiated with a subscript *a* (anti) or *g* (gauche). [b] Average distance (Å) between oxygens in five-membered chelate rings. [c] Average O–M–O angle for oxygen pairs within five-membered chelate rings.

THF groups exhibit a Ψ angle of 3°. Similarly, in the tetrakis-(1,2-dimethoxyethane) complex of potassium (**22**) the C–O–C plane of the single unidentate 1,2-dimethoxyethane ligand exhibits a Ψ angle of 17°. These values are much closer to the Ψ angle of 0° expected for a trigonal planar oxygen than to the Ψ angle of 53° expected for a tetrahedral oxygen.

2. Analysis of the O–CH$_2$–CH$_2$–O Chelate. The basic building block of the multidentate aliphatic ether is the O–CH$_2$–CH$_2$–O group. This group typically forms a five-membered chelate ring on metal ion complexation. Examination of the experimental structure of the five-membered chelate rings formed by O–CH$_2$–CH$_2$–O provides further evidence for the planar preference of the coordinated ether functional groups. The experimental data, summarized in Table 3, reveal trends in structural features as the metal ion is varied. While C–O and C–C bond lengths remain relatively constant, the M–O bond lengths increase from Li to Cs and from Mg to Ba. The bite shows a significant increase from 2.72 Å for Li to 2.87 Å for Cs and 2.61 Å for Mg to 2.78 Å for Ba (see Figures 3 and 4). The O–M–O angle decreases as the size of the metal increases. The M–O–C and O–C–C angles both show a slight tendency to open from Li to Cs and from Mg to Ba. The M–O–C–C and O–C–C–O torsion angles increase from Li to Cs and from Mg to Ba. Although some of these trends are expected on the basis of the size of the metal ion, e.g. those in the M–O length, O–M–O angle, and M–O–C angle, the origins of other trends, e.g. those in the bite and the O–C–C–O torsion angle, are not as obvious. In the following analysis, it will be shown that the latter behavior is consistent with an increasing preference for planar ether coordination from Li to Cs and from Mg to Ba.

Consider the simplest polyether ligand that can form the five-membered chelate ring 1,2-dimethoxyethane. Figure 5 shows this ligand in the *tgt* conformation that is required for bidentate metal ion complexation. MM3′ yields an O–C–C–O torsion angle

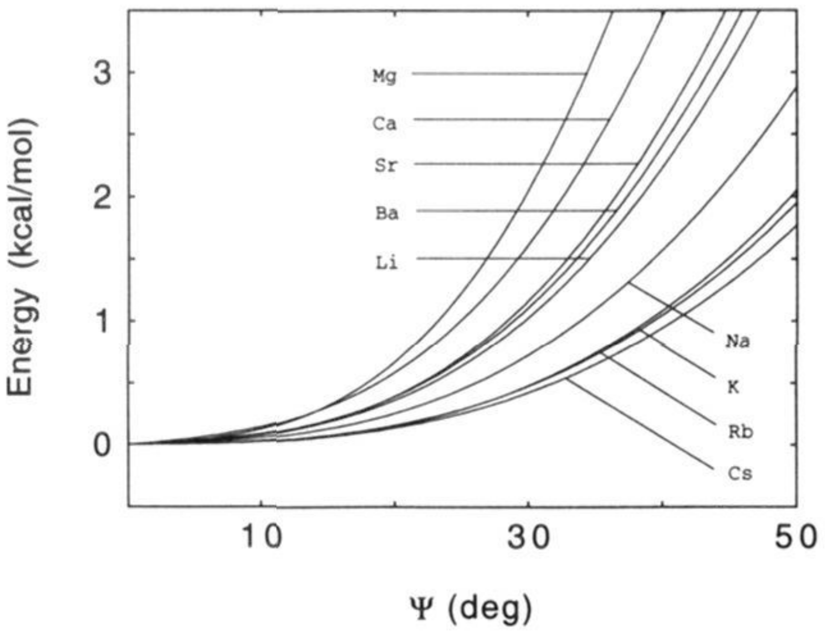


Figure 2. Plots of calculated (MM3′) energy (kcal/mol) versus the angle Ψ (deg) for the out-of-plane distortion of the metal ion in M–O$(Me)_2$ (see text).

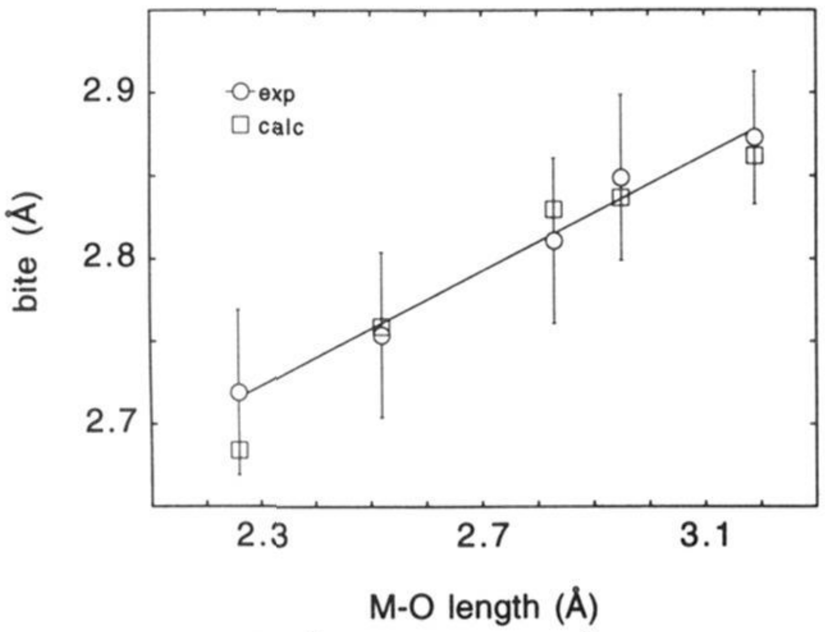


Figure 3. Plot of the bite (Å) versus M–O length (Å) for the alkali metal ions.

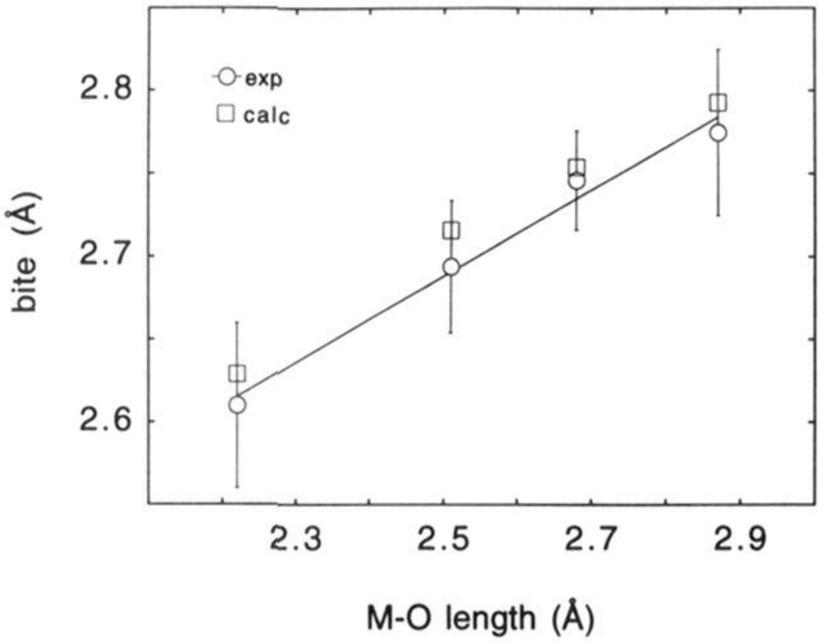


Figure 4. Plot of bite (Å) versus M–O length (Å) for the alkaline earth metal ions.

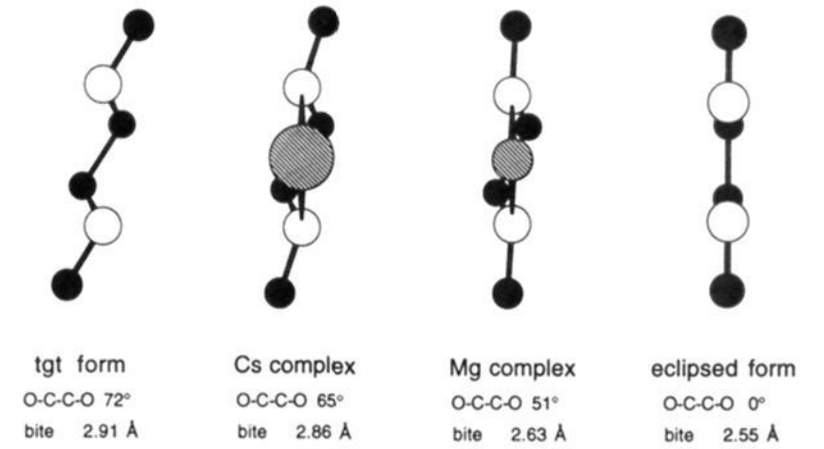


Figure 5. Structure of C–O–C–C–O–C backbone of 1,2-dimethoxyethane in the *tgt* conformer, the Cs complex, the Mg complex, and the eclipsed conformer.

of 72° and a bite of 2.91 Å for this conformer. It can be seen that the two C–O–C groups are not coplanar, and it is not possible for both C–O–C groups to simultaneously adopt a trigonal planar geometry on metal ion complexation. Such a geometry can be obtained only when both C–O bonds are eclipsed to give an O–C–C–O angle of 0°. While this eclipsed conformation yields the preferred geometry for the coordinated ether oxygens, it results in a large amount of torsional strain in the chelate backbone (MM3′ energy for gauche to eclipsed O–C–C–O conformation is 13.25 kcal/mol). Therefore, the observed chelate ring geometries are the result of a compromise between the competing structural preferences. Metal ion coordination causes a decrease in the O–C–C–O angle because this allows the oxygens to move toward the desired trigonal planar geometry. This yields a shorter bite as the two oxygens are brought closer to one another as a result of the C–C bond rotation. The stronger the preference for planar orientation becomes, the smaller the O–C–C–O angle and the bite become.

This behavior is quantitatively reproduced by the MM3′ model. With M–O bond lengths constrained to their experimental average values, MM3′-optimized structures for M(1,2-dimethoxyethane) exhibit the same structural trends as those found in the five-membered chelate rings in experimental structures (see Table 3 and Figures 3 and 4). The two extremes of these structural trends occur for Cs and Mg, which have the weakest and strongest oxygen geometry preferences, respectively. These optimized structures are compared to the metal-free *tgt* conformer and the eclipsed conformer in Figure 5. This comparison shows that the C–O–C–C–O–C backbone tends to flatten, i.e. change from a *tgt* conformation to an eclipsed conformation, on going from Cs to Mg.

Finally, it should be noted that while the experimental trends given in Table 3 are consistent with a preferred trigonal planar geometry for coordinated oxygen, they are not consistent with either a tetrahedral preference or the absence of a preference. Use of a tetrahedral oxygen in the M(1,2-dimethoxyethane) calculations yields bites and O–C–C–O angles that are larger than the values calculated for the metal-free *tgt* conformer for all metal ions larger than Na. In the absence of an oxygen geometry preference, the M(1,2-dimethoxyethane) calculations yield the metal-free *tgt* conformation for all metal ion complexes; i.e., the variation in M–O length is accommodated without changing the ligand structure.

3. Ether Oxygen versus Amine Nitrogen. The addition of neutral oxygen donors to multidentate ligands in such a way as to form additional five-membered aliphatic chelate rings frequently results in an enhanced selectivity for larger metal ions.[14,18a] No such enhancement is obtained when additional five-membered aliphatic chelate rings containing amines are introduced. For example, the addition of an ether oxygen to 1,2-diaminoethane to give oxybis(2-aminoethane) results in an increase in Pb/Ni selectivity of +2.8 log units.[32] The analogous addition of an amine nitrogen to give diethylenetriamine results in a decrease in Pb/Ni selectivity of –0.1 log units.[33] It has been proposed that because strain energy effects in five-membered chelate rings are similar for amines and ethers (assuming that both types of donor atom exihibit a tetrahedral geometry preference when coordinated to the metal ion), the enhanced selectivity for larger metal ions

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(32) Thom, V. J.; Shaikjee, M. S.; Hancock, R. D. *Inorg. Chem.* **1986**, *25*, 2992.

(33) Smith, R. M.; Martell, A. E. *Critical Stability Constants*; Plenum: New York, 1975; Vol. 2.

that is associated with ether oxygens must be due to differences in donor atom basicity.[18a] In contrast, our results suggest that because of differing geometry preferences for the donor atoms the degree of chelate ring strain is a function of the identity of the donor groups and the enhanced selectivity may, to a large extent, result from steric effects.

It is clear that amine nitrogen donor atoms prefer a tetrahedral geometry when coordinated to metal ions. Extensive conformational analyses on the five-membered chelate rings formed by simple bidentate amines of the structure R_2N–CR_2–CR_2–NR_2 have quantified this preference.[34] In addition, molecular mechanics calculations have been used to examine the effect of metal ion size on ring strain in M(1,2-diaminoethane).[35] When the M–N length was varied in the absence of any N–M–N preference, an M–N bond length of 2.5 Å was found to yield the preferred geometry of the chelate ring, i.e. a geometry with torsion angles close to 60° and bond angles near 109.5°. The coordination of smaller or larger metal ions resulted in steric strain that could be traced primarily to the inability to achieve the preferred tetrahedral geometry at nitrogen.

We have shown that ether oxygen donor atoms prefer a trigonal planar geometry when coordinated to the alkali and alkaline earth cations. Our calculations on M(1,2-dimethoxyethane) establish that there is no M–O length that will allow the chelate ring to achieve its preferred geometry, i.e. the ligand in the metal-free *tgt* conformation and both oxygens in a trigonal planar geometry. For metal ions of a given charge, the steric strain in the chelate ring decreases montonically as the metal ion becomes larger. This behavior is due to weakening of the trigonal planar preference as M–O lengths increase. Our results reveal that five-membered chelate rings of aliphatic ethers exhibit a significant steric preference to bind large, low-valent metal ions over small, high-valent metal ions. For example, we calculate a 1.04 kcal/mol increase of steric strain within the 1,2-dimethoxyethane ligand on complexation of cesium and a corresponding value of 5.34 kcal/mol on complexation of magnesium.

The results obtained in this study establish that the steric requirements of five-membered aliphatic chelate rings formed by trigonal planar ether donor groups are fundamentally different from those of rings formed by tetrahedral amine donor groups. When such rings contain tetrahedral donor groups, they will sterically favor monovalent cations the size of sodium or divalent cations the size of calcium, i.e. M–L lengths of ~2.5 Å.[35] However, when such rings contain ether donor groups, they will always sterically favor the larger of two metal ions of the same charge. These results are consistent with the observation that the addition of five-membered ether chelate rings to multidentate ligands yields enhanced selectivity for larger metal ions and establish that, for the alkali and alkaline earth cations, this enhanced selectivity can largely be explained in terms of steric effects. Given the likely possibility that other metal ions will share the requirement of planar coordination to ether oxygens, our results suggest that the differing steric requirements of amines and ethers may also prove important in understanding the observed size selectivity for other systems.

4. M–O Length Preference. While the other metal-dependent parameters were deduced by fitting potential functions to *ab initio* energy surfaces, those for the M–O stretch were determined by empirical fitting to crystal structures. This alternate method was chosen for several reasons. First, *ab initio* calculations on the unidentate M–O(Me)$_2$ and M–O(Me)(Et) models would be expected to yield strain-free M–O lengths that are too short and M–O stretching force constants that are too stiff. More realistic values would require calculations to be performed on models with full inner coordination spheres. Second, adequate energy surfaces for the distortions of M–O bonds would require calculations at higher levels of theory.[36] Third, because of the variability found in experimental M–O lengths, it is possible to deduce the M–O stretch parameters through empirical fitting.[37]

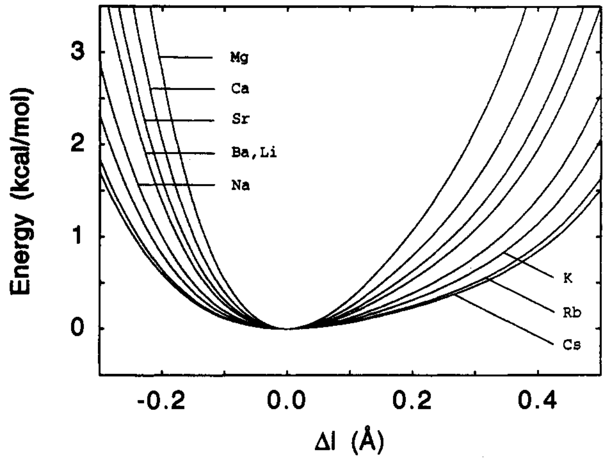

Figure 6. Plots of calculated (MM3′) energy (kcal/mol) versus M–O bond length.

Values obtained for strain-free M–O lengths are close to the M–O lengths observed for sterically unencumbered unidentate oxygen donors. For example, the strain-free lengths obtained in this study for M–O(ether) are comparable to the experimental M–O(water) lengths that have been observed in crown ether complexes:[9] metal ion, r_0 in Å (M–OH$_2$ lengths in Å); Li, 2.05 (1.91–2.00); Na, 2.38 (2.27–2.35); K, 2.75 (2.72); Rb, 2.92 (n.a.); Cs, 3.10 (n.a.); Mg, 2.05 (2.10); Ca, 2.40 (2.38–2.42); Sr, 2.58 (2.55–2.58); Ba, 2.83 (2.73–2.88).

Stretching force constants show trends expected on the basis of the size and charge of the cation: (i) they decrease from Li to Cs and from Mg to Ba and, (ii) for similar sized metal ions, the divalent force constant is greater than the monovalent force constant. These force constants define the strain that accompanies a distortion from the preferred M–O length. Plots of energy versus length distortion in an isolated M–O bond are presented in Figure 6. Consistent with the experimental variation in M–O bond length, these plots reveal that the alkali and alkaline earth cations are able to tolerate significant variations in M–O length without incurring a large energy penalty. This is especially true for the larger cations. Variation in M–O length yielding ≤1 kcal/mol of strain is as follows: metal ion, range (Å); Mg, –0.13–0.19; Ca, –0.15–0.23; Sr, –0.16–0.26; Ba, –0.17–0.29; Li, –0.17–0.29; Na, –0.20–0.34; K, –0.22–0.38; Rb, –0.24–0.42; Cs, –0.24–0.43.

5. Ligand Design Criteria. The goal in ligand structure design is to control complex stability through the choice of connecting groups for sets of donor atoms. A knowledge of the structural requirements that define minimum steric strain in the interaction between the metal ion and the donor atom provides the design criteria. The results obtained in this study establish that, for the aliphatic ether donor atom, these requirements include both a preferred M–O length and trigonal planar geometry preference of the coordinated oxygen. The relative importance of these requirements is discussed below.

Examination of crystal structures reveals that the M–O bonds in ether complexes are actually quite flexible. If they were not,

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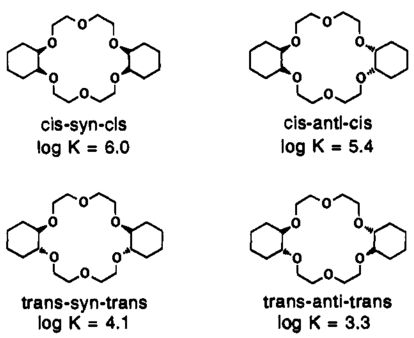
[34] (a) Corey, E. J.; Bailar, J. C. *J. Am. Chem. Soc.* **1959**, *81*, 2620. (b) Gollogly, J. R.; Hawkins, C. J. *Inorg. Chem.* **1969**, *8*, 1168. (c) Gollogly, J. R.; Hawkins, C. J. *Inorg. Chem.* **1970**, *9*, 576. (d) Gollogly, J. R.; Hawkins, C. J. *Inorg. Chem.* **1971**, *10*, 317. (e) DeHayes, L. J.; Busch, D. H. *Inorg. Chem.* **1973**, *12*, 1505. (f) Niketic, S. R.; Rasmussen, K. *Acta Chem. Scand.* **1978**, *A32*, 391. (g) Hald, N. C. P.; Rasmussen, K. *Acta Chem. Scand.* **1978**, *A32*, 735. (h) Hald, N. C. P.; Rasmussen, K. *Acta Chem. Scand.* **1978**, *A32*, 879. (i) Laier T.; Larsen, E. *Acta Chem. Scand.* **1979**, *A33*, 257. (j) Hilleary, C. J.; Them, T. F.; Tapscott, R. E. *Inorg. Chem.* **1980**, *19*, 102.

[35] Hancock, R. D. *Prog. Inorg. Chem.* **1989**, *37*, 187.

[36] Herhe, W. J.; Radom, L.; Schleyer, P. v .R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

[37] Allured, V. S.; Kelly, C. M.; Landis, C. R. *J. Am. Chem. Soc.* **1991**, *113*, 1.



cis-syn-cis
log K = 6.0

cis-anti-cis
log K = 5.4

trans-syn-trans
log K = 4.1

trans-anti-trans
log K = 3.3

Figure 7. Diastereomers of dicyclohexyl-18-crown-6 and their stability constants for potassium complexation in methanol at 25 °C.[38]

then all M–O lengths for each metal ion would fall within a narrow range. Instead, M–O lengths within the same complex are often found to vary over a range of 0.3 Å. For ligands with a low degree of cavity organization, e.g. podands and coronands, the metal ion is usually able to adopt a position that achieves the preferred M–O lengths or only slightly distorted M–O lengths without requiring a significant change in the ligand structure. This situation is attained most easily for the large, low-valent metal ions because they have more flexible M–O bonds that can tolerate a significant range of distortion without incurring large strain energies.

For the 51 complexes examined in this study, **7–57**, instances of significant M–O length strain were the exception rather than the rule. These instances occur only in complexes of the smaller metal ions, e.g. the bis(12-crown-4)Li complexes **9** and **10**, where interligand repulsion yields elongated bonds; the (18-crown-6)-Na complex **19**, where the D_{3d} ring conformation presents a cavity that is too large; and the (18-crown-6)Mg complexes **32** and **33**, where again the cavity is too large. In the rest of the complexes, MM3′ calculations reveal that the strain due to M–O length distortion is not a major contribution to the steric strain of the complex.

In contrast, MM3′ calculations reveal that failure to achieve the preferred oxygen geometry makes a significant contribution to the steric strain in all of the complexes that were examined. Even when M–O strain is present, the strain due to the failure to achieve the preferred oxygen geometry is greater than the strain due to M–O length distortion. As discussed above, complexation of a metal ion to form a five-membered aliphatic chelate ring results in steric strain due to unfavorable closure of the O–C–C–O torsion angles. While the M–O length preference can be satisfied either by adjusting the position of the metal ion or by changing the conformation of the ligand to resize the cavity, the ability to achieve the preferred geometry around the coordinated oxygen is controlled primarily by the strong intraligand structural preferences. Unlike the strain due to M–O length distortion, the strain arising from oxygen geometry preference cannot be relieved by repositioning the metal ion. Similarly, while changing from one ligand conformer to another may change the cavity size to yield a preferred M–O length, it does not remove the undesirable steric interactions that result from the presence of the five-membered chelate rings. Therefore, in ligands with a relatively low level of cavity preorganization, such as the podands and coronands examined in this study, ligand structure has a much greater impact on the degree to which the ligand can satisty the preferred trigonal planar geometry of the coordinated ether oxygens than on the ability of the ligand to satisty the M–O length preferences.

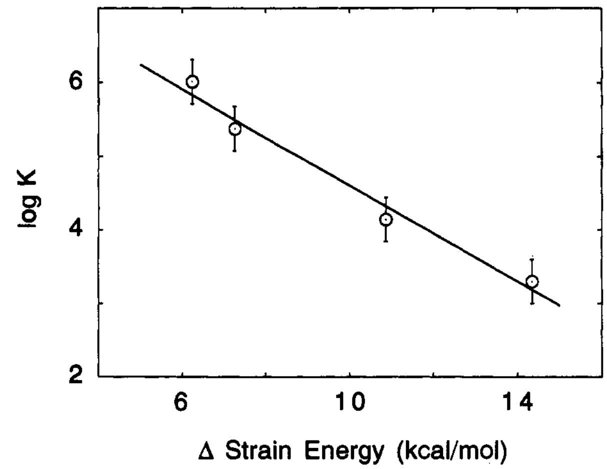


Figure 8. Plot of log *K* versus the change in strain energy (kcal/mol) that accompanies potassium complexation by the four diastereomers of dicyclohexyl-18-crown-6.

Table 5. Breakdown of the Strain Increase for Potassium Complexation by the Diastereomers of Dicyclohexyl-18-crown-6[a]

diastereomer	strain from K–O length distortn[b]	strain from oxygen geometry distortn[c]	increase in strain within the crown ether[d]	total increase in strain[e]
cis-syn-cis	0.22	3.51	2.51	6.24
cis-anti-cis	0.47	4.05	2.74	7.26
trans-syn-trans	0.98	5.63	4.26	10.87
trans-anti-trans	0.73	5.93	7.69	14.35

[a] Strain values are given in kcal/mol. [b] The sum of the strain in the six K–O bonds. [c] The sum of the strain in all other metal-dependent terms, i.e. the K–O–C, K–O–D, and C–O–D bond angles and K–O–C–C and K–O–C–H torsions. [d] The difference between the sum of the strain in all metal-independent terms of the complex and the total strain in the free ligand. [e] See footnote 39.

An example of the influence of the oxygen geometry preferences on complex stability is provided by the four diasteriomers of dicyclohexyl-18-crown-6 shown in Figure 7. The stability constants for the potassium complexes of these isomers cover a range of 2.7 log units in methanol.[38] In our previous study,[19] molecular mechanics calculations were used to compute the increase in strain energy from the free ligand to the potassium complex. The calculated increases in strain energy were linearly correlated with the experimental log *K* values (see Figure 8).

A more detailed analysis of the calculated increase in strain reveals the importance of the oxygen geometry preferences.[39] The increase in strain can be broken into three contributions: (i) the strain from M–O length distortions, (ii) the strain from oxygen geometry distortions (M–O–C, M–O–D, C–O–D, M–O–C–C, and M–O–C–H interactions), and (iii) the strain from changes within the crown ether. These data are summarized in Table 5. The contribution from M–O distortion represents only 4–9% of the total strain. The contribution from oxygen geometry distortion accounts for 41–56% of the total strain. The remaining strain, 38–54%, is due to structural changes within the crown ether as it attempts to accommodate the structural preferences of metal ion coordination. Given the relative magnitude of the first two contributions, the primary cause of the strain within the crown ether is the structural changes that occur to achieve oxygen geometry preferences rather than to achieve M–O length preferences. This example demonstrates that failure to achieve

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(38) (a) Frensdorff, H. K. *J. Am. Chem. Soc.* **1971,** *93,* 600. (b) Burden, I. J.; Coxon, A. C.; Stoddart, J. F.; Wheatley, C. M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 220.

(39) Calculations on the potassium complexes performed in our earlier study[19] were carried out with the MM2 program with a modified force field. This previous force field differs from the MM3′ force field in that the MM3 program uses additional interactions and altered forms of the potential functions. As a check, we have repeated all calculations of our earlier study with the current MM3′ force field. For all 11 crown ethers, MM3′ values for the increase in strain for potassium complexation differ only slightly from the earlier MM2 values. MM3′ values for the dicyclohexyl-18-crown-6 isomers are used in Table 5 and Figure 8.

the desired oxygen geometry can decrease complex stability by orders of magnitude.

From the foregoing discussion it follows that structural modification to provide the desired oxygen geometry could increase complex stability by orders of magnitude. In agreement with the findings of the prior crystallographic survey,[17] we conclude that it is not merely a coincidence that the most stable complex known to be formed by a multidentate either and the lithium cation,[8] the spherand complex shown in Figure 9, possesses an architecture that provides the preferred oxygen orientation. Analysis of the crystal structure[40] reveals that all six C–O–C groups are essentially coplanar with the metal (the out-of-plane angle, Ψ, is only 4°). Unlike the majority of other multidentate ethers, the structure of this spherand is ideally organized for complexation because it provides for both M–O length and oxygen geometry requirements. The destabilizing conformational strain that accompanies complexation by ligands containing O–CH_2–CH_2–O groups is not present. The results obtained in this study suggest that significant enhancement of complex stability can be obtained by replacement of the CH_2–CH_2 linkages, commonly found in podands, coronands, and cryptands, with connecting structure that allows the trigonal planar coordination of the ether oxygen.

IV. Summary

Hartree–Fock calculations performed on the simple models M–O(Me)$_2$ and M–O(Me)(Et) revealed a trigonal planar geometry preference for aliphatic ether donor atoms coordinated to alkali and alkaline earth cations. This information was incorporated in the MM3 force field to yield a molecular model for the alkali and alkaline earth complexes of multidentate aliphatic ethers. The molecular model (i) reproduced experimental crystal structures of 51 different complexes, (ii) reproduced experimental trends in the structure of five-membered chelate rings of aliphatic ethers, (iii) revealed the difference between the size-selectivity of five-membered chelate rings of ethers versus those of amines, and (iv) rationalized trends in the stability of four potassium complexes with the diasteriomers of dicyclohexyl-18-crown-6.

Two structural criteria for ligand design, M–O length preference and oxygen trigonal planar geometry preference, were identified and quantified. The relative importance of M–O length versus oxygen geometry was discussed. It was demonstrated that the degree to which the ligand can satisfy the preferred trigonal planar geometry of the coordinated ether oxygens can have a greater impact on complex stability than the ability of the ligand to satisfy the M–O length preferences.

Figure 9. Crystal structure of the Li(spherand) complex[40] showing the trigonal planar geometry of the oxygen donors.

We conclude that it is important to consider both the M–O length preference and the oxygen geometry preference when attempting to understand the effect of structure on stability. The augmented MM3 force field developed in this study provides a means to quantitatively assess the influence of these structural factors in terms of steric strain and, thus, provides a tool for the rational design of more highly organized binding sites.

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Supplementary Material Available: MM3′ structure input file for the potassium complex of 18-crown-6 and an example MM3′ parameter input file (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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