formalism.[51] A suggestion that Cu(II) → imidazole(π^*) MLCT absorptions contribute to the near UV spectra of type 1 Cu(II) recently has been published.[52] We are unable to discern any obvious justification for this suggestion.

Conclusions

The association of well-resolved π_1,π_2(ligand) → Cu(II) LMCT spectra with structurally constrained Cu(alkylated imidazole)$_4^{2+}$ chromophores has been further documented by crystallographic and spectroscopic studies of **1**. Steric effects of the 1,4,5-trimethylimidazole ligand serve to orient the ligand rings nearly perpendicular to the planar CuN_4 unit. ESR studies of methanolic **1** show that this structural feature may be retained by the tetragonal solution complex. INDO/S molecular orbital calculations show that ring methylation of imidazole raises the n, π_1, and π_2 orbital energies of imidazole and slightly destabilizes the vacant π^* orbitals as well. Di- and trimethylation of imidazole experimentally is observed to cause (a) a red-shift of the imidazole $\pi \rightarrow \pi^*$ absorption of 400–3500 cm^{-1} and (b) a red-shift of the π_2,π_1(ligand) → Cu(II) LMCT absorptions of ~5000 cm^{-1}. The energy separation between the π_2,π_1(imidazole) → Cu(II) LMCT absorptions in the solid state (~8000 cm^{-1}) is greater than that exhibited by solution Cu(im)$_4^{2+}$ chromophores (~4000 cm^{-1}). Various Ni(II) tetrakisimidazole and tetrakispyrazole chromophores exhibit a π_1(ligand) → M(II) LMCT absorption that is blue-shifted (>2500 cm^{-1}) from the corresponding absorption exhibited by structurally similar Cu(II) analogues. This result confirms the assignment as LMCT, not MLCT, and is supported by studies of pseudotetrahedral Cu(II), Ni(II), and Co(II) chromophores, which will be presented elsewhere.

Acknowledgment. This work was supported by the National Institutes of Health (Grant AM-16412 to H.J.S.), the Rutgers Computing Center, and the Rutgers Research Council (K.K.-J.).

Registry No. 1, 85337-05-9; Ni(1,2-dmi)$_4$·2ClO$_4$, 39734-28-6; Cu(1,2-dmi)$_4$·2ClO$_4$, 39734-29-7; Cu(im)$_4$·2NO$_3$, 33790-63-5; 1,4,5-tmi, 20185-22-2; im, 288-32-4; 1,2-dmi, 1739-84-0; 4-methylimidazole, 822-36-6; 4,5-dimethylimidazole, 2302-39-8; 1,2,4-trimethylimidazole, 1842-63-3.

Supplementary Material Available: Stereoscopic packing diagram and tables of calculated hydrogen atom positions, anisotropic thermal parameters, and observed and calculated structure factors for **1** (11 pages). Ordering information is given on any current masthead page.

(51) Bernarducci, E. E.; Bharadwaj, P. K.; Lalancette, R. A.; Potenza, J. A.; Schugar, H. J., to be submitted for publication.
(52) Downes, J. M.; Whelan, J.; Bosnich, B. *Inorg. Chem.* **1981**, *20*, 1081–86.

Computational Design of Polylactone Macrocyclic Ionophores§

Shneior Lifson,*† Clifford E. Felder,† and Abraham Shanzer*‡

Contribution from the Departments of Chemical Physics and Organic Chemistry, Weizmann Institute of Science, 76100 Rehovot, Israel. *Received September 27, 1982*

Abstract: Empirical energy functions of bond lengths, bond angles, torsional angles, and interatomic Coulombic and Lennard–Jones interactions are applied to predict ionophoric properties of macrocyclic polylactones. Equilibrium conformations and energies of candidate molecules and their complexes with Li^+, Na^+, and K^+ are derived. The ability to form a cage surrounded by polar groups is considered a necessary condition for ionophoric behavior. The calculated dimensions of the cage and its structural and symmetry properties, as well as the binding energy of the ion/molecule complex, are used as criteria for the efficiency and specificity of the ionophore. Calculations on DL-cyclohexalactyl, an enniatin analogue, are used to test the method. They indicate good ionophoric properties and preference for Na^+, in qualitative agreement with experiment. Cyclic tetralactones with structural "reflection-symmetry" (ref-lactones) $(C'O'O(CH_2)_mOC'O'(CH_2)_n)_2$ are all found to lack the conformational symmetries required for ionophoric behavior. Cyclic tripropiolactones with a rotational symmetry (roto-tripropiolactones) $(C^1H_2C^2H_2C'O'O)_3$ are predicted to complex well with the alkali ions. Their dimers are predicted to form octahedral cages of almost perfect structure and symmetry. Hydrophobic side chains attached at either C^1 or C^2 in either equatorial or axial positions are considered as factors for stabilization of the dimer and its cage parameters. They confer chirality on the molecule (L or D) and lead to two dimer/ion complexes (LL or LD). Isopropyl substituents are found not to be large enough to make hydrophobic contact in the LD configuration but do form stable cages in LL when attached to C^2, with preference for Na^+.

Introduction

Ionophores, otherwise known as ion carriers or complexones, are naturally occurring cyclic molecules whose biological function is to transport ions across lipid membranes of living cells.[1] Since this function is essential for the very existence of a wide variety of life processes, a large number of ionophores of specific and highly optimized properties are found in nature. They bind ions very efficiently and subsequently release them with the same ease.[2] Some of them are amazingly selective for specific ions, and all of them reduce the electric resistance of lipid membranes by several orders of magnitude.

Although ionophores may vary widely in chemical composition and molecular size, they all function using the same principles. A comprehensive discussion of the thermodynamics and kinetics

§ Dedicated to Prof. Jack D. Dunitz on the occasion of his 60th birthday.
† Department of Chemical Physics.
‡ Department of Organic Chemistry.

(1) C. Moore and B. C. Pressman, *Biochem. Biophys. Res. Commun.*, **15**, 562 (1964); B. C. Pressman, E. J. Harris, W. S. Jagger, and J. H. Johnson, *Proc. Natl. Acad. Sci. U.S.A.*, **58**, 1949 (1967); Yu. A. Ovchinnikov, V. T. Ivanov, and A. M. Shkrob, *BBA Libr.*, **12** (1974); Yu. A. Ovchinnikov, in "Frontiers in Bioorganic Chemistry and Molecular Biology", Yu. A. Ovchinnikov and M. N. Koslov, Ed., Elsevier/North Holland Biomedical Press, Amsterdam, 1979, p 129; B. C. Pressman, *Ann. Rev. Biochem.*, **45**, 501 (1976).
(2) H. Diebler, M. Eigen, G. Ilgenfritz, G. Maass, and R. Winkler, *Pure Appl. Chem.*, **20**, 93 (1969); G. Eisenman and S. J. Krasne, "The Ion Selectivity of Carrier Molecules, Membranes and Enzymes", Chapter 2, and W. Epstein, "Membrane Transport", Chapter 10, in *MTP Int. Rev. Sci. Biochem. Ser.*, Vol. 2, Butterworths, London, 1975.

0002-7863/83/1505-3866$01.50/0

of ionophoric behavior is contained in a review by Burgermeister and Winkler-Oswatitsch.[3] The following are the most important characteristic properties:

(1) As a rule, an ionophore is a macrocyclic oligomer, whose monomers are composed of alternating polar and apolar groups, arranged so as to confer a high degree of symmetry on the molecules. The polar groups are amides, esters, or ethers. The oxygens (or nitrogens) of these groups carry partial negative charges, and the carbons bonded to them are positively charged, thus forming extended electric dipoles. These dipoles tend to attract ions by electrostatic dipole–ion forces, similar to the forces that bind the ions to the molecules of a polar solvent, e.g., water.

(2) The ionophore forms a cavity, around which the polar groups are symmetrically arranged at the vertices of a more or less regular polyhedron, with the dipoles directed toward the center. Although the octahedron, with six such dipoles, is the most common structure, tetrahedral and cubic structures occur as well. The dipoles may be located on the ring skeleton and/or on side chains. In addition, sometimes a single cavity is formed by two ionophore molecules, in which case the stoichiometry of binding the ion to the ionophore is 1:2. The dimensions of the cavity are particularly well fitted to the diameter of the target ion, and this is a main factor in the specificity of binding.

(3) The ionophore molecule contains apolar groups of sufficient size and hydrophobicity so as to make both the ionophore and its ion complex soluble in the lipid membrane. The free energy of the ion/ionophore complex is properly balanced against those of the solvated ion and the unligated ionophore, so that the complex is favored in the apolar environment of the lipid membrane and disfavored in the polar environment of water.

(4) The ionophore molecule is sufficiently flexible to allow a gradual exchange of solvent molecules of the solvation shell of the ion by the binding dipoles of the ionophore and vice versa, so that the energy barrier of the transition is fairly low.

Since the characteristics of macrocyclic ionophores are recognized, it should be possible to design and synthesize analogues of the natural ionophores. Such synthesis is highly desirable. It may further our basic physicochemical understanding of ionophores. It may also serve practical purposes in pharmacology and medicine.

We have at our disposal an efficient "template method" for synthesizing macrocyclic compounds containing polar bonds.[4] A metalloid derivative is reacted with an organic molecule containing protic groups under absolutely anhydric conditions to form an organometalloid complex, in which organic residues are bound covalently to the metalloid nucleus. By exposing this complex to difunctional organic reagents, the metalloid is extracted from the complex, and the organic residues are joined together to form macrocyclic compounds. Being an essentially two-step procedure, its yields are high, varying mostly in the range 30–90%.

This template method is versatile, general, and efficient in synthesizing a wide variety of molecules with alternating polar and hydrophobic groups. It is therefore well suited to the purpose of searching for synthetic ionophores of some particular specificity. Because of the very large number of possible candidates for synthesis, such a search can greatly benefit from theoretical predictions of the binding capacity of molecules not yet synthesized, and of the specificity of such binding. In order to make such predictions, we calculate the various equilibrium conformations and the relative strain energies of the expected ionophores and their ion complexes. The modes and relative affinities of ion binding, as well as the conformational and energetic changes that accompany such binding, are deduced from these calculations with a reasonable degree of confidence.

In this study, we are concerned with macrocyclic polylactones, namely, rings formed by ester linkages, and with their binding to the alkali cations Li^+, Na^+, and K^+. Two classes of these polylactone ionophores have been synthesized hitherto by the template method. The first class, which we call the reflectolactones, or, for short, ref-lactones, consists of four identical segments whose structural formulas (though not necessarily the actual molecular conformations) contain two mirror-reflection symmetries. A number of ref-lactones were examined experimentally for ion binding, always with negative results. The second class, the roto-*n*-propiolactones, consist of three or more identical residues oriented in the same direction along the ring, so that the structural formula has rotational symmetry.

In the progress of this research, we developed a number of conformational and energetic criteria for deciding whether a molecule would be a suitable ionophore, using an enniatin analogue as a "sounding board". Application of these criteria to ref-lactones explains the failure of those examined experimentally to serve as ionophores and predicts similar failure for other members of this family. On the other hand, roto-tripropiolactone dimers are predicted to bind alkali ions by forming almost perfect octahedral cages. Specificity for particular ions, as well as solubility in lipid membranes, is expected to depend on the size and location of hydrophobic side chains. These predictions are now in the process of being examined experimentally. A preliminary communication of this study was presented at the International Symposium on Peptides, Polypeptides and Proteins, Padova, Italy, June 1982.[5]

Theoretical Considerations and Computational Procedures

The selective transport of ions across apolar, or lipophilic, membranes by ionophores is a complex process, resulting from a delicate balance between several strong interactions. The enthalpies of hydration of Li^+, Na^+, and K^+ are −130, −104, and −83 kcal/mol, respectively.[6] Thus, the interaction energies of binding between the ion and its carrier must be of the same order of magnitude for binding to occur. Other interactions, though smaller in magnitude, are still important in determining the free-energy balance. Such are the solvation energies of the bare ionophore and its ion complex, in both the membrane and the aqueous phases. While enumeration of these and other contributions is obvious, their detailed numerical evaluation is next to impossible. It is possible, however, to recognize the primary factors that determine whether or not a molecule has a chance to be a good ionophore. Most of these factors can be evaluated to a reasonable approximation with the help of empirical energy functions. Consequently, reliable predictions of the relative ionophoric merits of candidates for synthesis can be made.

Calculable Ionophoric Factors. Ring molecules can exist in only a limited number of equilibrium conformations. Each conformation possesses a *strain energy* determined by deviations of the internal coordinates from their standard values, imposed by the closure of the ring, as well as by electrostatic and van der Waals intramolecular interactions. By the Boltzmann distribution law, the only significant conformations are those whose strain energies are among the lowest.

Ionophoric characteristics are easily recognized by examining molecular conformations. If the dipolar bonds are not arranged symmetrically around a central cavity or if they point divergently toward the solvent, the molecule is not a potential ionophore. On the other hand, a molecule is a good ionophore if the number of dipoles forming the cavity matches the number of solvent molecules in the solvation shell, if the dipoles are arranged symmetrically around the center of the cavity and are well aligned toward its center, and if the size of the cage matches the van der Waals radius of the ion to be enclosed within it.

The electrostatic interaction between an ionophore and an ion located at the center of a well-structured cavity can be very large, as noted in the subsection below on the enniatin analogue. Such strong interactions can twist the equilibrium conformation of a molecule into a favorable cage structure, at the cost of increasing its strain energy.

The solvent interactions with the unligated molecule are small compared to the ion/ionophore interaction, not only in the lipid membrane phase but also in the water phase. Their change upon complexation is even smaller. Therefore, its calculation is not required in order to tell a good ionophore from a poor one. The essential solvation requirement for good ionophoric behavior is that the outer shell of the molecule contain sufficient hydrophobic groups to dissolve favorably in the lipid

(3) W. E. Morf, D. Ammann, E. Pretsch, and W. Simon, *Pure Appl. Chem.*, **36**, 421 (1973); R. M. Izatt and J. J. Christensen, Eds., "Synthetic Multidentate Macrocyclic Compounds", Academic Press, New York, 1978); W. Burgermeister and R. Winkler-Oswatitsch, *Top. Curr. Chem.*, **69**, 91 (1977).

(4) A. Shanzer, J. Libman, and F. Frolow, *Acc. Chem. Res.*, **16**, 60 (1983).

(5) A. Shanzer, C. Felder, and S. Lifson, *Biopolymers*, **22**, 409 (1983).

(6) R. M. Noyes, *J. Am. Chem. Soc.*, **84**, 513 (1962), quoted in ref 3. Single ion hydration energies depend on the choice of models and differ among many authors (see ref ref 11b); however, their differences are more directly related to experiment.

phase. They should be incorporated either in the ring or in side chains, as is the case in most natural ionophores.

Force Field. The present calculations of ionophoric characteristics are based on a set of empirical energy functions of intra- and intermolecular interactions, commonly known as a *force field*. The empirical method has been advanced to yield highly accurate predictions of molecular properties by consistently optimizing the force field on a host of experimental data,[7] but for our present purpose, we neither need nor can achieve a high degree of accuracy. In fact, the present force field is an eclectic, rather than consistently optimized, set of functions. We use available empirical energy functions for internal coordinates such as bond stretching, angle bending, and torsion angle twisting. For nonbonded atom–atom interactions we use a Lennard–Jones ($A/r^9 - C/r^6$) potential or its equivalent form $2\epsilon(r^*/r)^9 - 3\epsilon(r^*/r)^6$ to represent van der Waals interactions and a Coulombic potential to represent electrostatic interactions between atomic partial charges. The functions for internal coordinates involving aliphatic carbons and hydrogens were taken from Warshel and Lifson;[8] those involving the ester bond were adapted from Hagler et al.;[9] the nonbonded interaction potentials for atoms of the aliphatic and ester groups were adapted from Lifson et al.[10]

These parameters are supplemented by Lennard–Jones potentials for the ions Li^+, Na^+, and K^+, which are not available in the literature and are most important for the present force field. Unfortunately, the application of available experimental data to obtain uniquely the Lennard–Jones parameters for the ions from an objective least-squares optimization is an extensive task not yet undertaken. Having, therefore, to resort to a "learned guess" of the parameters ϵ and r^*, we reasoned as follows: The r^* values of the Lennard–Jones potential related to the ion/atom interactions are necessarily larger than the atomic radii of these ions as obtained from X-ray diffraction of crystals[11a] or thermodynamic data on ion solvation.[11b] The latter are related to the equilibrium distances, determined by the energy balance between the van der Waals repulsion and the strong electrostatic attraction, while r^* represents the minimum of the Lennard–Jones potential, where the repulsion is balanced by the weak dispersion force, as is the case in noble gases. Therefore, each parameter r^* applying to an interaction between two ions of the same kind is taken as twice the atomic radius for that noble gas with the same electronic configuration as the given ion,[12] namely, Li^+ 2.58, Na^+ 3.20, and K^+ 3.84 Å. The energy parameters ϵ are estimated by using dispersion constants C given by Buckingham[13] and are 0.00156, 0.01653, and 0.04984 kcal/mol, respectively, for the three ions. The parameters r^* and ϵ for interactions between different atom types are taken as the arithmetic and geometric means, respectively, of those for the homogeneous interaction. As will be seen in the following sections, these estimates were good enough for our purpose.

Computational Procedures. Equilibrium conformations of unligated molecules and their corresponding strain energies were obtained by choosing trial sets of initial internal coordinates and then minimizing the total energy by a fast convergent minimization algorithm (Harwell programs VA08A and VA09A).[14] The torsional angles of the trial sets were estimated roughly from mechanical molecular models, and standard values were used for bond lengths and bond angles. Since a ring of n bonds has $3n$ internal coordinates, only $3n - 6$ of which are independent, we left unspecified one bond length and its adjacent two bond angles and three torsional angles, as if we had a linear molecule. Then we transformed the internal coordinates to a set of Cartesian coordinates, using the routine ATCOOR.[15] The ring thus obtained was generally distorted around the severed bond. We then minimized the total energy of the ring in Cartesian coordinates, in which ring closure is automatically provided.[8] The calculation was repeated, moving the severed bond from one place to another along the ring. This procedure often led to different local minima of the energy, i.e., different equilibrium conformations. Although the initial trial set was thus mostly asymmetric, it was always possible to arrive, after some attempts, at symmetric conformatios when the molecules possessed them.

Table I. Torsional Angles[a] of Calculated and Experimental Enniatin Analogues

angles	ϕ(O–C)			ψ(C'–C')			ω(C'–O)		
residues	1	2	3	1	2	3	1	2	3
LAC6 calcd[b]	−64	64	−64	141	−141	141	179	−179	179
HIV6 exptl[c]									
molecule 1	−129	121	−89	20	−44	5	172	−167	−176
molecule 2	−108	117	−97	18	−38	22	177	−169	172

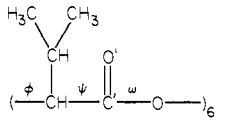
[a] Due to a molecular center of inversion symmetry, the dihedral angles of residues 4–6 have the same value and opposite signs as those of residues 1–3, respectively. [b] For isolated molecules. [c] For the two molecules in the unit cell of the crystal.[17]

Results

Results of our calculations are divided into three sections. The first deals with a polylactone analogue of enniatin, known to be a good and mildly selective ionophore, and considers useful criteria for ionophoric behavior and ion selectivity. The second deals with ref-lactones and demonstrates the ability of our method to predict their ionophoric characteristics. The third deals with a set of roto-propiolactones, for which conditions are examined for favorable ionophore characteristics and predictions are made of ionophores suitable for future synthesis.

Polylactone Analogue of Enniatin

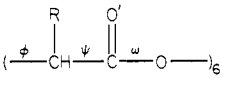
Enniatin B is a natural cyclotridepsipeptide antibiotic compound, composed of alternating residues of *N*-methyl-L-valine (L-NMV) and D-hydroxyisovaleric acid (D-HIV). A polylactone analogue of enniatin, known as cyclohexahydroxyvaleryl, is obtained when the L-NMV residues are replaced by L-HIV. Its structural formula is



I

with the skeletal C's in the LDLDLD stereoisomeric configuration. It may also be written as $(\text{L-HIV-D-HIV})_3$ or, in short, LD-HIV6. It was synthesized[16] and was found to resemble enniatin in its conformation[17] as well as in its binding constants to alkali ions.[18] Details of the crystalline conformation[17] are given in Table I.

We used LD-HIV6 as an experimental reference in calculating the ion-binding character of the LD cyclic hexalactone set of molecules of the type



II

(The Greek letters denote the torsional angles.) As a representative of this set we chose, for computational convenience, LD-cyclohexalactyl or, in short, LD-LAC6, where methyl is the R group, rather than the isopropyl of HIV6. Since the isopropyl group of LD-HIV6 points extraannularly, its replacement by a methyl is expected to affect the hydrophobic character of the hexalactone but not its ring conformation.

Using the computational procedure described in the preceding section, we calculated several equilibrium conformations of the DL-LAC6 enniatin analogue. One of these conformations is

(7) For a recent review and further references, see S. Lifson, in "Structural Molecular Biology: Methods and Applications", B. D. Davies, W. Saenger, and S. S. Danyluck, Eds., Plenum Publishing, 1982, pp 359–386.
(8) A. Warshel and S. Lifson, *J. Chem. Phys.*, **53**, 582 (1970).
(9) A. T. Hagler, P. S. Stern, R. Sharon, J. M. Becker, and F. Naider, *J. Am. Chem. Soc.*, **101**, 6842 (1979).
(10) S. Lifson, A. T. Hagler, and P. Dauber, *J. Am. Chem. Soc.*, **101**, 5111 (1979).
(11) (a) References were collected by using the Cambridge Structural Database. See *Acta. Crystallogr., Sect. B*, **B35**, 2331 (1979). (b) B. E. Conway, *J. Solution Chem.*, 7, 721 (1978).
(12) J. A. A. Ketelaar, "Chemical Constitution", Elsevier, Amsterdam, 1953, p 28.
(13) R. A. Buckingham, *Proc. R. Soc. London, Ser. A*, **A160**, 113 (1937).
(14) Harwell Subroutine Library.
(15) E. Norlander, Computer Code ATCOOR, Case Western Reserve University, Cleveland, OH, 1973.
(16) M. M. Shemyakin, Yu. A. Ovchinnikov, V. T. Ivanov, A. V. Evstratov, I. I. Mikhaleva, and I. D. Ryabova, *J. Gen. Chem. USSR (Engl. Transl.)*, **42**, 2316 (1972).
(17) T. G. Shishova and V. I. Simonov, *Kristallografiya*, **21**, 736 (1976); *Soviet Phys. Crystallogr.*, **21**, 417.
(18) I. I. Mikhaleva, A. V. Evstratov, V. T. Ivanov, and Yu. A. Ovchinnikov, Peptides—1972, Proceedings of the 12th European Peptide Symposium, Elsevier, Amsterdam, 1973, p 346.

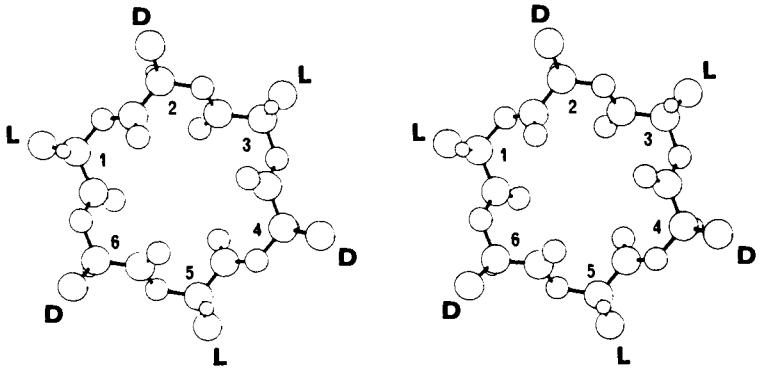


Figure 1. LD-LAC6 enniatin analogue. The circles are the atomic sizes reduced by 0.25. The hydrogens of the methyl side groups are omitted.

Table II. Ionophoric Characterization of the Enniatin Analogue Ring Torsion Angles (deg) and Binding Energies (kcal/mol)

	ϕ	ψ	ω	E_{bind}[a]	E_{strain}
unligated molecule	−64, 64	141, −141	179, −179		
Li^+ complex	−58, 50	147, −135	170, −173	−75	20
Na^+ complex	−65, 65	144, −144	172, −172	−57	22
K^+ complex	−78, 63	159, −132	−179, 169	−35	21

[a] E_{bind} is the difference between the total energies of the complex and the unligated molecule, and E_{strain} is the corresponding difference between the nonelectrostatic strain energies.

Table III. Ionophoric Characterization of the Enniatin Analogue Ion Cavity Geometric Parameters (Å)[a]

	r(ion-O′)	$\sqrt{2}$r(ion-O′)	r_1(O′-O′)	r_2(O′-O′)
unligated	2.68[b]	3.79	3.64	3.94
Li^+ complex	1.89, 2.48[c]	2.67, 3.51[c]	2.88, 2.86[d]	3.06, 3.41[c]
Na^+ complex	2.30	3.25	3.05	3.45
K^+ complex	2.57, 2.84[c]	3.64, 4.02[c]	3.31, 3.17[d]	4.46, 3.05[c]

[a] r(ion-O′) is the distance from the bound ion to a carbonyl oxygen; r_1(O′-O′) is the distance between two carbonyls belonging to nearest-neighbor residues and residing on opposite sides of the ring plane; r_2(O′-O′) is the distance between carbonyls belonging to second-nearest-neighbor residues and residing on the same side of the ring plane. [b] The distance between the center of the molecule and O′. [c] The first number relates to the carbonyls of one side of the ring, say 1, 3, and 5; the second, to those of the other side of the ring, say 2, 4, and 6. These numbers are equal for Na^+, which is bound in a higher symmetry, S_6. [d] The two numbers are the distances of the same carbonyl to its two first neighbors. They are different in Li^+ and K^+ binding, as one side of the ring is rotated relative to the other around the C_3 symmetry axis of the molecule; they are the same in Na^+ binding, since this complex possesses S_6 symmetry.

particularly suitable for ion binding. It has a perfect 6-fold rotation-reflecting symmetry S_6, with the carbonyl oxygens forming an octahedron, as seen in the stereo Figure 1.[19] (All stereoviews were produced by the program PLUTO[19] and are viewed along the axes perpendicular to the mean ring planes.) The experimental crystalline conformation of LD-HIV6[17] is somewhat similar to the calculated LD-LAC6 but not the same. The unit cell contains two molecules with slightly different conformations. In both conformations the S_6 symmetry was distorted, probably due to the balance between crystal packing forces and ring flexibility. Table I presents the torsional angles ϕ(O–C), ψ(C–C′), and ω(C′–O) of the calculated LAC6 and of the two experimental HIV6 conformations.

The next step was to minimize the total energy of the ion/molecule complex, starting from the symmetric conformation of the unligated molecule and putting the ion somewhere along the principal symmetry axis (usually at the center). The calculations were performed with Li^+, Na^+, and K^+. The results indicated three main criteria of ionophoric characterization: first, the change in torsional angles and gain or loss of symmetry by complexation; second, the detailed geometry of the cage and the location of the ion within it; third, the total binding energy and its strain component. These latter data are presented in Tables II and III.

It is seen from Table II that the torsional angles are least distorted by binding Na^+. The distortions in ψ and ω are probably related to bending the C=O bonds toward the ion. The angle between the vectors C=O and O--Na^+ is 63°. The 6-fold rotation-reflection symmetry S_6 is retained, and the Na^+ ion is located at the center of a cage formed by the six carbonyl oxygens.

Both Li^+ and K^+ distort the molecule and reduce its S_6 symmetry to a lower 3-fold rotation symmetry C_3, but for different reasons. While the cage is too big for Li^+, it is too small for K^+. This is indicated by examining the various distances between the oxygens of the cage and the ion inside the cage, given in Table III. Consider the two pyramids: one, formed on one side of the ring by the carbonyl oxygens of residues 1, 3, and 5 as its equilateral base and the ion at its apex; the other formed similarly on the other side of the ring by the ion and the oxygens of residues 2, 4, and 6. The two pyramids are congruent for Na^+. For Li^+, the first is smaller than the second in both its base and edges. Since the cage is too large for Li^+, the ion is attracted to the oxygens on one side of the cage and pulls them inward, while being farther away from the oxygens on the other side. For K^+, on the other hand, the first pyramid, comprising K^+, O′[1], O′[3], and O′[5], has a wider base and shorter edges than the other. Here the cage is too small for a symmetric accommodation of the ion, which makes room for itself between the oxygens 1, 3, and 5 by pushing them apart while receding from the oxygens on the other side.

Another sensitive measure of the ionophore/ion mode of binding is the distortion of the octahedron cage, formed by the six oxygens. In a perfect octahedron all edges have equal length, which is $\sqrt{2}$ times the distance of the vertices from the center. In the unligated molecule, the distances r_2(O′–O′) of carbonyls located on one side of the ring are 0.3 Å longer than the distances r_1(O′–O′) of adjacent oxygens on opposite sides. In Na^+ the difference increases to 0.4 Å while the cage shrinks because the bending of the C=O dipoles toward the ion require more energy than bringing the two sides nearer to it. The cage retains, however, its S_6 symmetry, and the (r(Na^+–O′) distance times $\sqrt{2}$ is intermediate between the r_1(O′–O′) and r_2(O′–O′) distances. In the Li^+ complex the octahedral cage is distorted as the r_2(O′–O′) distances are different on the two sides of the ring, but the six r_1(O′–O′) distances are still almost the same. For K^+ the octahedron is even more distorted. The difference between the r_2(O′–O′) distances on opposite sides of the ring increases to 1.4 Å, and the r_1(O′–O′) distances are no longer the same, indicating a twist of the triangle O′[1], O′[3], O′[5] with respect to the triangle O′[2], O′[4], O′[6].

The total binding energies of the three alkali ions as given in Table II are much too small to match the enthalpies or even the free energies of hydration of these ions. It is obvious that a major component of ion/ionophore binding energy has been overlooked. A significant contribution to the binding energy that was not included in our force field was the electrostatic energy of polarization of the ionophore by the ion. We made a rough estimate

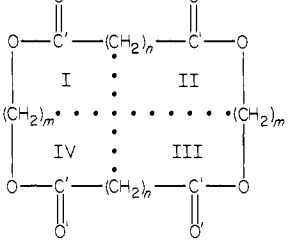
(19) All stereoviews were produced by using S. Motherwell's Computer Code PLUTO, University Chemical Laboratory, Cambridge, England, 1979.

of this energy, counting the polarization of all the atoms of the ionophore in the field of the central ion and ignoring the mutual interactions of the induced dipoles. Using experimental values for atomic polarizabilities, we obtained −68, −53, and −32 kcal/mol for Li^+, Na^+, and K^+, respectively, roughly the size necessary to close the above-mentioned gap. Thus a satisfactory evaluation of the polarization energy might perhaps improve our calculation of the binding energy. However, since it was ignored in the past, its incorporation in the force field might require a reexamination of other empirical components of the force field. Such a calculation seems unjustified here, since it can not be subject to independent tests within the limits of the present study. It is also unnecessary, in view of the general level of accuracy required or available for the present study. Furthermore, the polarization energy is expected to show the same trend as the ion–dipole interaction, namely, to be larger for cases of better ionophoric behavior. Therefore, ionophoric behavior may be recognized without including polarization. Indeed, the binding energy differences between the three ions, as taken from Table II, support the indications obtained from the geometric criteria, that Na^+ is preferred by the enniatin analogue over Li^+ and K^+. The calculated binding energies to Na^+ and Li^+ differ by 18 kcal/mol, while the corresponding enthalpies of hydration differ by 26 kcal/mol. The corresponding differences for K^+ and Na^+ are 22 and 21 kcal/mol, respectively. It implies that Na^+ is preferred over Li^+ by 8 kcal/mol and over K^+ by 1 kcal/mol. The origin of these differences is partly the better fit of the cage geometry to the van der Waals radius of Na^+. We conclude therefore that our calculated energy difference may be good enough to indicate qualitatively, though not quantitatively, ionophoric preferences.

Are these conclusions borne out by the experimental facts? The stability constants of alkali ion binding for most enniatins, as well as for the enniatin analogue HIV6, were found to follow the order $Li^+ \ll Na^+ < K^+ \cong Ru^+ \cong Cs^+$.[18] However, K^+ and the heavier ions were shown to bind externally, sandwiched between ionophores.[20] Thus, our calculations are essentially consistent with the available experimental data. A more quantitative comparison requires refinement of both theory and experiment.

Cyclic Tetralactones with Reflection Symmetry

The next group of molecules whose conformations and cation binding were estimated by our computational method is a group of tetralactones, which we shall call the reflecto-lactones or reflactones, of the general structure III.



III

An efficient template method for synthesizing a number of such molecules with high yields has recently been developed by Shanzer and co-workers.[4] Covalent templates were obtained under strictly anhydric conditions, by reacting $(Bu)_2SnO$ with diols $HO(CH_2)_mOH$. Diacyl dihalides $ClC'O'(CH_2)_nC'O'Cl$ condense around the stannoxane template to form centrosymmetric macrocyclic tetralactones of structural formula III as the sole ring products.

A number of compounds of this group have been synthesized, including $m = 2$, $n = 2$–8, as well as $m = 4$, $n = 4$, and a few other modifications.[21] The molecular structures and cation binding properties of some of these molecules have been measured. We have therefore used this group to improve the predictive power of our method.

Table IV. Calculated Conformations of Ref-lactones[a]

m,n	conf	E_{rel}[b]	symmetry[c]	positions of O'
1,1	1	0.0	C_{2x}, C_{2y}, C_{2z}	I, III up; II, IV down
	2	1.4	C_{2y}, i, σ_{xz}	I, II up; III, IV down
	3	2.4	C_{2x}, $\sim i$, $\sim\sigma_{yz}$	I, IV up; II, III down
	4	2.7	C_{2z}	I–IV up
2,2	1	0.0	none	I, IV up; II out; III down
	2	1.9	$\sim C_{2z}$	I, III up; II, IV down
2,3	1	0.0	none	I, III up; II, IV down
	2	2.2	i	I, II up; III, IV down
	3[d]	6.3	i	I, II up; III, IV down
2,4	1	0.0	C_{2z}	I, III up; II, IV down
	2	0.1	i	I, II up; III, IV down
	3	1.2	C_{2z}	I–IV up
	4	2.3	i	I, II up; III, IV down
3,3	1	0.0	$\sim\sigma_{yz}$	I–IV up
	2	4.4	C_{2z}	I, III up; II, IV down
	3	6.0	C_{2z}	I, III up; II, IV down

[a] Only those calculated conformations that are the most stable or that have symmetry elements are presented here. [b] The calculated molecular energy (kcal/mol) relative to the most stable conformation of the same compound. [c] See text for notation; ~ denotes approximate. [d] This conformation has alternating trans and cis ester bonds. All other conformations reported here have the ester bonds all trans.

Structural formula III has a considerable degree of symmetry. Whether or not such molecules are potential ionophores may depend on the symmetry properties of their equilibrium conformations. It is necessary, therefore, to examine the relations between structural and conformational symmetries.

Formula III is comprised of four identical segments, I–IV, each of which consists of the unit $(CH_2)_{m/2}OC'O'(CH_2)_{n/2}$, which run consecutively in opposite directions. Consequently, the allowed (but not necessarily fulfilled) conformational symmetry elements are (1) a center of inversion symmetry, i, (2) three 2-fold rotation symmetries about three perpendicular axes in the x, y, and z directions (z taken to be perpendicular to the ring plane), denoted C_{2x}, C_{2y}, and C_{2z}, respectively, and (3) two reflections through mirror planes perpendicular to each other and to the ring plane, denoted by σ_{yz} and σ_{xz}. Whether a given equilibrium conformation possesses one or more of these allowed symmetry elements can be judged by inspecting the torsional angles: if two units of the molecule are related by a rotational symmetry, then their corresponding torsional angles are identical, while if the units are related by inversion or mirror symmetries, then the corresponding torsional angles have opposite signs.

We obtained equilibrium conformations and electrostatic and nonelectrostatic intramolecular interaction energies for the following molecules and also examined their ionic complexes for Li^+, Na^+, and K^+: $m = 1$, $n = 1$; $m = 2$, $n = 2$–4; $m = 3$, $n = 3$; and partially $m = 1$, $n = 3$. Table IV presents the main results for these molecules. The calculations revealed a number of general properties of this group: The molecules are all rather flexible, their flexibility being derived mainly from the unhindered rotation about the C–C′ and C–O bonds. They have several minima of low energy and can change easily from one conformation to the other by thermal agitation, the transition involving mainly rotations around the C–C bonds across a maximum of their torsional potentials. The CC′–OC torsional angle of the ester bond is mostly in the trans conformation, although twisted by varying amounts. The conformational symmetry is generally much lower than that allowed by the structure; in fact, in most of the molecules examined by us, we found no symmetric conformations at all, even though we were looking specifically for them. The symmetric conformations we did obtain had mostly inversion and 2-fold rotation (C_{2z}), in which only the nonadjacent units I–III and II–IV were symmetry related.

(20) Yu. A. Ovchinnikov, *FEBS Lett.*, **44**, 1 (1974).
(21) A. Shanzer, N. Mayer-Shochet, F. Frolow, and D. Rabinovich, *J. Org. Chem.*, **46**, 4662 (1981); A. Shanzer, J. Libman, H. Gottlieb, and F. Frolow, *J. Am. Chem. Soc.*, **104**, 4220 (1982).

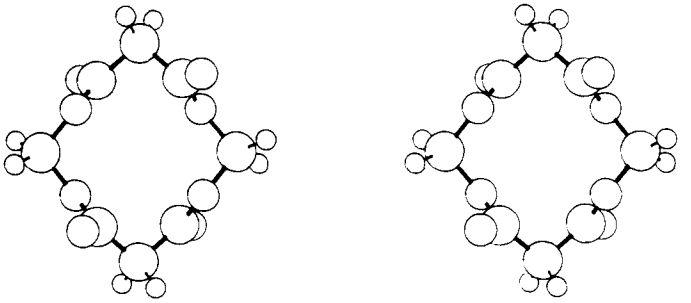


Figure 2. Ref-lactone $m = n = 1$; conformation 1.

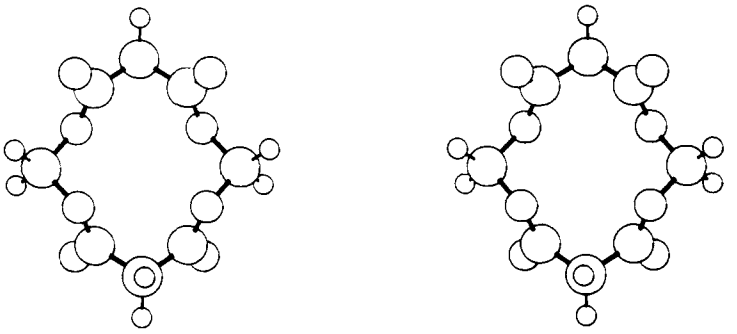


Figure 3. Ref-lactone $m = n = 1$; conformation 2.

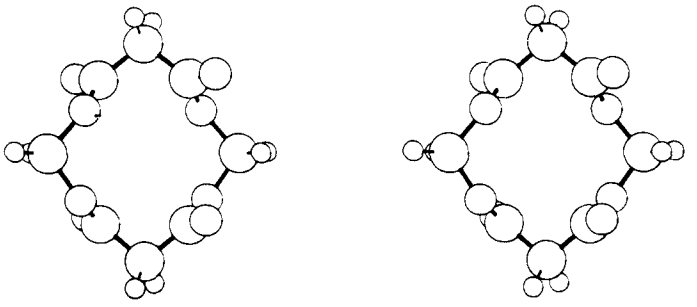


Figure 4. Ref-lactone $m = n = 1$; conformation 3.

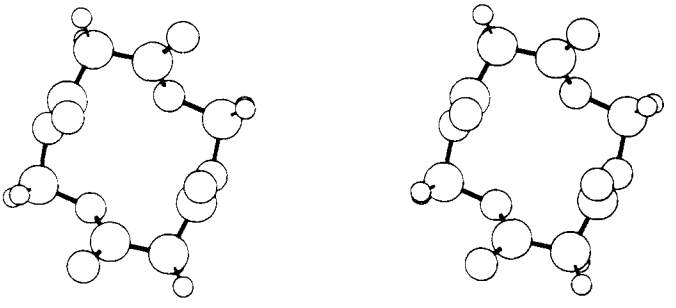


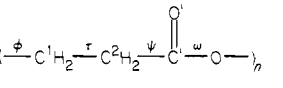
Figure 5. Ref-lactone $m = n = 1$; conformation 4.

None of the molecules listed in Table IV is a good ionophore. The C=O dipoles are in all cases pointing divergently outward and lack even approximate symmetry. The complexes of all these molecules with the three alkali ions considered here are all external and do not form tetrahedral cavities, except in two instances ($n = 3$ and 4; $m = 2$), where the binding dipoles of the respective Li^+ complexes form badly distorted tetrahedrons. Sandwiching of an ion between two ref-lactones is also ruled out, since in no molecule were all four carbonyls located on the ring in a manner deemed suitable for forming a cavity. These results are in agreement with the experimental observations that no ion binding could be observed with these molecules.

An exception to these general rules is the smallest ring $m = n = 1$, in which the lowest energy conformation has all three C_2 rotation axes. The cavity formed in this conformation is a perfect tetrahedron; however, the C=O′ dipoles are directed outward, so it could only bind an anion or perhaps capture an electron, and its size is too small to accommodate any ion. The structural features of the four calculated conformations of this molecule may be inspected by examination of their respective stereoviews, given in Figures 2–5, as viewed along the axes perpendicular to the ring planes. None of these conformations appears to be an ionophore candidate.

Cyclic Propiolactones with Rotational Symmetry

The second set of polylactone molecules synthesized by the template method is the group of roto-*n*-propiolactones of the general structure (where the Greek letters denote the torsional



IV

angles, for later reference). It is derived[22] by reacting stannoxane

Table V. Torsional Angles for Roto-tripropiolactone

	ϕ	τ	ψ	ω
exptl, residue 1	−167	73	−88	165
exptl, residue 2	−138	62	−134	178
exptl, residue 3	−99	72	−88	−178
calcd, all residues	−125	63	−110	−176

ring templates with propiolactone. This reaction produces a distribution of roto-*n*-propiolactones of ring sizes n = 3–8, with a total yield of up to 80%. The individual roto-*n*-propiolactones are separated by chromatography.

Roto-tripropiolactones. The structure of roto-tripropiolactone has been determined recently by X-ray diffraction.[22] It has a somewhat distorted C_3 symmetry. The distortion is probably caused by the crystal packing forces. The calculated equilibrium conformation, obtained without using the experimental prior information, has a precise C_3 symmetry. The same conformation is obtained also by initiating the calculation (energy minimization) from the experimental coordinates. Table V presents the torsional angles of the unligated roto-tripropiolactone for both the experimental and calculated conformations. The range of variation of the experimental ϕ, τ, ψ, and ω angles is 68, 10, 46, and 17°, respectively. It is seen that the angles ϕ and ψ yield most readily to the packing forces. This is compatible with their having the softest torsion potential (zero in our force field). The three carbonyl bonds are located on one side of the main molecular plane (the plane through the center of mass of the ring and perpendicular to the C_{3z} symmetry axis). In the calculated conformation the C′--C′ and O′--O′ distances are 3.57 and 4.19 Å, respectively, and the carbonyl bond is bent outward at an angle of 17° from the symmetry axis. The outward bending is mainly due to the electrostatic repulsion between the carbonyl oxygens.

An alkali ion can bind to the three carbonyls simultaneously, bending the carbonyl bonds inward and forming a pyramid with the O′ atoms at the base and the ion at the top. The calculated binding energies are −65, −46, and −35 kcal/mol for Li^+, Na^+, and K^+, respectively. It can also bind to the three ester oxygens on the other side of the ring, although this binding is considerably weaker (−48, −26, and −15 kal/mol, respectively). A single roto-tripropiolactone molecule cannot act as an ionophore since the ion binding is external and no cavity is formed, and the three dipole–ion bonds replace only half of the hydration shell of the ion. On the other hand, an ion may be sandwiched between two molecules to form an ion/dimer complex, in which the six carbonyls of the dimer engulf the ion in a cagelike structure.

Roto-tripropiolactone Dimers. Such dimers can be realized in two sterically different configurations, which we shall denote by LL and LD. In the LL configuration, the two molecules have the same configuration L and the same torsional angles, and the juxtaposition of their carbonyls to form a cage is obtained when the directions C^1–C^2–C′O′–O of the two rings run in opposite senses. In the LD configuration one molecule is the mirror image of the other, the respective torsional angles have opposite signs, and the rings run parallel to each other. Note that the roto-propiolactones represented by formula IV do not possess optically active groups, and the chirality is determined only by the signs of the torsional angles. The transformation of the monomer from L to D and vice versa can be obtained by rotating these angles. The potential barriers for such rotations are expected to be rather low, so that L and D are equilibrated by thermal agitation. Table VI presents the various structural parameters of such complexes. The parameters pertain to both the LL and LD dimers, since the differences between the two were found to be negligibly small. The distinction will appear, however, to be significant when we consider below roto-tripropiolactones with substituted methylene groups. It is seen that the cages of the dimer/ion complexes of Li^+ and Na^+ are in many ways similar to those of the enniatin analogue LD-LAC6-ion complexes. However, the carbonyl dipoles are better aligned toward the ion (e.g., the supplementary angle Na^+···O=C is 43° in the dimer, while it is 63° in enniatin), the binding energies are considerably larger, and the various binding parameters exhibit less specificity in the dimer case as compared to the LD-LAC6 case. This is to be expected since the two monomers can adapt separately, and therefore more freely, to the electrostatic attraction and the geometric requirements of the ion/molecule interactions. For Li^+ and Na^+, the two molecules form almost perfect cages. For K^+, however, the two molecules of the dimer seem to be too widely separated. They are not parallel to each other but rather tilted, as indicated by the large variation of the O′--O′ between-ring distances (3.36–5.06 Å). As a result of the asymmetric interaction between the tilted monomers, the C_3 symmetry of each monomer is also somewhat distorted, as indicated by minor changes in the torsion angles ϕ and ψ and the various interatomic distances presented in Table VI.

Substituted Roto-propiolactone Dimers. Ionophoric properties of roto-propiolactone dimers may be improved and their specificities enhanced when appropriate hydrophobic side chains are attached to the propiolactone ring, by analogy with the hydrophobic side chains of all members of the enniatin family of native ionophores. The substituent side group R is bound to either C^1 or C^2 (see formula IV), and the substituted carbon becomes chiral. Using racemic monomers in synthesizing the roto-propiolactones is expected to produce rings of mixed chirality, while using chiral monomers enhances structural symmetry and consequently ionophoric behavior. We consider, therefore, only substituted roto-tripropiolactones of uniform chirality, one of the two possible enantiomers. We noted above that the unsubstituted roto-propiolactone may exist in two enantiomeric conformations, L and D, which possess torsional angles of the same absolute values and opposite signs. In the case of substituted roto-propiolactones, the L and D conformations become diastereoisomers, since the side chains occupy inequivalent positions in the two conformations, which we denote as equatorial and axial, respectively. The L–D conformational transition is expected again, as in the unsubstituted case, to have a low barrier, so that the axial and equatorial conformations maintain thermal equilibrium. In the following we discuss the conformational and ionophoric characteristic parameters of such rings with simple substituents such as methyl or isopropyl groups.

Methyl-Substituted Roto-tripropiolactones and Their Ion Complexes. Table VII presents results for methyl-substituted roto-tripropiolactone single molecules and their ion complexes, indicating their torsional angles, relative energies, and relevant interatomic distances.

A number of interesting observations may be made by inspecting Table VII. First, the equatorial conformations of substituted roto-tripropiolactones are significantly more stable than the axial ones. This is particularly true for the C^1-substituted tripropiolactones, for which the calculated energy difference is 9 kcal/mol. Second, the equatorial conformations of both the C^1 and C^2 substitutions are practically the same as that of the unsubstituted tripropiolactones, with only slight deviations in the angles ϕ and ψ. On the other hand, the axial conformations are significantly twisted, particularly that of the C^1-substituted molecule. Third, the electrostatic forces exerted by a metal ion are so much stronger than the intramolecular interactions that the geometric parameters of the ligated complex are practically independent of the location of substituent methyl and only slightly dependent on the conformation of the ring. Yet, the binding energy is different in all four cases, pointing to the equatorial C^2 case as the most stable complex.

Isopropyl-Substituted Dimers and Their Ion Complexes. Methyl side chains are too small to form a hydrophobic shell around the dimer/ion complex. Isopropyl substituents are therefore examined next, in view of the fact that isopropyl is a major component of the hydrophobic shell of the enniatins, whose ion cage is similar to that of the tripropiolactone dimers. Because of computational limitations we replaced the aliphatic carbons and their hydrogens by "extended atoms" representing the methyl, methylene, and methine groups.[23] The results of this simplified force field differ

(22) A. Shanzer, J. Libman, and F. Frolow, *J. Am. Chem. Soc.*, **103**, 7339 (1981).

Table VI. Binding Angles (deg), Energies (kcal/mol), and Distances (Å) of Unsubstituted Roto-tripropiolactone Dimer Complexes

	ϕ	τ	ψ	ω	E_{bind}	ion-O′	$\sqrt{2}$(ion-O′)	same ring O′-O′	same ring C′-C′	between rings, O′-O′
monomer	−125	63	−110	−176				4.19	3.57	
Li^+ complex	−104	62	−127	179	−105	2.07	2.93	2.90	3.34	2.97
Na^+ complex	−108	62	−123	180	−86	2.32	3.28	3.12	3.40	3.42
K^+ complex[a]	−107	62	−120			2.68	3.79	3.22	3.39	3.36
	−112	63	−123	−179	−67	2.71	3.83	3.36	3.44	5.06

[a] The C_3 symmetry of the molecules is slightly distorted in the K^+ complex. The two bottom rows give the smallest and largest values of the various parameters, respectively.

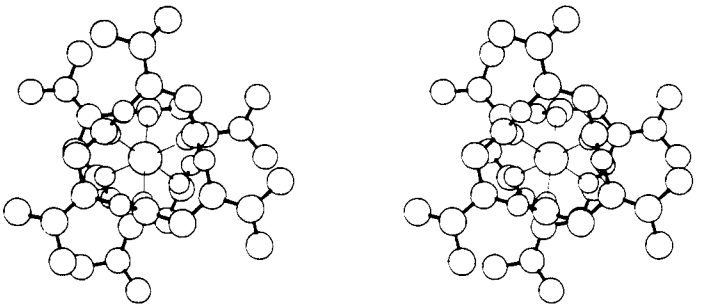


Figure 6. C^1,LL Li^+ dimer complex of roto-tripropiolactone with equatorial isopropyl side chains.

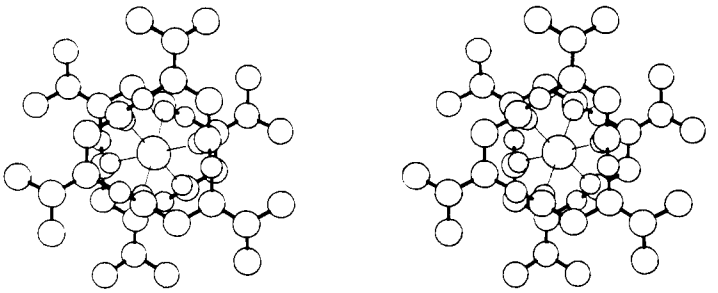


Figure 7. C^1,LD Li^+ dimer complex of roto-tripropiolactone with equatorial isopropyl side chains.

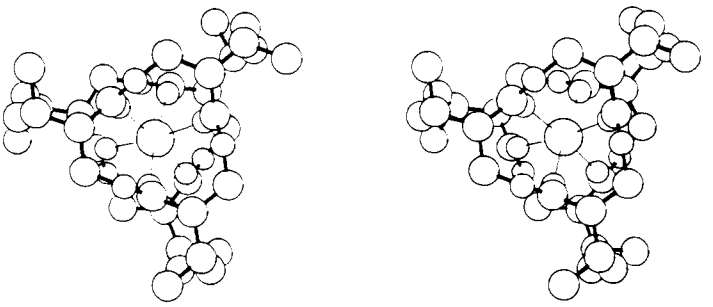


Figure 8. C^2,LL Li^+ dimer complex of roto-tripropiolactone with equatorial isopropyl side chains.

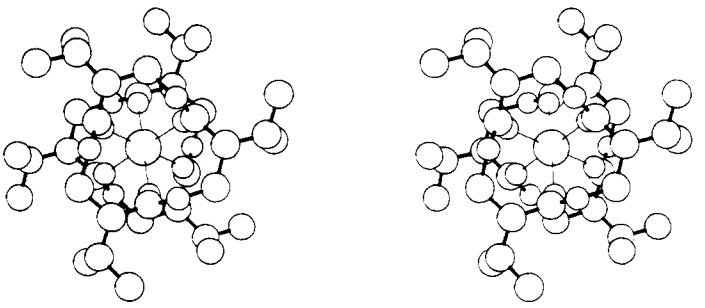


Figure 9. C^2,LD Li^+ dimer complex of roto-tripropiolactone with equatorial isopropyl side chains.

by up to 4° in torsional angles and by up to 3 kcal/mol in monomer strain energies, but these are relatively minor defects and do not seem to affect significantly the calculated ionophoric characteristics. We have limited the calculations to equatorial conformations, since the axial ones were disfavored already in the case of the methyl substitutions. The equatorial conformations of the isopropyl-substituted molecule and its ion complexes are almost exactly the same as those of the methyl substitutions and are well represented by Table VII. Therefore, only dimer complexes are

(23) The nonbonded parameters, adapted from Levitt and Lifson (unpublished results), were r^* 4.19 Å, ϵ 0.092; partial charges were set to zero.

Table VII. Roto-tripropiolactones with Methyl Side Chains on C^1 (Next to O) or C^2 (Next to C')

	ϕ	τ	ψ	ω	$E_{bind}{}^a/E_{ax}{}^b$	ion-O'	$\sqrt{2}$(ion-O')	O'-O'
				C^1, equatorial				
unligated	−129	64	−107	−177				4.23
Li^+ complex	−110	63	−121	178	−63	1.82	2.57	2.86
Na^+ complex	−110	62	−121	180	−44	2.28	3.22	3.08
K^+ complex	−111	62	−120	−179	−34	2.68	3.78	3.22
				C^1, axial				
unligated	−179	−65	68	−179	9			6.04
Li^+ complex	101	−59	124	−176	14	1.80	2.54	2.84
Na^+ complex	101	−58	124	−178	17	2.26	3.19	3.06
K^+ complex	102	−58	124	180	18	2.65	3.75	3.20
				C^2, equatorial				
unligated	−119	62	−115	−175				3.77
Li^+ complex	−110	61	−120	180	−68	1.81	2.56	2.85
Na^+ complex	−110	61	−120	−178	−48	2.27	3.21	3.07
K^+ complex	−111	61	−120	−178	−38	2.66	3.77	3.19
				C^2, axial				
unligated	143	−64	95	179	6			4.71
Li^+ complex	108	−63	123	−178	11	1.81	2.56	2.86
Na^+ complex	109	−62	123	180	10	2.27	3.22	3.09
K^+ complex	111	−62	122	179	10	2.67	3.78	3.23

[a] E_{bind} (kcal/mol) is the difference between the total energies of the ion/molecule complex and the unligated molecule in the equatorial conformations. [b] E_{ax} (kcal/mol) is the difference between the total energies of the corresponding complexes in the axial and equatorial conformations.

Table VIII. Dimer Complexes of Roto-tripropiolactones with Equatorial Isopropyl Side Chains

ion	conf	E_{bind}	ion-O'	$\sqrt{2}$(ion-O')	r_{11}(O'-O')	r_{12}(O'-O')	r_{12}(Me-Me)[a]
Li^+	C^1,LL	−92	2.09	2.95	2.92	2.92, 3.00	5.9, 6.5
	C^1,LD	−92	2.09	2.95	2.92	2.98	6.2
	C^2,LL	−97	2.11	2.98	2.91	2.94, 3.16	3.4, 5.2
	C^2,LD	−100	2.07	2.93	2.89	2.96	5.3, 5.6
Na^+[b]	C^2,LL	−80	2.33	3.30	3.09	3.33, 3.67	3.7, 5.4
	C^2,LD	−80	2.32-2.35	3.28-3.33	3.06-3.16	3.16-3.82	5.1-6.5

[a] Only the two shortest Me-Me distances between pairs of isopropyls are given. They are the same for all three pairs whenever C_3 symmetry is maintained. [b] In C^2,LD of Na^+ the range of variation due to the tilt is given (see text).

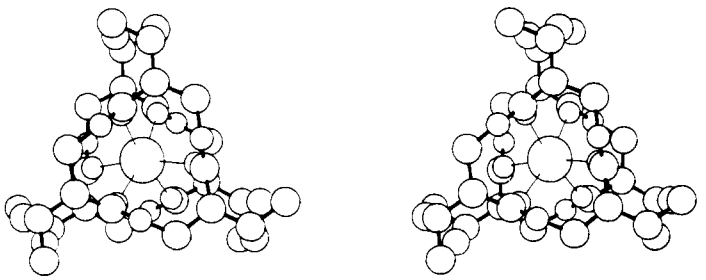


Figure 10. C^2,LL Na^+ dimer complex of roto-tripropiolactone with equatorial isopropyl side chains.

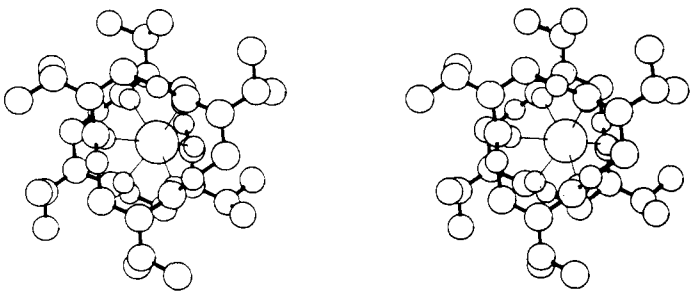


Figure 11. C^2,LD Na^+ dimer complex of roto-tripropiolactone with equatorial isopropyl side chains.

discussed. Two equatorial enantiomers, L and D, can form dimers of two distinct conformations, LL (or its enantiomer DD) and LD. In the LL dimer the two molecules have the same chirality. In the LD dimer the two rings are mirror images of each other. In both configurations the decisive factors are the ion–dipole interactions, which force the six carbonyls of the two molecules to form an octahedral cage around the ion. However, the juxtaposition of the isopropyl side chains is different, as is seen from the stereoviews of the four different Li^+ complexes, as well as the C^2, LL complex for Na^+, shown in Figures 6–11. The main ionophoric parameters of these dimers are summarized in Table VIII.

In both the C^1- and C^2-substituted LD dimer/ion complexes, the isopropyls of the two rings are staggered, just like the carbonyls, as a consequence of the inherent reflection symmetry between the L and D configurations. Thus the LD configurations possess an

S_6 symmetry, like the unsubstituted dimer/ion complexes. The two shortest Me–Me distances between neighboring isopropyls (last column of Table VIII) are larger than contact distances. It seems, therefore, that larger side chains might be necessary to form a better, continuous, hydrophobic shell.

In the LL complexes, on the other hand, the three pairs of adjacent isopropyls are closer to each other, leaving the inner core more exposed to solvent, and the dimers possess only a C_3 symmetry at most. In particular, in the C^2,LL configuration the isopropyls are eclipsed and form close contacts, so much so as to repel each other, especially when binding Li^+. In this configuration the Li^+ complex may be less favored than the Na^+ one, as can be seen by inspecting Table VIII, since the binding energy and ion–O′ distance of the LL Li^+ complex are different from those of the LD. There are no such differences for the Na^+ complexes. In the C^2,LL K^+ complex, the contact between the isopropyls is lost. Thus, the C_3 symmetry conformation is unstable in this case. In the stable conformation, the two tripropiolactone rings are tilted with respect to each other, as in the unsubstituted K^+ dimer complex.

The Na^+ complex of the C^2,LD configuration, as presented at the bottom of Table VIII, is also seen to have lost the C_3 symmetry (as have both C^1 Na^+ complexes, which are not presented in Table VIII), by the tilting of the rings with respect to each other. Such a calculated tilt is expected whenever there is no close contact between the two molecules of the dimer complex, except through the ion in its center. However, this is the expected behavior of the system in vacuum. In a solvent, whenever the distance between the rings and their side chains is larger than close contact, solvent forces either press the molecules into contact, or insert solvent molecules between them. In this way, solvation interactions affect the ion selectivity of the complex. Thus, while the C^2,LL ion complex showed selectivity toward Na^+ over Li^+ in our model, solvent forces may change this trend.

The above discussion included LD and LL configurations for the sake of comparison between the two. However, it should be kept in mind that, while LL (or DD) dimers occur in isolation when the solution contains only L (or D) monomers, LD dimers cannot be separated from LL, since their relative distributions are in thermal equilibrium. Since L and D monomers must be synthesized separately, it is gratifying to observe that no compelling argument for preference of LD configurations has been found.

In summary of the above, it may be concluded that the C^2 isopropyl-substituted roto-tripropiolactone is an interesting candidate for ionophoric behavior of its ion/dimer complexes, with perhaps some potential for ion selectivity for either Li^+ or Na^+. Larger side groups might be necessary for completing the hydrophobic shell, and, moreover, bulkier side groups may increase the size of the cage, thus shifting the selectivity toward the K^+ ion. However, the details of such properties as close packing of the side chains, forming the hydrophobic shells, or fixing the size of the central cavity depend to a large extent on solvent interactions and cannot be derived by the present method.

Acknowledgment. We are grateful to Dr. Hirshfeld and Dr. Warshel for reading the manuscript and offering useful comments, to Dr. Zipora Shakked for her friendly help in scanning the literature on ion–carbonyl distances through the Cambridge Structural Database, and to the U.S.–Israel Binational Science Foundation for their support of this work.

Registry No. I, 39541-66-7; II (R = Me), 85407-30-3; II (R = Me) Li^+ complex, 85407-35-8; II (R = Me) Na^+ complex, 85407-36-9; II (R = Me) K^+ complex, 85407-37-0; III ($m = n = 1$), 85407-31-4; III ($m = n = 2$), 62538-52-7; III ($m = 2$; $n = 3$), 74783-06-5; III ($m = 2$; $n = 4$), 64066-17-7; III ($m = n = 3$), 85407-32-5; IV ($n = 3$), 80109-29-1; IV ($n = 3$) Li^+ dimer complex, 85407-38-1; IV ($n = 3$) Na^+ dimer complex, 85407-39-2; IV ($n = 3$) K^+ dimer complex, 85407-40-5; C^1,C^1,C^1-trimethyl-IV ($n = 3$), 85407-33-6; C^1,C^1,C^1-trimethyl-IV ($n = 3$) Li^+ complex, 85407-41-6; C^1,C^1,C^1-trimethyl-IV ($n = 3$) Na^+ complex, 85407-42-7; C^1,C^1,C^1-trimethyl-IV ($n = 3$) K^+ complex, 85407-43-8; C^2,C^2,C^2-trimethyl-IV ($n = 3$), 85407-34-7; C^2,C^2,C^2-trimethyl-IV ($n = 3$) Li^+ complex, 85407-44-9; C^2,C^2,C^2-trimethyl-IV ($n = 3$) Na^+ complex, 85407-45-0; C^2,C^2,C^2-trimethyl-IV ($n = 3$) K^+ complex, 85407-46-1; C^1,C^1,C^1-triisopropyl-IV ($n = 3$) Li^+ dimer complex, 85407-47-2; C^2,C^2,C^2-triisopropyl-IV ($n = 3$) Li^+ dimer complex, 85407-48-3; C^2,C^2,C^2-triisopropyl-IV ($n = 3$) Na^3 dimer complex, 85407-49-4.