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Salt Effects on the Conformational Behavior of 5-Carboxy- and 5-Hydroxy-1,3-dioxane[1]

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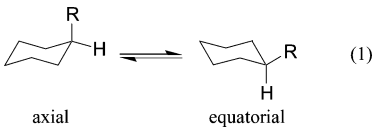
The varied and essential involvement of metal ions and inorganic salts in biological and chemical processes motivated the present study where 5-carboxy- and 5-hydroxy-1,3-dioxanes are used as model frameworks for the evaluation of the conformational behavior of oxygen-containing receptors in the presence of Li^+, Na^+, K^+, Ag^+, Mg^{2+}, Ca^{2+}, Ba^{2+}, and Zn^{2+}. Thus, the position of equilibria, established by means of BF_3, between diastereomeric *cis*- and *trans*-5-substituted-2-phenyl-1,3-dioxanes, in solvent THF and in the presence of 0, 1, and 5 equiv of salt, has been determined. The observed $\Delta G°$ values for the conformational equilibria of 5-carboxy-1,3-dioxane show that Ag^+, Li^+, and Ca^{2+} complexation leads to increased stability of the axial isomer. In the case of the 5-hydroxy-1,3-dioxane, Mg^{2+}, Ag^+, and Zn^{2+} are the metal ions that stabilize the axial conformer of the heterocycle upon association. Interpretation of the experimental observations was based on DFT molecular modeling studies at the Becke3LYP/6-31G* and Becke3LYP/6-31+G** levels of theory. Although gas-phase calculations give ΔE values that are too large when modeling equilibria involving ionic species in polar solution, the computational results confirm the structural and energetic consequences of metal cation coordination to the oxygen atom in carbonyls or ethers. The results derived from the present study contribute to our understanding of the chemical processes involved in molecular recognition and physiological events.

Introduction

In 1950, D. H. R. Barton demonstrated the fundamental importance of axial versus equatorial orientation of the substituent on chemical reactivity and molecular energy of chair-shaped substituted cyclohexanes (eq 1).[2] Indeed, the conformational behavior of monosubstituted cyclohexanes effectively models larger and more complex molecules.[3]



(1)

The fact that many important natural products contain heteroatoms motivated the study of six-membered rings incorporating oxygen, nitrogen, and sulfur atoms.[4] A particularly useful system for examination is that of 2,5-disubstituted 1,3-dioxanes, which are readily equilibrated with Lewis or Brønsted acids. Properly 5-substituted derivatives have proved most valuable in the study of steric,[4a] electrostatic,[5] and stereoelectronic interactions[6] in these heterocycles. 2-Substituted 1,3-dioxane derivatives have also proved very useful in the study of the anomeric effect, one of the most studied topics in physical organic chemistry.[7,8]

Many biological processes such as enzymatic activity, molecular recognition, and signal transduction depend on the presence and interaction of free metal ions and inorganic salts.[9] A dramatic example is the sequence of events that is triggered by Ca^{2+} coordination to calmolu-

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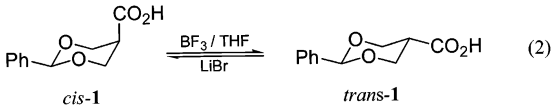
din, a protein that then undergoes substantial structural changes, becomes activated, and in turn activates other enzymes involved in muscle contraction.[10] Furthermore, metal ion complexation may lead to conformational changes that alter the biological activity of natural and synthetic substances. For example, a recent study provides evidence for the Fe^{3+} effect that reduces the toxicity of gossipol.[11] Interestingly, the activity of antitumor antibiotic (+)-duocarmycin SA correlates with the relative stability of its metal complexes (Cu^{2+} > Ni^{2+} > Zn^{2+} > Mn^{2+} > Mg^{2+}), providing the opportunity to "tune" the drug activity profile.[12] Special mention is deserved by the well-established biological relevance of cation interactions in acetylcholine esterase activity[13] and in protein structure.[14]

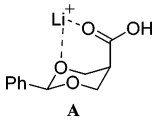
On the other hand, a variety of metal ion salts coordinate to electrophilic groups and activate them for reaction with nucleophiles.[15] Furthermore, metal ions can also promote free radical reactions and electron-transfer reactions.[16] In addition, metal-mediated self-assembly has proved to be a very effective methodology for the construction of two- or three-dimensional supramolecular architectures.[17]

In view of the advantages offered by 1,3-dioxane derivatives for the evaluation of conformational effects (vide supra), a few years ago we carried out the preparation and chemical equilibration of a series of 5-substituted 1,3-dioxanes, both in the presence and absence of lithium bromide.[18,19] Particularly interesting was the salt (LiBr) effect measured in 2-phenyl-5-carboxy-1,3-dioxane, *cis*-**1** ⇆ *trans*-**1**, which shows stabilization of the axial-substituted isomer (eq 2).[18]



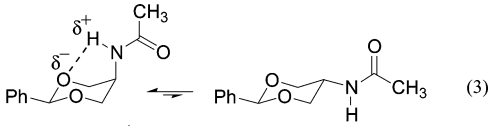
cis-**1** *trans*-**1** (2)

Spectroscopic and molecular modeling studies support species **A** as responsible for the stabilization of *cis*-**1**.[18]

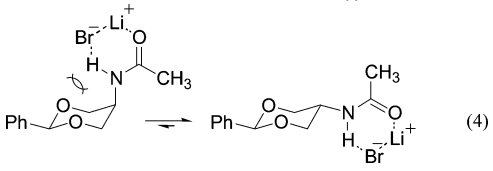


A

On the other hand, the dramatic reversal of conformational preference in 2-phenyl-5-acetamido-1,3-dioxane, *cis*-**2** ⇆ *trans*-**2**, from a robust axial predominance in the absence of salt ($\Delta G°$ = +0.94 kcal/mol) to a clear preference for the equatorial orientation in the presence of 10 equiv of LiBr ($\Delta G°$ = −0.13 kcal/mol) was explained in terms of a disruption of an intramolecular hydrogen bond.[18] (eqs 3 and 4).



(3)



(4)

We now have extended the conformational study of 2-phenyl-5-carboxy-1,3-dioxane (*cis*-**1** ⇆ *trans*-**1**) and 2-phenyl-5-hydroxy-1,3-dioxane (*cis*-**3** ⇆ *trans*-**3**) to include alkali metals Li^+, Na^+, and K^+; alkaline earth metals Mg^{2+}, Ca^{2+}, and Ba^{2+}; and transition metals Ag^+ and Zn^{2+}. The experimental results reported here were well reproduced by molecular modeling studies and actually helped in the interpretation of the observed conformational behavior and salt effects.[20]

Results and Discussion

A. Synthesis of Diastereomeric *cis*- and *trans*-5-Substituted-2-phenyl-1,3-dioxanes. *cis*- and *trans*-2-Phenyl-5-carboxy-1,3-dioxane (*cis*- and *trans*-**1**) were prepared by condensation of benzaldehyde and diethyl bis(hydroxymethyl)malonate, followed by saponification, according to the described procedure.[21] The separation of diastereomeric *cis*- and *trans*-**1** was accomplished by flash chromatography[22] (Scheme 1).

cis- and *trans*-2-Phenyl-5-hydroxy-1,3-dioxane (*cis*- and *trans*-**3**) were prepared by condensation of benzaldehyde

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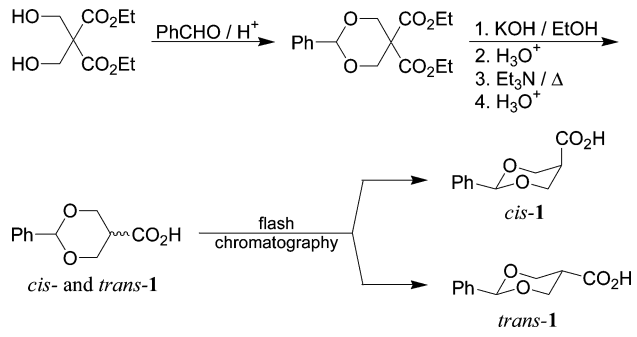
SCHEME 1



and glycerol followed by chromatographic separation, according to the described procedure[6] (Scheme 2).

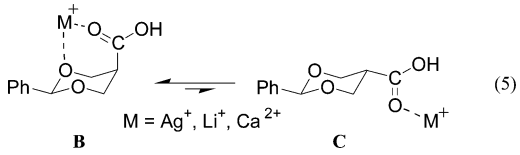
B. Conformational Analysis of 1 and 3 in the Presence of Salts. Equilibration of diastereomeric 2-phenyl-5-substituted-1,3-dioxanes (*cis*-**1** ⇆ *trans*-**1** and *cis*-**3** ⇆ *trans*-**3**) was readily performed by means of Lewis acid BF_3, via open-chain intermediates[23] (Scheme 3). Equilibrium is attained from both the *cis* and *trans* diastereomers, and integration of appropriate signals in the proton NMR spectra served for the determination of the isomeric ratios. Tables 1 and 2 summarize the corresponding free energy differences in the presence of 0.0, 1.0, and 5.0 equiv of salt [LiBr (ref 18), Na(OTf), K(OTf), Ag(OTf), $Mg(OTf)_2$, $Ca(OTf)_2$, $Ba(OTf)_2$, or $Zn(OTf)_2$].[24]

It should be appreciated that the phenyl substituent at C(2) serves as an "anchoring" group,[3,6] since its preference for the equatorial position is so large (3.12 kcal/mol[25]) that it usually overcomes any tendency exhibited by the C(5) substituent. (See, however, gas-phase calculations below.) Although some association of the metal ion with the aromatic phenyl ring is to be anticipated,[14] the participation and impact of such cation-π complexes in the overall equilibria is probably not significant. Indeed, unpublished observations in our group[26] indicate that the presence of LiBr and $ZnBr_2$ in the conformational equilibrium of *cis*- and *trans*-2-isopropyl-5-phenyl-1,3-dioxane does not change significantly the conformational free energy differences measured in the absence of salt.

B.1. In the absence of salt, both the 5-CO_2H and 5-OH groups exhibit a substantial preference for the equatorial position, $\Delta G° = -0.80$ and -0.40 kcal/mol, respectively (first entries in Tables 1 and 2). This observation is in line with expected steric and electrostatic (dipole−dipole) repulsive interactions operative in the axial isomers (cf. Scheme 3) and argue against the existence of *intramolecular* O−H···O hydrogen bonding in the axial isomers *in THF solvent*, since such interaction is expected to lower the energy of these conformers. (Compare Scheme 4a presenting the anticipated *intermolecularly* H-bonded species in THF solvent with Scheme 4b that depicts the *intramolecular* hydrogen bond in axial (*cis*) **1** or **3** in non-hydroxylic solvents or the gas phase.)

B.2. The salt effects measured in the present work for 5-carboxy revealed three distinct tendencies upon salt addition: (1) Significantly increased axial preference when Ag^+ is present in the equilibrium. This effect [$\Delta\Delta G° = \Delta G°$(5 equiv salt) − $\Delta G°$(reference) = +0.70 − (−0.80) = +1.50 kcal/mol] is even larger than that previously found with LiBr[18] [$\Delta\Delta G° = \Delta G°$(5 equiv salt) − $\Delta G°$(reference) = −0.17 − (−0.80) = +0.63 kcal/mol]. (2) Reduced equatorial preference in the presence of Ca^{2+} [$\Delta\Delta G° = -0.39 - (-0.80) = +0.41$ kcal/mol]. (3) No significant salt effect by Na^+, K^+, Mg^{2+}, Ba^{2+}, and Zn^{2+} on the conformational equilibrium of *cis*- and *trans*-**1**.

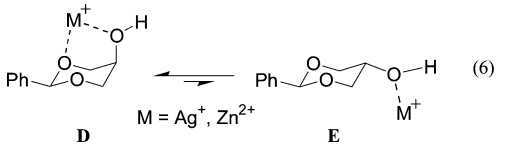
A plausible explanation for the increased axial preference of the carboxy group in the presence of LiBr, $Ca(OTf)_2$ and specially Ag(OTf) is that the metal cations interact with both the endocyclic oxygen atoms and the carbonyl group, leading to a stabilization of the *cis* (axial CO_2H) form (cf. **B** in eq 5). The stronger binding force exhibited by silver relative to that of lithium may be due to the increased binding ability of the former metal ion.[27]



(5)

The experimental results (Table 3) suggest that the softer and larger (relative to Li^+ and Ag^+) cations Na^+, K^+, Mg^{2+}, Ba^{2+}, and Zn^{2+} may be too large to fit the binding site provided by *cis*-**1** (cf. **B** in eq 5).

B.3. With regard the conformational equilibria of 5-hydroxy-2-phenyl-1,3-dioxane (*cis*-**3** ⇆ *trans*-**3**) summarized in Table 2, significant salt effects were recorded only in the presence of Mg^{2+} and transition metals Ag^+ and Zn^{2+}. The observed increased axial preference upon salt addition suggests metal ion coordination to both endocyclic and exocyclic oxygens in *cis*-**3** (cf. **D** in eq 6). Nevertheless, it is appreciated that silver ion salt effects in hydroxy-dioxane **3** are substantially weaker than those measured in carboxy-dioxane **1** (eq 5): $\Delta\Delta G° = \Delta G°$(5 equiv salt) − $\Delta G°$(reference) = + 0.13 − (−0.40) = + 0.53 kcal/mol in dioxane **3**, relative to $\Delta\Delta G° = 1.50$ kcal/mol in dioxane **1** (see above).



(6)

C. Molecular Modeling Studies. Calculation of the conformational data described in section B was deemed essential in order to increase our understanding of the equilibria and salt effects involved and to gain support for the interpretations advanced.

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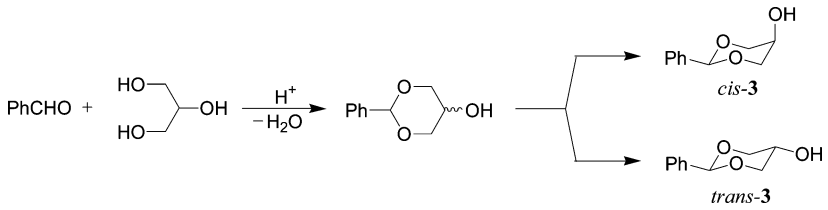
SCHEME 2



SCHEME 3

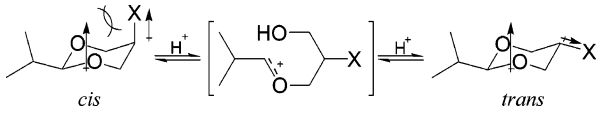
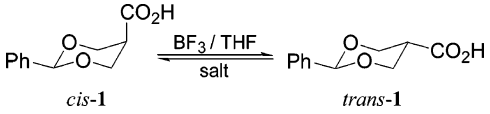


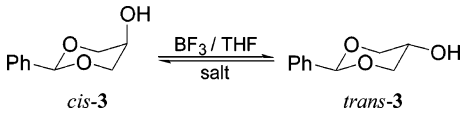
TABLE 1. Conformational Equilibria in 5-Carboxy-2-phenyl-1,3-dioxane 1, in Absence or Presence of Salt, at 25 °C in THF



	ΔG° (kcal/mol)[a]		
salt	1.0 equiv	5.0 equiv	salt effect
− [−0.80 ± 0.03]			
LiBr[b]	−0.41 ± 0.03	−0.17 ± 0.08	(+)
Na(OTf)	−0.59 ± 0.08	−0.61 ± 0.09	
K(OTf)	−0.72 ± 0.09	−0.56 ± 0.12	
Ag(OTf)	−0.42 ± 0.07	+0.70 ± 0.12	(++)
$Mg(OTf)_2$	−0.51 ± 0.02	−0.62 ± 0.14	
$Ca(OTf)_2$	−0.62 ± 0.20	−0.39 ± 0.05	(+)
$Ba(OTf)_2$	−0.68 ± 0.08	−0.68 ± 0.07	
$Zn(OTf)_2$	−0.59 ± 0.10	−0.56 ± 0.07	

[a] Positive values indicate a predominance of the *cis* (axial X) diastereoisomer, whereas negative ΔG° values correspond to exoergic processes where the *trans* (equatorial X) diastereoisomer is more stable. [b] Taken from ref 18.

TABLE 2. Conformational Equilibria in 5-Hydroxy-2-phenyl-1,3-dioxane 3, in Absence or Presence of Salt, at 25 °C in THF



	ΔG° (kcal/mol)[a]		
salt	1.0 equiv	5.0 equiv	salt effect
− [−0.40 ± 0.02]			
LiBr[b]	−0.38 ± 0.04	−0.43 ± 0.03	
Na(OTf)	−0.37 ± 0.04	−0.25 ± 0.05	
K(OTf)	−0.44 ± 0.04	−0.33 ± 0.11	
Ag(OTf)	−0.22 ± 0.03	+0.13 ± 0.05	(+)
$Mg(OTf)_2$	+0.74 ± 0.15	+0.98 ± 0.03	(++)
$Ca(OTf)_2$	−0.24 ± 0.15	−0.33 ± 0.07	
$Ba(OTf)_2$	−0.36 ± 0.04	−0.38 ± 0.08	
$Zn(OTf)_2$	−0.31 ± 0.02	+0.19 ± 0.08	(+)

[a] Positive values indicate a predominance of the *cis* (axial X) diastereoisomer, whereas negative ΔG° values correspond to exoergic processes where the *trans* (equatorial X) diastereoisomer is more stable. [b] Taken from ref 18.

Full geometry optimizations (no symmetry constraints) of axial and equatorial 5-carboxy-1,3-dioxane (**4**), its corresponding carboxylate derivate (**5**), 5-hydroxy-1,3-dioxane (**6**), and their corresponding metal ion complexes were carried out using the Gaussian suite of programs.[28]

SCHEME 4

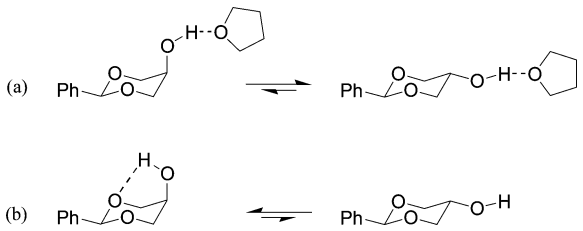
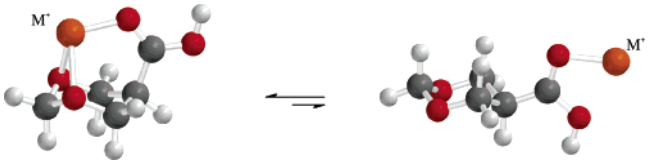


TABLE 3. Relative Energies (Δ*E*, B3LYP/6-31+G) for Axial to Equatorial Equilibria of 5-Carboxy-1,3-dioxane 4 in the Presence of Metal Ions**



			ΔS° (cal/mol·K)			
M^+	ΔE (kcal/mol)	ΔH° (kcal/mol)	ΔS° total	ΔS° mixing	ΔS°[a]	$\Delta G°_{298K}$ (kcal/mol)
Li^+	+21.6	+21.3	+8.50	+1.21	+7.29	+18.76
Na^+	+15.6	+15.9	+12.4	+0.99	+11.4	+12.20
K^+	+11.9	+11.6	+6.01	+1.09	+4.92	+9.80
Mg^{2+}	+53.9	+52.7	+8.21	+0.86	+7.35	+50.25
Ca^{2+}	+37.7	+36.8	+7.48	+0.96	+6.52	+34.57

[a] Sum of the vibrational, rotational, translational, and electronic entropies.

Density Functional Theory (DFT)[29] calculations were carried out using the Becke's three-parameter hybrid functional incorporating the Lee, Yang, and Parr (B3LYP) method.[30] Molecular energy single-point calculations on the optimized structures were carried out using the second-order Møller−Plesset perturbation (MP2) method.[31] Both the 6-31G* and 6-31+G** basis sets were employed in most calculations, including gradient-corrected correlation functionals.[32] All minima were confirmed by frequency analysis.

(28) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millan, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adano, C.; Clifford, S.; Ochterski, J.; Petterson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkava, A.; González, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogde, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.; Pittsburgh, PA, 1998.

(29) Jonson, B. G. *Modern Density Functional Theory. A Tool for Chemistry*; Elsevier: Amsterdam, 1995.

(30) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *B37*, 785. (b) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200.

(31) Curtiss, L. A.; Raghavachari, K.; Pople, J. A. *J. Chem. Phys.* **1993**, *98*, 1293.

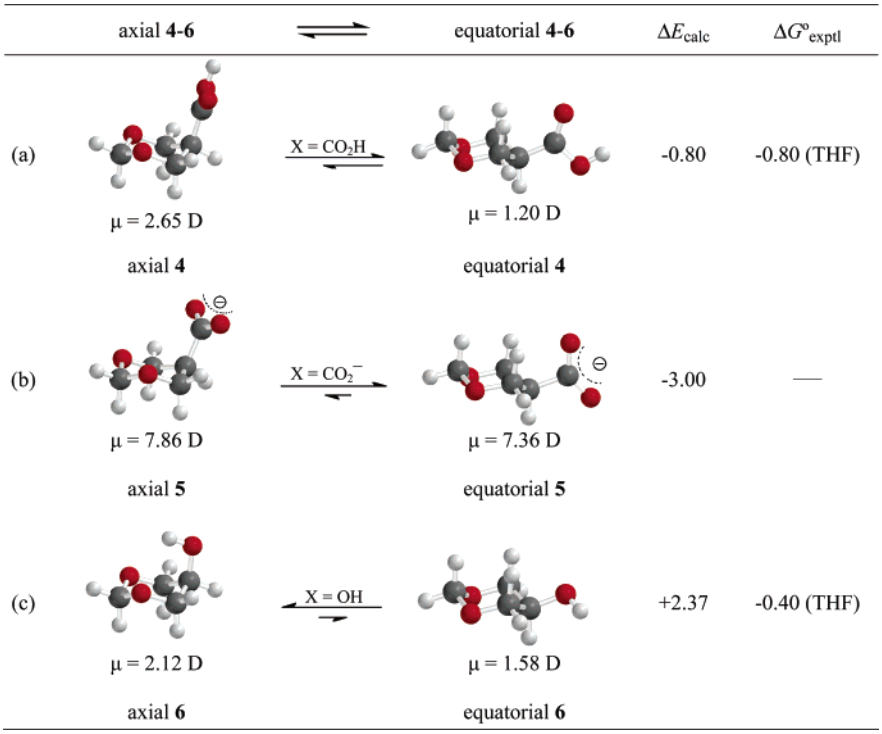


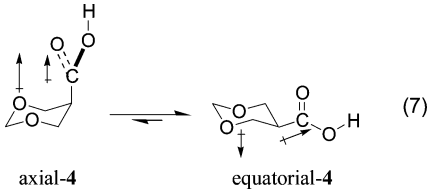
FIGURE 1. Calculated and experimental (kcal/mol) relative energies for (a) axial and equatorial 5-carboxy-1,3-dioxane (**4**), (b) axial and equatorial 5-carboxylate-1,3-dioxane (**5**), and (c) axial and equatorial 5-hydroxy-1,3-dioxane (**6**).

As indicated in section B, the experimental equilibrium data are for 2-phenyl-5-substituted-1,3-dioxanes, whereas the computational data are for the equilibria of axial and equatorial 1,3-dioxanes in which there is no phenyl substitution at the 2-position. Of course, this was done in order to optimize the use of the available amount of computational resources. That the effect of phenyl substitution on the equilibria is negligible was confirmed by optimization of the axial (*cis*) and equatorial (*trans*) 2-phenyl-5-carboxy-1,3-dioxane: no significant difference in ΔE (<0.1 kcal/mol) relative to model system **4** was observed; that is, the 2-phenyl substituent plays only a role as anchoring group.[33]

Figure 1 presents the computed [B3LYP/6-31G*] relative energies of the most stable structures for axial and equatorial **4**−**6**.

C.1. Fortuitously, the agreement between the experimental $\Delta G°$ value obtained from the chemical equilibration of *cis*- and *trans*-5-carboxy-2-phenyl-1,3-dioxane **1** (in THF solvent) and the calculated ΔE value for axial versus equatorial **4** is perfect.[33]

Steric and electrostatic dipole−dipole repulsion in the axial isomer accounts for the $\Delta E = -0.80$ kcal/mol preference for equatorial **4** (eq 7).



(7)

Interestingly, the lowest energy rotamer for axial 5-carboxy-1,3-dioxane **4** presents the carboxy group nearly perpendicular to the plane that bisects the ring

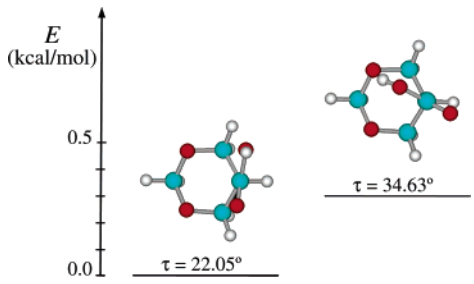


FIGURE 2. Calculated energy minima for axial 5-carboxy-1,3-dioxane (**4**).

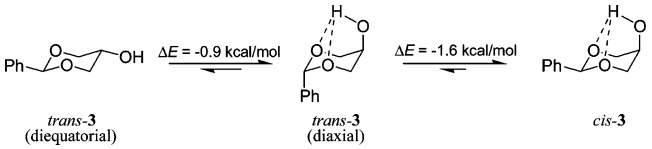
(see Figure 2a). This conformation does not orient the carboxylic group in a way that hydrogen bonding with the endocyclic oxygens is possible. Nevertheless, rotation at the O−C−C(5)−C(4) segment bonds leads to an alternative rotamer with a dihedral angle $\tau = 34.63°$, where the carboxyl OH group does participate in hydrogen bonding. Apparently, partial eclipsing renders this conformation 0.3 kcal/mol higher in energy relative to the lowest energy rotamer with $\tau = 22.05°$ (Figure 2).

C.2. Proton removal from carboxylic acid **4** affords carboxylate **5**, which exhibits an even higher predominance of the equatorial conformer ($\Delta E = -3.0$ kcal/mol, Figure 1b). Although no experimental data are available for comparison purposes, it seems quite reasonable that

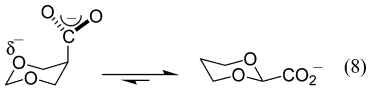
(32) The use of larger basis sets such as B3LYP/6-311G** (cf. Rabuck, A. D.; Scuseria, G. E. *Theor. Chem. Acc.* **2000**, *104*, 439) did not result in significant differences when comparing calculated energies or geometries for the optimized structures.

(33) The calculated [B3LYP/6-31G*] ΔE value between *cis*-**1** and *trans*-**1** is −0.73 kcal/mol (diequatorial *trans*-**1** being more stable). By comparison, calculated ΔE for axial versus equatorial **4** is −0.80 kcal/mol (Figure 1a).

SCHEME 5



electrostatic repulsion between the carboxylate group and the negatively charged endocyclic oxygens is responsible for the high energy content in the axial isomer (eq 8).



(8)

Experimentally, one observes the equilibrium between protonated and deprotonated species; thus the recorded values in Table 1 in the absence of salt ($\Delta G° = -0.80$ kcal/mol) must reflect some contribution of the carboxylate species and their preference for the equatorial conformation.

C.3. In the case of 5-hydroxy-1,3-dioxane (**6**), calculations (gas phase) predict that hydrogen bond formation between axial hydroxyl and *both* endocyclic oxygens results in a large stabilization of the axial isomer, $\Delta E_{calcd} = +2.37$ kcal/mol (Figure 1c). In fact, the gas-phase calculated (B3LYP/6-31G*) energy difference for di-equatorial-**3** ⇆ diaxial-**3** shows the latter to be ca. 0.9 kcal/mol more stable (Scheme 5). Nevertheless, *cis*-**3** (equatorial phenyl, axial hydroxyl) is estimated to be ca. 1.6 kcal/mol lower in energy than diaxial *trans*-**3** (Scheme 5). This is in line with expectation that the phenyl group effectively anchors the 1,3-dioxane hererocycle, as argued in section B.

Figure 3a presents the initial geometry of axial 5-carboxy-1,3-dioxane **4** coordinated to lithium cation, but presenting the metal ion *outside* the heterocyclic ring.[34–37] Figure 3b presents the geometry-optimized (B3LYP/6-31G*) structure for the complex between axial **4** and Li^+. It is appreciated that the metal ion is now coordinated to both endocyclic oxygens and to the carbonyl oxygen.

C.4. Topological analysis of complex axial-**4**·Li^+ (Figure 3b) was possible by means of Bader's AIMPAC (Atoms in Molecules Package),[38] a set of programs that defines the properties of atoms and bonding patterns in a molecule.[39] Most relevant, the bond trajectories O(1,3)−Li and (C═O)−Li, as well as the corresponding

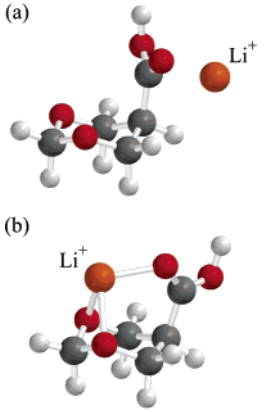


FIGURE 3. (a) Initial geometry of axial-**4** associated to Li^+ via the carbonyl oxygen. (b) Optimized geometry of the complex axial-**4**·Li^+, showing the cation coordinated to the carbonyl oxygen and both endocyclic oxygens.

critical points, confirm the coordination of lithium cation to the carbonyl oxygen and *both* endocyclic oxygens in axial-**4**·Li^+ (Figure 4a). By contrast, the topological analysis carried out in the complex between equatorial **4** and Li^+ (Figure 4b) shows metal ion association to the carbonyl oxygen exclusively.

Similar topological analysis for complexes axial-**5**·Li^+ and equatorial-**5**·Li^+ (Figure 4c and d) confirms the exclusive binding of Li^+ to the carboxylate group in both conformers. Finally, the bond and ring critical points in axial-**6**·Li^+ (Figure 4e) shows bonding of the lithium cation to all three oxygens, whereas the metal binds preferably to the endocyclic oxygens but not to the hydroxyl oxygen in equatorial-**6**·Li^+ (Figure 4f).

C.5. It is appreciated in Table 3 that metal ion coordination to 5-carboxy-1,3-dioxane **4** leads to association and concomitant stabilization, which is particularly effective in the axial conformer. Thus, in the gaseous state, the axial complexes are estimated to be much more stable than the equatorial complexes. According to the calculations (B3LYP/6-31+G**) the magnitude of this metal ion effect decreases in the order $Mg^{2+} > Ca^{2+} > Li^+ > Na^+ > K^+$, which is to be compared with the experimentally observed (Table 1) order $Ag^+ > Li^+ > Ca^{2+} \gg Mg^{2+}, Na^+, K^+$.

It is to be expected that association of the metal ion to O(1,3) and to the carbonyl oxygen in complexes axial-**4**·M^+ reduces rotational freedom in this isomer relative to the equatorial complexes, where the metal ion is solely coordinated to the carbonyl moiety. Therefore, Table 3 includes differences in entropy of mixing for the axial and equatorial complexes, $\Delta S°_{mixing}$, which were calculated according to eq 10, where R is the gas constant, n is the number of conformational states sampled, and P_i is the Boltzmann probability of the ith conformational state:[40,41]

$$S° = -R\sum_{i=1}^{n} P_i \ln P_i \qquad (10)$$

(34) In the gaseous state, association between lithium and carbonyl compounds amounts to up to 40−45 kcal/mol: (a) Wieting, R. D.; Staley, R. H.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1975**, *97*, 924. (b) Murthy, A. S. N.; Bhardwaj, A. P. *J. Chem. Soc., Perkin Trans. 2* **1984**, 727. (c) Rao, C. P.; Balaram, P.; Rao, C. N. R. *J. Chem. Soc., Faraday Trans. 1* **1980**, *76*, 1008.

(35) For a recent theoretical study (DFT) of Li^+ complexation to methyl esters, see: Kaanumalle, L. S.; Sivaguru, J.; Sunoj, R. B.; Lakshminarasimhan, P. H.; Chandrasekhar, J.; Ramamurthy, V. *J. Org. Chem.* **2002**, *67*, 8711.

(36) For a recent theoretical study (DFT) of Ni^+ binding to alkanes, silanes, and germanes, see: Corral, I.; Mó, O.; Yáñez, M. *New J. Chem.* **2003**, *27*, 1657.

(37) For a recent theoretical study of Ca^{2+} binding to formaldehyde, see: Corral, I.; Mó, O.; Yáñez, M.; Scott, A. P.; Radom, L. *J. Phys. Chem. A* **2003**, *107*, 10456.

(38) Beigler-König, F. W.; Bader, R. F. W.; Tang, T.-H. *J. Comput. Chem.* **1982**, *3*, 317.

(39) (a) Bader, R. F. W. *Atoms in Molecules, a Quantum Theory*; Clarendon Press: Oxford, 1990. (b) Bader, R. F. W. *Chem. Rev.* **1991**, *91*, 893. (c) Bader, R. F. W. *Acc. Chem. Res.* **1985**, *18*, 9.

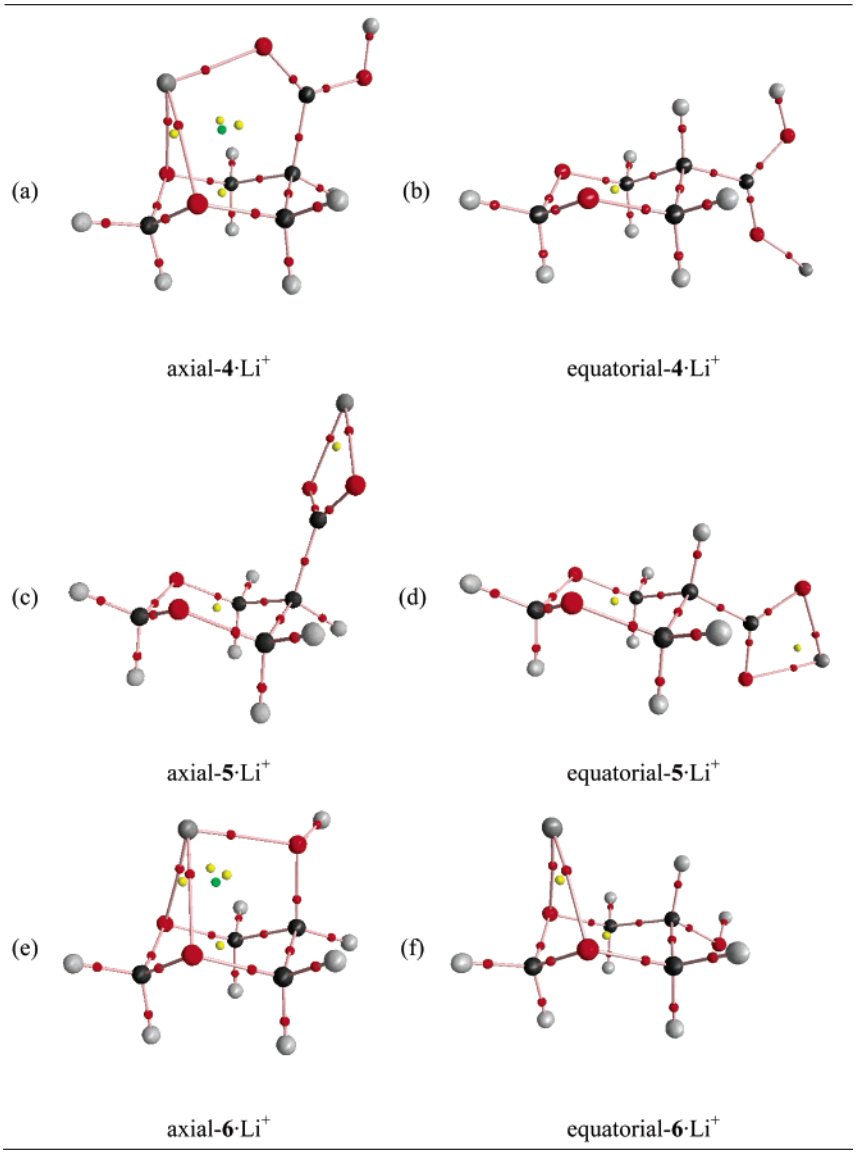


FIGURE 4. Critical points and bonding trajectories in the electron density of (a) complex of axial **4** with Li^+, (b) complex of equatorial **4** with Li^+, (c) complex of axial **5** with Li^+, (d) complex of equatorial **5** with Li^+, (e) complex of axial **6** with Li^+, (f) complex of equatorial **6** with Li^+, calculated at the Becke3LYP/6-31G* level of theory.

The P_i data, in turn, were computed from the relationship in eq 11, where E_i is the intramolecular conformational energy of the ith state:

$$P_i = \frac{e^{-E_i/RT}}{\sum_{i=1}^{n} e^{-E_i/RT}} \qquad (11)$$

As anticipated, the conformational confinement provoked by the more extensive coordination in the axial complexes is manifested in positive $\Delta S°_{mixing}$ values for the axial to equatorial processes. Of course, it is dangerous to attribute entropy contributions to a certain part of the system; entropy is a function of the entire system. Thus, Table 3 includes the calculated values for total entropy differences, i.e., the sum of the vibrational, rotational, translational, and electronic entropy differences.

Figure 5 presents a comparison of relative energies of axial and equatorial 5-carboxylate **5** and the same conformational equilibrium in the presence of Li^+ cation. The large predominance of the equatorial conformer in the former equilibrium is inverted in the latter, where coordination of lithium ion to the carboxylate group obviously neutralizes its negative charge and minimizes electrostatic repulsion in the axial complex (Figure 5).

The metal ion effect on the axial ⇆ equatorial equilibrium of carboxylate **5** with other cations is similar (Table 4). Geometry optimization of the corresponding complexes confirms that association of the metal to the carboxylate group is so strong that no additional coordination to the endocyclic oxygens in the axial isomer is required.

(40) (a) Flory, P. J. *Statistical Mechanics of Chain Molecules*; Wiley: New York, 1969. (b) López de Compadre, R. L.; Pearlstein, R. A.; Hopfinger, A. J.; Seydel, J. K. *J. Med. Chem.* **1987**, *30*, 900.
(41) (a) Juaristi, E.; Labastida, V.; Antúnez, S. *J. Org. Chem.* **1991**, *56*, 4802. (b) Antúnez, S.; Juaristi, E. *J. Org. Chem.* **1996**, *61*, 6465. (c) Muñoz-Muñiz, O.; Juaristi, E. *J. Phys. Org. Chem.* **2002**, *15*, 808.

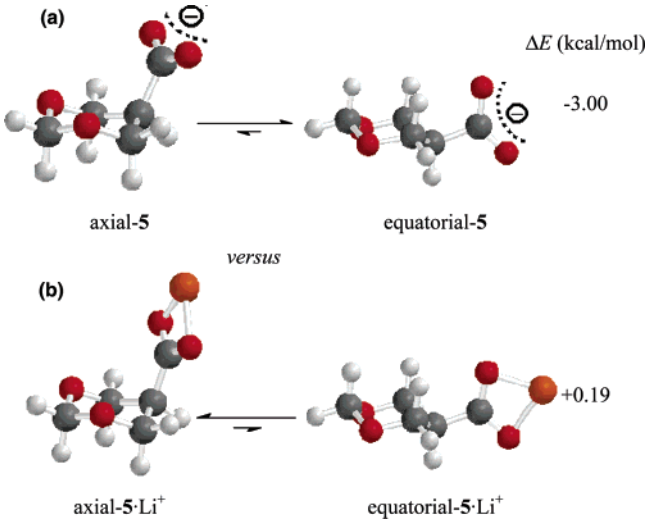
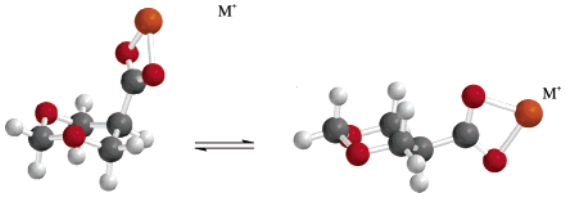


FIGURE 5. Relative energies (Δ*E*, B3LYP/6-31+G**) for (a) axial and equatorial 1,3-dioxane-5-carboxylate **5** and (b) axial and equatorial complexes **5**·Li^+.

TABLE 4. Metal Ion Effect on the Conformational Energies (Δ*E*, B3LYP/6-31G*) of 5-Carboxylate-1,3-Dioxane 5

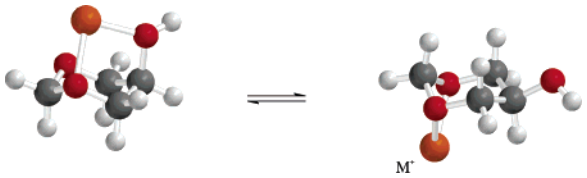


M^+	Δ*E* (kcal/mol)	μ total (debye) axial	μ total (debye) equatorial
–	−3.00	7.86	7.36
Li^+	+0.19	2.87	5.36
Na^+	+0.08	5.12	7.74
K^+	+0.19	6.80	9.83
Mg^{2+}	+13.36	12.05	15.82
Ca^{2+}	+4.05	15.29	19.53

C.6. As reported in section B, 5-hydroxy-1,3-dioxane **6** is predicted by calculation (gaseous state) to favor the axial conformer, where intramolecular hydrogen bonding stabilizes this isomer. Incorporation of metal ions leads to even higher predominance of the axial complexes (Table 5), and the collected data show a distinct tendency that clearly depends on the size of the cation: the smaller ions are the more effective, either because of their increased Lewis acidity[42] or because they are better accommodated by the "cavity" available in the axial 5-substituted 1,3-dioxane ligand. Indeed, it can be appreciated in Table 5 that the calculated M^+ effect decreases in the order $Zn^{2+} > Mg^{2+} > Ca^{2+} > Ag^+$, which is approximately inversely related to the ionic atomic radii, 0.74 ≈ 0.71 < 1.14 = 1.14 Å, respectively.[43] Similarly, for alkali metals the calculated effect decreases in the order $Li^+ > Na^+ > K^+$, which is opposite to the corresponding atomic radii, 0.73 < 1.13 < 1.51 Å, respectively.[43] Of course, a "hole size relationship"[42] is

(42) Gokel, G. W.; Leevy, W. M.; Weber, M. E. *Chem. Rev.* **2004**, *104*, 2723.
(43) Reference 27b, appendix 4, pp 1301−1304.

TABLE 5. Relative Energies (Δ*E*, B3LYP/6-31+G) for the Axial ⇆ Equatorial Conformational Equilibrium of 6 in Absence or Presence of Metal Ions**



M^+	Δ*E* (kcal/mol)	μ total (debye) axial	μ total (debye) ecuatorial
–	+2.37	2.12	1.58
Li^+	+20.09	2.79	6.28
Na^+	+15.82	3.51	7.17
K^+	+15.08	4.40	13.41
Mg^{2+}	+41.48	5.13	7.88
Ca^{2+}	+34.56	7.57	12.10
Zn^{2+}	+51.27	2.24	5.58
Ag^+	+21.70	3.07	1.86

expected to be modified by additional physical parameters of applied salts, for example, the hardness or softness.

C.7. We next proceeded to examine computationally the effect of THF solvent on the conformational equilibria of metal ion complexes **4**·Li^+. To be able to keep the model system as authentic as possible, with the available amount of computational resources, we chose a combined semiempirical and density functional approach. The semiempirical PM3 method[44] has been widely used in organolithium chemistry.[45] Recently, Abbotto, Streitwieser, and Schleyer have demonstrated that energies obtained by DFT with the B3LYP hybrid function on the PM3-optimized geometries reproduce high-level results of high accuracy.[46] Thus, we applied this B3LYP//PM3 method for our calculations.

The energy associated with equilibria depicted in Figure 6 show that solvation by one, two, or even three molecules of THF does not cause the annulment of the lithium ion effect that renders the axial **4**·Li^+ complex more stable. By contrast, stabilization of the axial metal ion complexes with sodium and potassium decreases substantially upon solvent association, and incorporation of three molecules of THF in the complex renders the equatorial isomers more stable, Δ*E* = −1.9 and −6.6 kcal/mol, respectively. These computational results are in line with the experimentally observed trends (cf. Table 1), which are likely to involve dynamic mixtures of the various ionic species and solvates.[47]

Finally, the role of the solvent was also modeled by means of the Polarizable Continuum Model (PCM) de-

(44) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.
(45) (a) Opitz, A.; Koch, R.; Katritzky, A. R.; Fan, W.-Q.; Anders, E. *J. Org. Chem.* **1995**, *60*, 3743. (b) Würthwein, E.-U.; Behrens, K.; Hoppe, D. *Chem.−Eur. J.* **1999**, *5*, 3459. (c) Nakamura, S.; Nakagawa, R.; Watanabe, Y.; Toru, T. *J. Am. Chem. Soc.* **2000**, *122*, 11340. (d) Gaul, C.; Arvidsson, P. I.; Bauer, W.; Gawley, R. E.; Seebach, D. *Chem.−Eur. J.* **2001**, *7*, 4117.
(46) (a) Abbotto, A.; Streitwieser, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 11255. (b) See, also: Juaristi, E.; Hernández-Rodríguez, M.; López-Ruiz, H.; Aviña, J.; Muñoz-Muñiz, O.; Hayakawa, M.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 1999.
(47) See, for example: (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448. (c) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271.

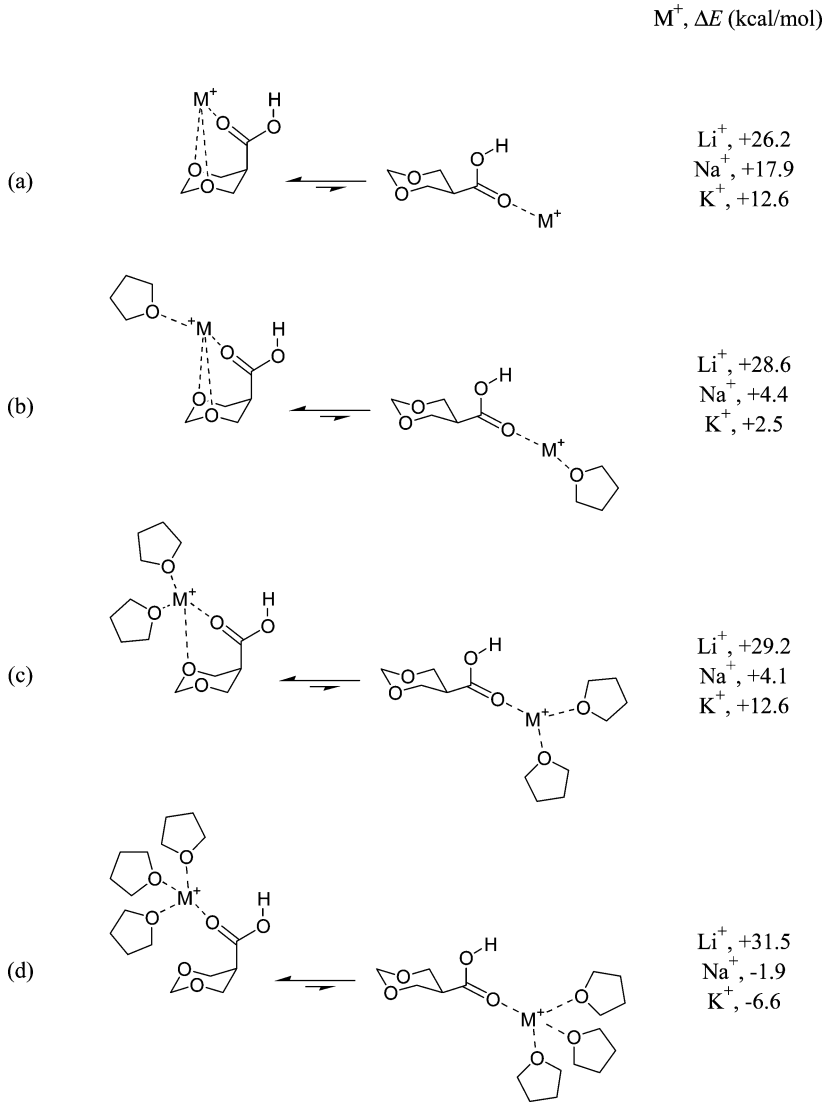


FIGURE 6. Relative energies (Δ*E*, B3LYP/6-31G*//PM3) of axial and equatorial **4**-Li^+, -Na^+, and -K^+ (a) in absence of solvent, (b) with incorporation of one THF molecule, (c) with incorporation of two THF molecules, and (d) with incorporation of three THF molecules.

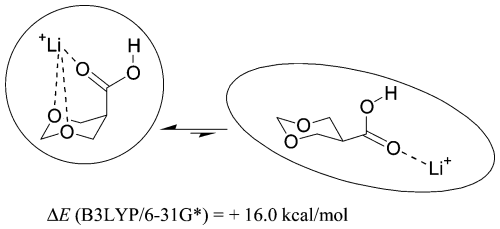


FIGURE 7. Relative energy (Δ*E*, B3LYP/6-31G*) of axial and equatorial **4**·Li^+, with THF solvent being simulated according to the PCM model.[48]

veloped by Tomasi and co-workers,[48] where the solvent is represented by an infinite dielectric continuum (ϵ), in which a cavity is created and the solute is placed in it. The charge distribution of the solute polarizes the continuum, which in turn creates an electrostatic field inside the cavity. The result (Figure 7) confirms the dominant Li^+ ion effect that stabilizes axial **4**.[49]

(48) (a) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027. (b) Cammi, R.; Tomasi, J. *J. Comput. Chem.* **1995**, *16*, 1449.

Conclusions

In absence of salt, steric and dipole−dipole repulsion present in the axial isomers of 5-carboxy- and 5-hydroxy-1,3-dioxane lead to the predominance of the equatorial isomers, by 0.80 and 0.39 kcal/mol, respectively.

The conformational equilibrium of 5-carboxy-1,3-dioxane was affected by the addition of Ag^+, Ca^{2+}, and Li^+ salts, which stabilize the axial isomer significantly, especially in the case of the former. Larger and softer

(49) A well-known drawback of the method of Tomasi[48] is that specific solvent interactions such as hydrogen bonds are not considered properly. As suggested by one of the reviewers, other computational methods, such as the Langevin dipoles model, have been developed that could be used in this type of studies; see: (a) Warshel, A. *Computer Modelling of Chemical Reactions in Enzymes and Solutions*; Wiley: New York, 1991. (b) Florián, J.; Warshel, A. *J. Phys. Chem.* **1997**, *101*, 5583. The same referee points out that the ultimate method for calculation of free energies of solvation is an all atom representation of solvent combined with molecular dynamics or Monte Carlo together with one of the methods for calculation of free energies; see: (a) van Gunsteren, W. F.; Berendsen, H. J. C. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 992. (b) Boresch, S.; Karplus, M. *J. Mol. Biol.* **1995**, *254*, 801. (c) Hansson, T.; Oostenbrink, C.; van Gunsteren, W. F. *Curr. Opin. Struct. Biol.* **2002**, *12*, 190.

ions Na^+, K^+, Mg^{2+}, Ba^{2+}, and Zn^{2+} had a marginal effect on the conformational equilibria of *cis*- and *trans*-5-carboxy-2-phenyl-1,3-dioxane.

The conformational equilibrium of 5-hydroxy-1,3-dioxane was affected by the presence of Ag^+, Mg^{2+}, and Zn^{2+}. Both of these metal ions stabilize the axial isomer. No significant effect was noticed with Li^+, Na^+, K^+, Ca^{2+}, or Ba^{2+}.

The ability of axial 5-carboxy and 5-hydroxy-1,3-dioxane derivatives *cis*-**1** and *cis*-**3** to bind some metallic cations is of course of similar nature as that encountered in crown ethers, where the ring heteroatoms act as donors to the metal ions. Nevertheless, it is realized that the complexation of a cation by dioxanes **1** or **3** or a crown ether is simple to conceptualize but more complicated in its details. For example, solvent plays a role in binding (section C7), which increases the complexity of the system. Furthermore, the host's interior cavity dictates the degree of binding for different cations (section C6). Thus, understanding the details of metal cation complexation by heterocycles remains a worthwhile pursuit.[42]

Molecular modeling (DFT) predicts that all metal ions should exhibit conformational effects that stabilize the axial isomers of 5-carboxy- and 5-hydroxy-1,3-dioxane. This effect is stronger for smaller cations that present higher positive charge density and fit more effectively in the binding site of the axially substituted heterocycle. It is apparent that the polar and oxygen-containing THF solvent competes in solution for coordination to the metal, although the final salt effect on conformational equilibria can be nevertheless significant.

Experimental Section

General experimental procedures, synthetic procedures for the preparation of *cis*- and *trans*-**1** and *cis*- and *trans*-**3**, and description of equilibrations and analysis are reported in ref 18.

Equilibration Procedure. For each pair of stereoisomeric 1,3-dioxanes at least four acid-catalyzed equilibria were established, two from the essentially totally *cis* isomer and two from the essentially totally *trans* isomer. Experimentally, 60 mg of dioxane was placed in an ampule, dissolved in 3 mL of dry THF, and treated with 1.0 equiv of salt and 0.03 mL of boron trifluoride etherate. The ampule was sealed and submerged in a constant-temperature bath at 25 °C. Following 15 days of incubation, the equilibration process was quenched by addition of aqueous 10% $NaHCO_3$. The organic materials were extracted twice with CH_2Cl_2, and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator. Equilibrium constants, K, were determined by ^1H NMR spectroscopy, by integration of suitable signals. $\Delta G°$ values (Tables 1 and 2) were calculated by means of the Gibbs equation, $\Delta G° = -RT \ln K$.[3]

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Supporting Information Available: Cartesian coordinates and total energies for calculated structures of minimum energy for axial and equatorial 5-substituted 1,3-dioxanes **4**–**6** and their metal complexes, 2-phenyl substituted analogue *cis*-**3** and *trans*-**3**, and Li^+, Na^+, K^+ complexes of **4** including one, two, and three associated molecules of THF. This material is available free of charge via the Internet at http://pubs.acs.org.

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