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# Conformational Analysis of 5-Substituted 1,3-Dioxanes. 7. Effect of Lithium Bromide Addition[†,1]

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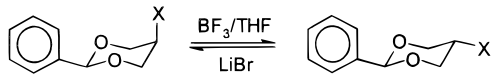
The position of equilibria, established by means of $BF_3$, between diastereomeric *cis*- and *trans*-5-substituted-2-phenyl-1,3-dioxanes, in solvents THF and $CHCl_3$, and in the presence of 0, 1, and 10 equiv of LiBr has been determined. The observed $\Delta G°$ values show that the addition of salt to the reaction medium influences the position of equilibrium. Lithium bromide effects on the conformational behavior are discussed in terms of lithium ion complexation events that lead to increased stability of the axial isomers when the substituent at C(5) is $CO_2H$, $CO_2CH_3$, $CONHCH_3$, and $CH_2OH$. By contrast, disruption of the intramolecular hydrogen bond present in the axial 5-acetamido derivative (*cis*-**9** substituent equal to $NHCOCH_3$) modifies the preference for the axial conformation in salt-free **9** to a net dominance of the equatorial isomer in the presence of LiBr. Interpretation of the experimental observations was based on models that are apparently supported by semiempirical AM1 calculations. The results derived from the present study contribute to our understanding of the processes involved in molecular recognition and may model salt effects in physiological events.

## Introduction

It has long been known that the course of a chemical reaction may be influenced by the surrounding medium. Thus, the solvent can alter reaction rates and yields, product stereochemistry, and the position of chemical equilibria.[2,3] Furthermore, such changes can also be produced by addition of chemically inert salts to the reaction medium. Nevertheless, while salt effects are well established in organic chemistry, not much is known as to how the electrolyte influences the mechanism and kinetics in the course of the reaction.[4,5] Of particular interest are salt effects on conformational equilibria; however, although solvent effects on conformational equilibria have received much attention, there are few available thermodynamic data dealing with salt effects.[6] For example, in a qualitative level, Angyal and Davies found that the conformational equilibrium of $\beta$-methylribopyranose is altered by the presence of $CaCl_2$.[7] Another remarkable example is provided by the strong influence of LiCl on the backbone conformation of cyclic undecapeptide cyclosporin A, a well known immunosuppressive agent.[8]

In a series of classical studies, Eliel demonstrated the utility of substituted 1,3-dioxanes for the evaluation and understanding of conformational effects,[9] and 1,3-dioxane derivatives continue to serve as excellent probes for the study of steric, electrostatic, and stereoelectronic interactions.[1,10] The present paper describes the preparation and chemical equilibration of a series of 5-substituted-1,3-dioxanes **1**−**9**, both in presence and absence of lithium bromide (Scheme 1).

**Scheme 1**




**1**, X = $CO_2H$
**2**, X = $CO_2CH_3$
**3**, X = $CONHCH_3$
**4**, X = $CH_2OH$
**5**, X = OH
**6**, X = $OCOCH_3$
**7**, X = $OCOCH_2OC_6H_4$-*o*-$OCH_3$
**8**, X = $NO_2$
**9**, X = $NHCOCH_3$

## Results and Discussion

**A. Syntheses of Diastereomeric *cis*- and *trans*-5-Substituted-2-phenyl-1,3-dioxanes.** Condensation of benzaldehyde and diethyl bis(hydroxymethyl)malonate,[11] according to the described procedure,[12] afforded 2-phenyl-5,5-dicarbethoxy-1,3-dioxane, **10**, whose saponification gave the dicarboxylic acid**,** which was decarbox-

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[⊗] Abstract published in *Advance ACS Abstracts,* May 15, 1997.

(1) For Part 6, see: Juaristi, E.; Antúnez, S. *Tetrahedron* **1992**, *48*, 5991.
(2) Reichardt, C. *Chem. Rev.* **1994**, *94*, 2321.
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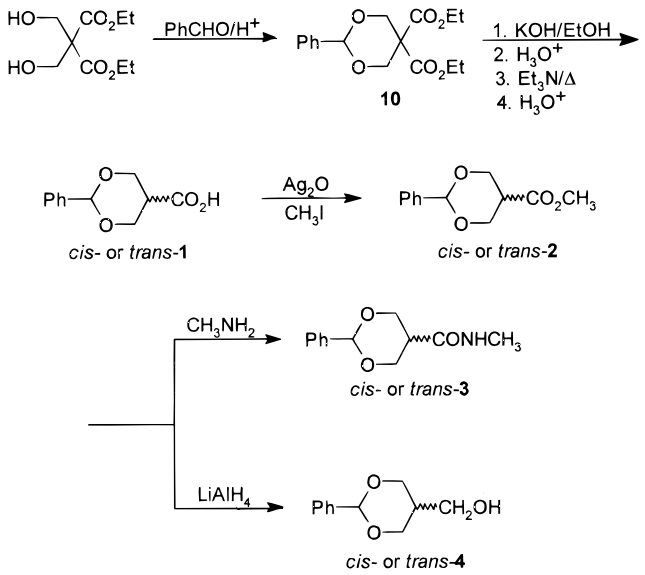
**Scheme 2**




ylated to afford a mixture of *cis*- and *trans*-2-phenyl-5-carboxy-1,3-dioxane (*cis*- and *trans*-**1**) (Scheme 2).

The diastereomeric carboxylic acids *cis*- and *trans*-**1** were separated by flash chromatography, and converted to the corresponding methyl esters **2** by means of silver oxide/methyl iodide (Scheme 2). Next, *cis*- and *trans*-**2** were treated with methyl amine to yield amides *cis*- and *trans*-**3**. Furthermore, the reduction of *cis*- and *trans*-**2** with lithium aluminum hydride produced *cis*- and *trans*-**4**, with conservation of configuration (Scheme 2). Tables 1 and 2 contain $^1$H and $^{13}$C NMR chemical shifts for *cis*- and *trans*-**1**−**4**.

*cis*- and *trans*-2-Phenyl-5-hydroxy-1,3-dioxane (*cis*- and *trans*-**5**) were prepared by condensation of benzaldehyde and glycerol, according to the described procedure.[1] Carbinols *cis*- and *trans*-**5** were converted to the corresponding acetates with acetic anhydride in pyridine[13] or treated with (2-methoxyphenoxy)acetic acid[14] and *p*-toluenesulfonyl chloride in pyridine to yield the desired derivatives **6** and **7**, respectively.[15] $^1$H and $^{13}$C NMR chemical shifts for compounds **5**−**7** are included in Tables 1 and 2.

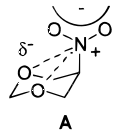
On the other hand, 2-phenyl-5-(hydroxymethyl)-5-nitro-1,3-dioxane, **12**, was prepared by condensation of commercially available tris(hydroxymethyl)nitromethane with benzaldehyde. Deformylation with lithium/ammonia[16] furnished 5-nitro-2-phenyl-1,3-dioxane, **8** (Scheme 3). The only isomer obtained from this procedure was *cis*-**8**, but sublimation of this material afforded a 1:1 mixture of *cis*- and *trans*-5-nitro-2-phenyl-1,3-dioxane (*cis*- and *trans*-**8**), which were separated by flash chromatography. Each individual isomer was reduced under catalytic conditions to give *cis*- and *trans*-**13** which were acetylated with acetic anhydride and pyridine to provide amides *cis*- and *trans*-**9** (Scheme 3). Tables 1 and 2 contain $^1$H and $^{13}$C NMR chemical shifts for compounds **8** and **9**.

**B. Conformational Analysis of 1−9.** Equilibration of diastereomeric 1,3-dioxanes (*cis*- and *trans*-**1**−**9**) was readily performed by means of $BF_3$.[17] The corresponding free energy differences are summarized in Table 3, which includes the $\Delta G°$ values of interest in the presence of 0.0, 1.0, and 10.0 equiv of LiBr. (Lithium bromide alone does not induce the equilibration of anancomeric dioxanes **1**−**9**). The last column in Table 3 presents the corresponding salt-free conformational free energy differences in the 2-isopropyl analogues, studied by Eliel[9] some 25 years ago.

**Conformational Preferences in the Absence of Lithium Bromide.** Comparison, when possible, between the 2-phenyl- (this work) and 2-isopropyl-5-substituted-1,3-dioxanes (Eliel's work[9]) show some similarities as well as some significant differences in conformational behavior. For example, the observed $\Delta G°$ values for the 5-hydroxy derivative (X = OH) are essentially identical in phenyl-substituted **5** ($\Delta G° = -0.38$ kcal/mol, in THF) and the isopropyl analogue (−0.41 kcal/mol, in $Et_2O$). For this system, Eliel has shown the absence, *in ether solvent*, of intramolecular hydrogen bonding in either the axial or equatorial isomers; thus, the lack of any salt effect in the equilibria of **5** (see below) is not surprising; i.e., addition of lithium bromide neither breaks up a potential hydrogen bond in 5-axial nor gives rise to a stabilizing complex.

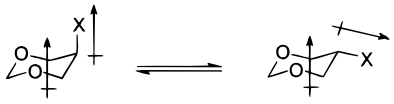
By contrast, significant differences ($\Delta\Delta G° \sim 0.5$ kcal/mol) are observed in the conformational preferences of **2** (X = $CO_2CH_3$),[18] **4** (X = $CH_2OH$), **6** (X = $OCOCH_3$), and **8** (X = $NO_2$) and those described for the 2-isopropyl analogues.

In the case of the 2-phenyl-5-nitro derivative **8**, the observed axial preference of the nitro group can be explained in terms of electrostatic attraction between the partially negative endocyclic oxygens and the positive nitrogen atom.[19]




**A**

The increased axial preference in going from carbon tetrachloride ($\Delta G° = +0.38$ kcal/mol) to THF solvent ($\Delta G° = +0.73$ kcal/mol) can be explained in terms of the higher polarity of the latter solvent, which reduces the well-known dipole−dipole repulsion in axial, 5-polar substituted 1,3-dioxanes[9] (eq 1). Similar solvent effect was observed in 2-isopropyl-5-nitro-1,3-dioxane, when the solvent was changed from $CCl_4$ to $CH_2Cl_2$.[19]




(1)

The increased axial preference of the 5-acetoxy group in **6** and the diminished equatorial preference of the 5-carbomethoxy group in **2**, relative to their 2-isopropyl analogues (+0.47 versus 0.00 kcal/mol and −0.50 versus −0.82 kcal/mol, respectively) may be explained if one assumes that the electronegative 2-phenyl substituent reduces the effective ring dipole and thus the resulting dipole−dipole interactions which favor the equatorial over the axial isomer for electron-withdrawing groups such as acetoxy and carbomethoxy.

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(17) Eliel, E. L.; Knoeber, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 3444.
(18) We found $\Delta G° = -0.52 \pm 0.03$ kcal/mol for the axial ⇌ equatorial equilibrium of the 2-isopropyl analogue in THF solvent.
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**Table 1. $^1$H NMR Chemical Shifts ($\delta$) for 1−9 at 27 °C in $CDCl_3$**

| compd | H(2) | H(4,6-ax) | H(4,6-eq) | H (5) | H (arom) | $CH_3$ | $CH_2O$ | other |
|---|---|---|---|---|---|---|---|---|
| *cis*-**1**[a] | 5.46 | 4.03 | 4.60 | 2.34 | 7.23−7.40 | | | |
| *trans*-**1** | 5.40 | 4.02 | 4.50 | 3.25 | 7.30−7.40 | | | |
| *cis*-**2** | 5.51 | 4.10 | 4.70 | 2.43 | 7.31−7.46 | 3.81 | | |
| *trans*-**2** | 5.40 | 3.97 | 4.45 | 3.13 | 7.34−7.46 | 3.70 | | |
| *cis*-**3** | 5.54 | 4.18 | 4.42 | 2.39 | 7.30−7.50 | 2.87 | | 6.90 (NH) |
| *trans*-**3** | 5.52 | 4.15 | 4.32 | 2.91 | 7.31−7.52 | 2.66 | | 5.91 (NH) |
| *cis*-**4** | 5.50 | 4.01 | 4.22 | 1.62 | 7.44−7.47 | | 4.01 | 2.20 (OH) |
| *trans*-**4** | 5.40 | 3.68 | 4.26 | 2.32 | 7.30−7.50 | | 3.38 | 2.00 (OH) |
| *cis*-**5** | 5.52 | 4.08 | 4.15 | 3.59 | 7.35−7.50 | | | 3.20 (OH) |
| *trans*-**5** | 5.31 | 3.45 | 4.16 | 3.81 | 7.35−7.46 | | | 2.90 (OH) |
| *cis*-**6** | 5.53 | 4.13 | 4.26 | 4.68 | 7.40−7.52 | 2.15 | | |
| *trans*-**6** | 5.45 | 3.36 | 4.38 | 5.01 | 7.34−7.49 | 2.05 | | |
| *cis*-**7** | 5.54 | 4.16 | 4.29 | 4.85 | 6.82−7.49 | 3.86 | 4.85 | |
| *trans*-**7** | 5.43 | 3.70 | 4.38 | 5.12 | 6.82−7.50 | 3.87 | 4.69 | |
| *cis*-**8** | 5.53 | 4.22 | 4.97 | 4.21 | 7.24−7.42 | | | |
| *trans*-**8** | 5.45 | 4.17 | 4.70 | 4.69 | 7.23−7.47 | | | |
| *cis*-**9** | 5.54 | 4.10 | 4.10 | 4.00 | 7.49−7.50 | 2.01 | | 6.95 (NH) |
| *trans*-**9** | 5.49 | 3.60 | 4.32 | 4.29 | 7.39−7.49 | 2.01 | | 5.50 (NH) |

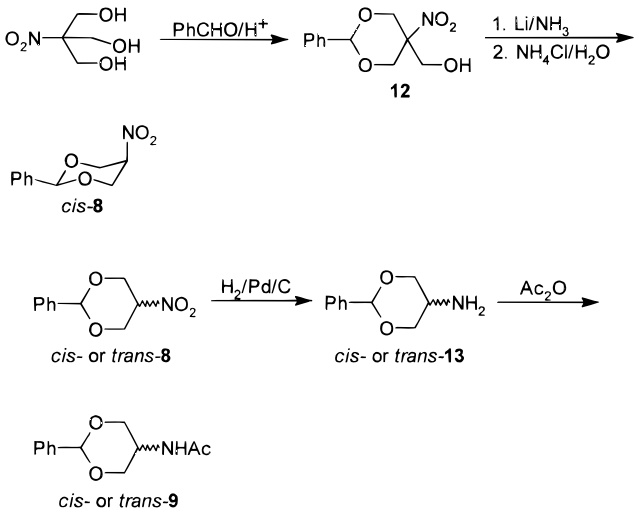
[a] In THF.

**Table 2. $^{13}$C NMR Chemical Shifts ($\delta$) for 1−9 at 27 °C in $CDCl_3$**

| compd | C(2) | C(4,6) | C(5) | C=O | $C_{arom}$ | other |
|---|---|---|---|---|---|---|
| *cis*-**1**[a] | 102.1 | 67.9 | 40.7 | 172.9 | 127.0−140.2 | |
| *trans*-**1** | 101.2 | 68.1 | 39.8 | 172.1 | 125.9−137.8 | |
| *cis*-**2** | 101.9 | 67.2 | 40.9 | 171.7 | 126.2−138.0 | 52.33 ($OCH_3$) |
| *trans*-**2** | 101.3 | 67.9 | 39.8 | 170.1 | 126.0−137. 7 | 51.70 ($OCH_3$) |
| *cis*-**3** | 101.9 | 68.3 | 26.6 | 173.5 | 125.8−137.9 | 41.6 ($NHCH_3$) |
| *trans*-**3** | 101.1 | 68.9 | 26.0 | 170.0 | 125.9−137.7 | 42.27 ($NHCH_3$) |
| *cis*-**4** | 101.9 | 68.8 | 36.5 | | 125.9−138.4 | 61.60 ($OCH_2$) |
| *trans*-**4** | 101.3 | 75.5 | 36.8 | | 125.9−138.1 | 69.50 ($OCH_2$) |
| *cis*-**5** | 101.6 | 72.3 | 63.9 | | 125.9−137.9 | |
| *trans*-**5** | 100.9 | 71.5 | 61.0 | | 126.9−137.3 | |
| *cis*-**6** | 101.1 | 70.0 | 66.0 | 170.9 | 126.0−137.8 | 21.15 ($CH_3$) |
| *trans*-**6** | 101.3 | 68.4 | 62.8 | 169.8 | 126.1−137.3 | 20.70 ($CH_3$) |
| *cis*-**7** | 101.2 | 68.9 | 66.5 | 169.0 | 112.0−149.0 | 55.9, 66.8 (OC) |
| *trans*-**7** | 101.3 | 68.1 | 63.5 | 168.2 | 112.0−149.0 | 55.9, 66.4 (OC) |
| *cis*-**8** | 101.7 | 66.5 | 77.1 | | 126.7−137.0 | |
| *trans*-**8** | 101.4 | 67.1 | 74.2 | | 126.0−136.1 | |
| *cis*-**9** | 101.4 | 70.6 | 56.5 | 169.6 | 125.7−137.7 | 23.2 ($CH_3$) |
| *trans*-**9** | 100.9 | 69.1 | 45.5 | 170.2 | 126.1−137.3 | 23.2 ($CH_3$) |

[a] In THF.

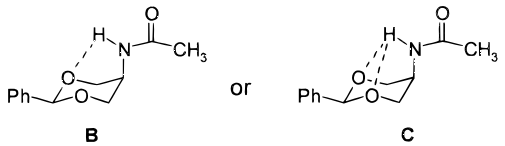
**Scheme 3**




On the other hand, the conformational behavior of 5-X-1,3-dioxanes with X = $CO_2H$, $CONHCH_3$, $OCOCH_2$-$OC_6H_4$-*o*-$OCH_3$, and $NHCOCH_3$ had not been determined previously. The substantial predominance of equatorial 5-$CO_2H$ ($\Delta G° = -0.77$ kcal/mol) and 5-$CONHCH_3$ ($\Delta G° = -0.76$ kcal/mol) is in line with expected steric and electrostatic (dipole−dipole, see above) repulsive interactions operative in the axial isomers and argue against the existence of intramolecular O−H---O or N−H---O hydrogen bonding in the axial isomers, since such interaction is expected to lower the energy of these isomers.

On the other hand, the thermodynamic stability of *axial* 5-$OCOCH_2OAr$, $\Delta G°$(**7**) = +0.56 kcal/mol, is of the same magnitude of that found in *cis*-**6** (X = $OCOCH_3$, $\Delta G° = +0.47$ kcal/mol), which has been interpreted in terms of the so-called gauche effect operative in O-C-C-O segments.[1,20]

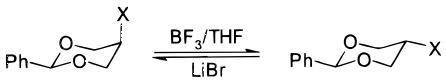
The large axial preference of the acetamido group in dioxane **9** (X = $NHCOCH_3$; $\Delta G° = +0.94$ kcal/mol) is unprecedented. IR spectra for *cis*- and *trans*-**9** showed the existence of an intramolecular hydrogen bond in the former, which accounts for its higher stability.




Indeed, the N−H stretching frequency in *cis*-**9** (3300 $cm^{-1}$, $1 \times 10^{-4}$ M THF solution) corresponds to intramo-

(20) (a) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102. (b) Juaristi, E. *J. Chem. Educ.* **1979**, *56*, 438. (c) Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley: New York, 1991; Chapter 18.

**Table 3. Conformational Equilibria in 5-Substituted-2-phenyl-1,3-dioxanes 1−9, in Absence or Presence of LiBr, at 25 °C in THF**




| | | ΔG° (kcal/mol) | | | |
|---|---|---|---|---|---|
| compd | X | 0.0 equiv | 1.0 equiv[d] | 10.0 equiv[e] | 2-isopropyl analogue[17] |
| **1** | $CO_2H$ | −0.77 ± 0.03 | −0.41 ± 0.03 | −0.17 ± 0.03 | |
| **2** | $CO_2CH_3$ | −0.50 ± 0.02 | −0.15 ± 0.03 | −0.43 ± 0.03 | −0.82 ± 0.02[b] |
| **3** | $CONHCH_3$ | −0.76 ± 0.05 | −0.67 ± 0.04 | −0.60 ± 0.04 | |
| **4** | $CH_2OH$ | −0.20 ± 0.01 | −0.04 ± 0.02 | +0.22 ± 0.02 | −0.03 ± 0.04 |
| **5** | OH | −0.38 ± 0.04 | −0.35 ± 0.03 | −0.43 ± 0.03 | −0.41 ± 0.03 |
| **6** | $OCOCH_3$ | +0.47 ± 0.01 | +0.45 ± 0.02 | +0.43 ± 0.02 | 0.00 ± 0.04 |
| **7** | $OCOCH_2OAr$[a] | +0.56 ± 0.02 | +0.89 ± 0.03 | +0.43 ± 0.02 | |
| **8** | $NO_2$ | +0.73 ± 0.02 | +0.52 ± 0.03 | +0.57 ± 0.02 | 0.38 ± 0.04[c] |
| **9** | $NHCOCH_3$ | +0.94 ± 0.03 | +0.44 ± 0.03 | −0.13 ± 0.03 | |

[a] Ar = 2-$CH_3OC_6H_4$. [b] In diethyl ether (30 °C). [c] In $CCl_4$ (30 °C). [d] Concentration, $8 \times 10^{-2}$ M. [e] Concentration, 0.8 M.

**Table 4. Conformational Equilibria in 5-Substituted-2-phenyl-1,3-dioxanes 1, 2, 4, 5, and 9, in Absence or Presence of $LiBPh_4$, at 25 °C in $CHCl_3$**

| | | ΔG° (kcal/mol) | | |
|---|---|---|---|---|
| compd | X | 0.0 equiv of $LiBPh_4$ | 1.0 equiv[a] of $LiBPh_4$ | equiv[b] of $LiBPh_4$ |
| **1** | $CO_2H$ | −0.80 ± 0.03 | −0.25 ± 0.04 | +0.28 ± 0.02 |
| **2** | $CO_2CH_3$ | −0.75 ± 0.02 | −0.11 ± 0.03 | +0.24 ± 0.02 |
| **4** | $CH_2OH$ | +0.18 ± 0.03 | +0.25 ± 0.02 | +0.30 ± 0.02 |
| **5** | OH | +0.80 ± 0.02 | +0.23 ± 0.03 | −0.25 ± 0.04 |
| **9** | $HNCOCH_3$ | +1.0 ± 0.03 | +0.50 ± 0.04 | − 0.25 ± 0.03 |

[a] Concentration, $5 \times 10^{-2}$ M. [b] Concentration, 0.5 M.

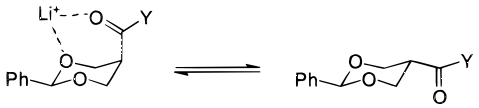
lecular hydrogen-bonded species; by contrast, *trans*-**9** present a free N−H group with its IR band at 3480 $cm^{-1}$.[21]

**Salt Effects on Conformational Equilibria.** As indicated in the introduction, Seebach, Arnett et al.[6] observed large heats of interaction between open-chain and cyclic peptides with $Li^+$ salts in THF, which suggested strong and specific interactions between the metal ion and polar groups such as C═O and C−OH. The salt effects measured in the present work revealed three tendencies upon salt addition: (1) increased axial preference when salt is present in the equilibria of dioxanes **1**−**4**, (2) increased equatorial preference most notably for **9**, and (3) no significant salt effect for the conformational equilibria of **5**−**8** (Table 3). Nevertheless, lithium ion is expected to remain in contact with THF solvent,[22] and thus the salt effects tend to be small and/or not monotonic with LiBr concentration.

In order to confirm the proposed lithium ion effects, equilibration of dioxanes **1**, **2**, **4**, **5**, and **9** was established in chloroform solvent, a medium where lithium ion is poorly solvated.[2−5] Because LiBr is not sufficiently soluble in $CHCl_3$, $LiBPh_4$ salt was used instead. The results are summarized in Table 4 and clearly confirm the tendencies found in the LiBr/THF system for **1**, **2**, **4**, and **9**. As anticipated, 5-hydroxy derivative **5** exhibits a strong intramolecular hydrogen bond in $CHCl_3$, which stabilizes the axial, *cis*-**5**, isomer. Addition of $LiBPh_4$ apparently breaks up such hydrogen bond since equilibrium shifts toward the equatorial, *trans*-**5**, isomer upon salt addition (Table 4).

A plausible explanation for the increased axial preference in the presence of lithium salt in dioxanes **1**−**4** is that addition of LiBr causes a general salt effect, that is, it mimicks a change to higher dielectric in the solvent. This may explain the result with $CO_2H$, where dipole−dipole interactions should favor the equatorial isomer (eq 1); such interaction is disminished in higher dielectric and presumably also higher ionic strength solutions.

**Table 5. Effect of LiBr on the $^{13}C$ Chemical Shifts (ppm) of the Carbonyl Group O═C−Y in the *cis*- and *trans*-Isomers of 1−3 in THF-$d_8$ at 25 °C**




| compd | Y | 0.0 equiv | 1.0 equiv[a] | 10.0 equiv[b] |
|---|---|---|---|---|
| *cis*-**1** | OH | 172.9 | 175.1 | 177.5 |
| *trans*-**1** | OH | 171.4 | 171.9 | 174.1 |
| *cis*-**2** | $OCH_3$ | 171.9 | 172.1 | 172.8 |
| *trans*-**2** | $OCH_3$ | 170.6 | 170.6 | 171.6 |
| *cis*-**3** | $NHCH_3$ | 175.0 | 175.1 | 175.4 |
| *trans*-**3** | $NHCH_3$ | 170.2 | 171.6 | 172.4 |

[a] Concentration, $8 \times 10^{-2}$ M. [b] Concentration, 0.8 M.

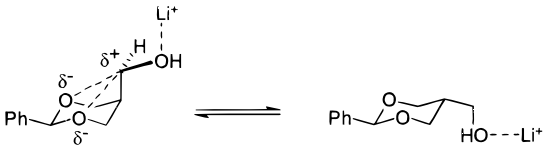
An alternative interpretation for the increased axial population of 5-X-1,3-dioxanes with X = $CO_2H$, $CO_2CH_3$, and $CONHCH_3$ in the presence of LiBr may be that lithium interacts both with the endocyclic oxygen atoms and the carbonyl group leading to a stabilization of the *cis* (axial) form (cf. **D** and **E**). Indeed, in gaseous state, association between lithium and carbonyl compounds amounts up to 40−45 kcal/mol.[23] In apparent agreement with this model, examination of the addition of 1.0 and 10.0 equiv of LiBr upon $^{13}C$ chemical shifts of carbonyl, shown in Table 5, shows significant downfield shifts for *cis*-**1** (X = $CO_2H$). For X = $CO_2CH_3$ and $CONHCH_3$ the difference between cis and trans is very small, however. Additional information regarding this point was sought

(21) Cf. Baggett, N.; Bukhari, M. A.; Foster, A. B.; Lehmann, J.; Webber, J. M. *J. Chem. Soc.* **1963**, 4157.

(22) Collum has shown that even TMEDA does not compete with THF in solvating lithium cations: Colum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.

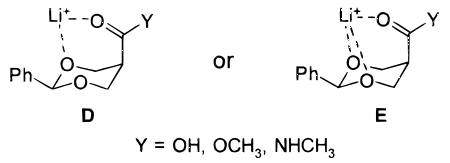
(23) (a) Wieting, R. D.; Staley, R. H.; Beauchamp, J. L. *J. Am. Chem. Soc.*, **1975**, *97*, 924. (b) Murthy, A. S. N.; Bhardwaj, A. P. *J. Chem. Soc., Perkin Trans. 2* **1984**, 727. (c) Rao, C. H. P.; Balaram, P.; Rao, C. N. R. *J. Chem. Soc. Faraday Trans. 1* **1980**, *76*, 1008.

**Table 6. Effect of LiBr on $^1$H Chemical Shifts ($\delta$) of *cis*- and *trans*-4 in THF at 27 °C**



| compd | LiBr equiv | H(2) | H(4,6-ax) | H(4,6-eq) | H(5) | $CH_2O$ | OH |
|---|---|---|---|---|---|---|---|
| *cis*-**4** | 0.0 | 5.40 | 4.00 | 4.14 | 1.50 | 3.83 | 3.90 |
| *trans*-**4** | 0.0 | 5.35 | 3.65 | 4.19 | 2.18 | 3.34 | 3.70 |
| *cis*-**4** | 1.0 | 5.45 | 4.02 | 4.18 | 1.72 | 3.90 | 4.80 |
| *trans*-**4** | 1.0 | 5.37 | 3.69 | 4.25 | 2.26 | 3.41 | 4.46 |
| *cis*-**4** | 10.0 | 5.50 | 4.12 | 4.21 | 1.98 | 3.96 | 5.57 |
| *trans*-**4** | 10.0 | 5.42 | 3.76 | 4.26 | 2.38 | 3.52 | 5.40 |

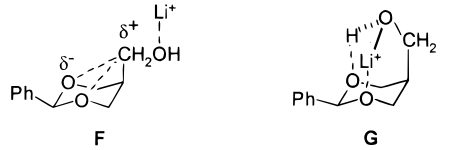
from semiempirical AM1 modeling studies, as discussed in section C below.



Y = OH, $OCH_3$, $NHCH_3$

We hasten to add that the dioxane substrates are likely to be competing with THF solvent for coordination sites on lithium.[22] Thus species **D** and **E** should be in complex equilibria with uncoordinated heterocycles. Furthermore, chelate substructures **D** and **E** are simplified models for the likely species in the system. In particular, lithium bromide is known to be aggregated in THF solutions and at our experimental concentrations probably dimeric.[24]

For dioxane **4**, X = $CH_2OH$, the axial isomer is preferred in high concentration of salt (both THF/LiBr or $CHCl_3$/$LiBPh_4$). In order to explain this phenomenon we recorded the $^1$H NMR spectra for *cis*- and *trans*-**4** with 1 or 10 equiv of lithium bromide (Table 6). The substantial downfield shifts experienced by the $CH_2O$, H(5), and OH protons in both the cis and trans isomers support the idea that the $Li^+$ ion interacts with the hydroxyl group. Noteworthy is also the observation that H(2) is more downfield shifted in the cis isomer ($\Delta\delta = 0.1$ versus 0.07 ppm). These observations are pertinent in view of the proposal by Borremans and Anteunis[25] that the conformational preference of 5-(hydroxymethyl)-1,3-dioxane is determined by a local electrostatic attraction between ring oxygens and the partially positive C−H moiety of the axial 5-$CH_2Y$ conformer (**F**). AM1 calculations (Section C) suggested, however, a different picture (**G**).

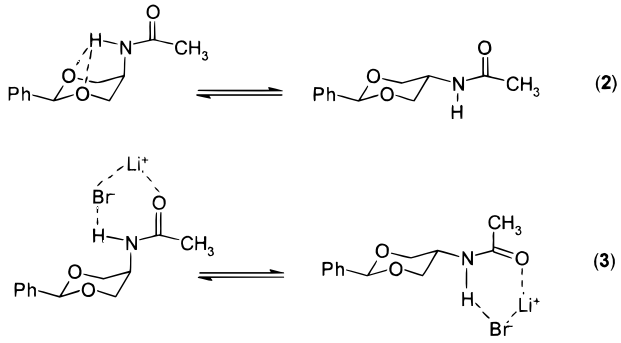


The most clear-cut case is with the NHAc substituent (dioxane **9**), where Li salt addition results in a complete reversal of conformational preference, from a robust axial predominance in absence of salt ($\Delta G° = +0.94$ kcal/mol in THF, $\Delta G° = +1.00$ in $CHCl_3$) to a clear preference for the equatorial orientation in the presence of 10 equiv of LiBr or $LiBPh_4$ ($\Delta G° = -0.13$ kcal/mol or $\Delta G° = -0.25$ kcal/mol, respectively). This salt effect could be understood when the infrared spectra of *cis*- and *trans*-**9** were determined. The cis isomer shows an intramolecular hydrogen bond (THF, 3330 $cm^{-1}$, stretching N−H) between amide hydrogen and ring oxygens, which is absent in the trans conformer (THF, 3480 $cm^{-1}$, stretching N−H). Upon addition of LiBr, the 3330 $cm^{-1}$ band disappears and a new band appears at 3480 $cm^{-1}$ (free NH). With this information at hand, it seems reasonable that the axial isomer is intramolecularly hydrogen bonded in absence of LiBr. When the salt is added, the lithium ion binds to the carbonyl oxygen.[26] Furthermore, it is known that the anion can bind to amide hydrogen[27] or amide nitrogen,[28] so the hydrogen bond is disrupted and the equilibrium shifts from the axial toward the equatorial isomer (eqs 2 and 3).

**Table 7. Conformational Equilibria of 2-Phenyl-5-carboxy-1,3-dioxanes 1, in the Presence of LiBr, LiI and $LiBPh_4$, in THF at 25 °C**

| | $\Delta G°$ (kcal/mol) | |
|---|---|---|
| salt | 1.0 equiv[a] | 10.0 equiv[b] |
| LiBr | $-0.41 \pm 0.03$ | $-0.17 \pm 0.03$ |
| LiI | $-0.20 \pm 0.02$ | $-0.11 \pm 0.02$ |
| $LiBPh_4$ | $-0.26 \pm 0.03$ | $-0.17 \pm 0.03$ |

[a] Concentration, $8 \times 10^{-2}$ M. [b] Concentration, 0.8 M.



**Is There a Counteranion Effect?** As pointed out in the previous section, we are dealing not with simple cations but with ion pairs.[29] Thus, the question arose as to whether the bromide counteranion does have a specific influence on the observed salt effects. To gain information on this question, 2-phenyl-5-carboxy-1,3-dioxane (**1**) was equilibrated in the presence of lithium iodide (LiI) and lithium tetraphenylborate ($LiBPh_4$), both in THF solvent. Comparison with the thermodynamic data obtained for the same equilibrium in the presence of LiBr (Table 7) shows a quite good correspondence of $\Delta G°$ values, suggesting that salt effects are mainly due to association with the lithium cation, rather than to the anion (bromide, iodide, or tetraphenylborate).

**C. AM1 Semiempirical Calculations.** Theorical modeling of the conformational analysis described in section B was deemed important in order to increase our understanding of the equilibria involved, and in order to

(24) (a) Abu-Hasanayn, F.; Streitwieser, A. *J. Am. Chem. Soc.* **1996**, *118*, 8136. (b) Wong, M. K.; Popov, A. I. *J. Inorg. Nucl. Chem.* **1972**, *34*, 3615.

(25) Borremans, F.; Anteunis, J. O. *Bull. Soc. Chim. Belg.* **1976**, *85*, 681.

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(28) Hinton, J. F.; Amis, E. S.; Mettetal, W. *Spectrochim. Acta* **1969**, *25A*, 119.

(29) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271, and references 11−15 therein.

gain support for the interpretations advanced. Table 8 (Supporting Information) collects the differences in heat of formation ($\Delta H°_f$) for the axial versus equatorial conformers of lowest energy, as derived from AM1 semiempirical calculations.[30] Table 8 also includes the corresponding $\Delta H°_f$ values in the presence of $H^+$, $Li^+$, $Na^+$, and $K^+$ ions. With very few exceptions, incorporation of a proton ($H^+$) or cation ($Li^+$, $Na^+$, $K^+$) leads to substantial stabilization of the axial isomers. While this observation could be in line with the idea of intramolecular bridging of the positive ion, closer examination of the modeled species suggests a more complex situation.

Figures 1−8 (Supporting Information) present the conformers of lowest energy for the 5-substituted 1,3-dioxanes affording the computed data summarized in Table 8. Furthermore, modeling of the lithium ion effects by means of AM1 semiempirical calculations argues against a unique interaction mechanism; rather, several different perturbation modes of conformational equilibria were revealed:

(1) Lithium ion shifts the position of the conformational equilibria of 5-carboxy- and (*N*-methylcarbamoyl)-1,3-dioxane toward the axial side via coordination to the carbonyl oxygen, which conducts to the formation of strong intramolecular O−H and N−H hydrogen bonding with both ring oxygens.

(2) Lithium cation perturbs the equilibrium of 5-carbomethoxy- and 5-(hydroxymethyl)-1,3-dioxane via coordination between lithium, the carboxy, or hydroxy group, and one of the endocyclic oxygens, stabilizing the axial isomer.

(3) Quite a different situation was observed for **9**, X = $NHCOCH_3$, where salt addition breaks up intramolecular hydrogen bonding present in the salt-free axial isomer.

Of course, the results of these calculations have the limitation that bare cations, rather than solvated ions and ions pairs, are used.

## Conclusions

In absence of salt, the conformational behavior of 5-polar-substituted-1,3-dioxanes is generally determined by an electrostatic dipole−dipole repulsion that favors the equatorial isomer. Nevertheless, compensating effects such as intramolecular hydrogen bonding, electrostatic attraction, and stereoelectronic effects may shift the equilibrium toward the axial isomers.

The conformational preference of 5-substituted-1,3-dioxanes can be affected by addition of lithium salts, and this effect is stronger in $CHCl_3$ relative to THF solvent, in agreement with expectation based on cation solvation abilities. By contrast, the nature of the counteranion does not play a significant role on the observed salt effects.

## Experimental Section

**General Information.** Melting points were determined with open capillary tubes and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$, DMSO-$d_6$, or THF-$d_8$ solution with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given as $\delta$ values (ppm) and coupling constants ($J$) in Hz.

THF was initially distilled over KOH and then heated to reflux over sodium/benzophenone (under nitrogen) until the blue color of the benzophenone ketyl persisted; at this point the THF was distilled and handled by means of syringes and cannulas.[31] Chloroform (spectroscopic grade) was distilled over Drierite and further dried over molecular sieves. Flasks, stirring bars, and hypodermic needles were dried for ca. 12 h at 120 °C and allowed to cool in a desiccator over anhydrous calcium sulfate.

Lithium bromide was dried at 190 °C for 4 days. Lithium tetraphenylborate was prepared by metathesis from a concentrate THF solution of $NaBPh_4$ which was added to a concentrated THF solution of LiCl.[32] The insoluble NaCl precipitate was removed by filtration, and the lithium salt was recovered by evaporating the solvent. The salt was recrystalized from chloroform and then dried over $P_2O_5$ under vacuum for 24 h at room temperature followed by 24 h at 80 °C.

Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

***cis*- and *trans*-2-Phenyl-5-carboxy-1,3-dioxane (*cis*- and *trans*-1).** These compounds were prepared as described in the literature.[12] Diethyl bis(hydroxymethyl)malonate (11.4 g, 0.06 mol) was condensed with 6.5 g (0.06 mol) of benzaldehyde, affording 16.1 g (95.2% yield) of 2-phenyl-5,5-dicarbethoxy-1,3-dioxane, **10**, as a yellow liquid, bp 170−175 °C/4 mmHg. Saponification was effected by addition of diester **10** (77.0 g, 0.25 mol) to 60 g (1.07 mol) of KOH in 500 mL of 95% ethanol and boiling for 1 h. The ethanol was evaporated, and the resulting solid was dissolved in 400 mL of dichloromethane. The solution was chilled in an ice bath and acidified with 10% hydrochloric acid. The organic layer was separated and dried over anhydrous $Na_2SO_4$. Concentration in a rotary evaporator afforded 24.1 g (40.4% yield) of 2-phenyl-5,5-dicarboxy-1,3-dioxane (**11**) as a white solid with mp 148−150 °C. Finally, a magnetically stirred mixture of dicarboxylic acid **11** (10.0 g, 0.039 mol) and 15 mL of triethylamine was heated to reflux for 40 min. The triethylamine was distilled, and the remaining solid was dissolved in 100 mL of dichloromethane. The solution was chilled in an ice bath and acidified until pH 2 with 10% hydrochloric acid. The reaction mixture was extracted with ether (2 × 100 mL), and the combined ether extracts were dried over anhydrous $Na_2SO_4$. Concentration in a rotary evaporator afforded 7.3 g (86.2% yield) of a mixture of isomers. The mixture was separated by flash chromatography over silica gel (hexane/ethyl acetate/dichloromethane/acetone/methanol, 8.0:0.5:0.5:0.5:0.5) to afford 2.5 g (34.2% yield) of *cis*-**1** as a white solid, mp 148−149 °C, and 3.8 g (52.0% yield) of *trans*-**1** as a white solid, mp 168−169 °C. $^1H$ and $^{13}C$ NMR spectra in Tables 1 and 2, respectively. Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found (*cis* isomer): C, 63.64; H, 6.05. Found (*trans* isomer): C, 63.49; H, 5.87.

***cis*- and *trans*-2-Phenyl-5-carbomethoxy-1,3-dioxane (*cis*- and *trans*-2).** A mixture of *cis*-**1** (13.4 g, 0.064 mol) and silver oxide (29.7 g, 0.13 mol) was cooled to 0 °C in an ice bath and treated with 36.5 g (16 mL, 0.25 mol) of methyl iodide. The reaction mixture was stirred at 0 °C for 2 h before the addition of 50 mL of dichloromethane, the solid was filtered, and the filtrate was concentrated in a rotary evaporator. Purification of the crude product was accomplished by crystallization from hexane to give 14.3 g (91.8% yield) of *cis*-**2** as a white solid, mp 75−76 °C. $^1H$ and $^{13}C$ NMR spectra in Tables 1 and 2, respectively. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.10; H, 6.48.

In similar fashion, *trans*-**1** was converted to *trans*-**2** in 94.2% yield, mp 79−81 °C. $^1H$ and $^{13}C$ NMR in Tables 1 and 2, respectively. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.82; H, 6.51.

***cis*- and *trans*-2-Phenyl-5-(*N*-methylcarbamoyl)-1,3-dioxane (*cis*- and *trans*-3).** A solution of 5.0 g (1.87 mmol) of *cis*-2-phenyl-5-carbomethoxy-1,3-dioxane (**2**), 15 mL of methanol, and 5 mL of 40% aqueous methylamine was left standing for 12 h at 4 °C. The reaction mixture was filtered,

(30) (a) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. (b) Dewar, M. J. S.; Reynolds, C. H. *J. Comput. Chem.* **1986**, *2*, 140. (c) Cramer, C. J., Truhler, D. G.; *Science* **1992**, *256*, 213. (d) Cramer, C. J.; Truhler, D. G. *J. Comput. Aided Mol. Des.* **1992**, *6*, 69

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(32) Kunze, R. W.; Fuoss, M. *J. Phys. Chem.* **1967**, *67*, 385.

and the resulting solid consisted of a mixture of *cis*-**3** and *trans*-**3** (30:70). Fractional recrystallization afforded 500 mg (10% yield) of *cis*-**3** as a white solid, mp 118−120 °C. $^1$H and $^{13}$C NMR spectra in Tables 1 and 2, respectively. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.13; H, 6.83. Found: C, 65.38; H, 7.05.

Similarly, *trans*-**2** was converted to *trans*-**3** in 96.4% yield, mp 193−195 °C. $^1$H and $^{13}$C NMR spectra in Tables 1 and 2, respectively. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.13; H, 6.83. Found: C, 64.75; H, 6.97.

***cis*- and *trans*-2-Phenyl-5-(hydroxymethyl)-1,3-dioxane (*cis*- and *trans*-4)**. A solution of *cis*-2-phenyl-5-carbomethoxy-1,3-dioxane (**2**) (4.0 g, 0.015 mol) in 50 mL of anhydrous ether was added (15 min) to a suspension of lithium aluminum hydride (1.5 g, 0.039 mol) in 50 mL of anhydrous ether under nitrogen atmosphere. The resulting suspension was stirred at rt for 1 h and then was heated to reflux for 30 min. The suspension was treated with ethyl acetate (15 mL) and a 10% solution of NaOH (ca. 100 mL). The reaction mixture was extracted two times with ether, and the combined organic extracts were dried over anhydrous $Na_2SO_4$ and concentrated to provide the crude product. Recrystallization from hexane gave 3.03 g (84.6% yield) of *cis*-**4** as a white solid with mp 61−62 °C. $^1$H and $^{13}$C NMR spectra in Tables 1 and 2, respectively. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.21; H, 7.48

Similarly, *trans*-**2** was converted to *trans*-**4** in 94.8% yield, mp 88−89 °C. $^1$H and $^{13}$C NMR in Tables 1 and 2, respectively. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.23; H, 7.57.

***cis*- and *trans*-2-Phenyl-5-hydroxy-1,3-dioxane (*cis*- and *trans*-5)**. These compounds were prepared by condensation of glycerol (50 g, 0.54 mol) and benzaldehyde (50 g, 0.48 mol) according to a published procedure.[1,33] The crude product (81.7 g) consisted of a mixture of 1,3-dioxanes and 1,3-dioxolanes. This mixture was separated by flash chromatography (hexane/ethyl acetate, 1:1) to afford 9.6 g (11.6% yield) of *trans*-**5** as a white crystals, mp 63−65 °C (lit.[33] mp 64.5−65.5 °C) and 25.1 g (29.2% yield) of *cis*-**5** as a white crystals, mp 83−85 °C (lit.[33] mp 83−85 °C). $^1$H NMR spectrum in Table 1. $^{13}$C NMR spectrum in Table 2.

***cis*- and *trans*-2-Phenyl-5-*O*-acetyl-1,3-dioxane (*cis*- and *trans*-6)**. These compounds were prepared as described in the literature.[33] Carbinol *cis*-**5** (3.0 g, 0.016 mol) in pyridine (0.5 g, 0.006 mol) was treated with acetic anhydride (15.0 g, 0.146 mol). The reaction mixture was stirred at rt for 15 h and then poured into ice-water; the precipitate was collected, dissolved in chloroform, washed successively with ice−cold 1 N hydrochloric acid, saturated aqueous hydrogen carbonate, and water, and finally dried over anhydrous $Na_2SO_4$. Concentration in a rotary evaporator afforded the crude product which was crystallized from hexane to give 3.38 g (95.3% yield) of *cis*-**6** as a white solid with mp 98−100 °C (lit.[33] mp 99−100 °C). $^1$H NMR and $^{13}$C NMR spectra in Tables 1 and 2, respectively.

Similarly, *trans*-**5** was converted to *trans*-**6** in 90% yield. This compound formed as white crystals with mp 114−116 °C (lit.[33] mp 115−116 °C).

***cis*- and *trans*-2-Phenyl-5-[(2-methoxyphenoxy)acetoxy]-1,3-dioxane (*cis*- and *trans*-7).** These compounds were synthesized according to the published procedure.[15] A solution of (2-methoxyphenoxy)acetic acid[14] (1.82 g, 0.01 mol) in pyridine (50 g, 0.63 mol) was treated with *p*-toluenesulfonyl chloride (4 g, 0.02 mol). The solution was cooled in an ice bath before the addition of 1.8 g (0.01 mol) of carbinol *cis*-**5.** The reaction mixture was stirred at 0 °C for 1 h and then poured into three to four volumes of ice and water. The resulting solid esters were collected by filtration to afford 3.1 g (90.1% yield) of *cis*-**7** as a white solid, mp 91−92 °C. $^1$H NMR and $^{13}$C NMR spectra in Tables 1 and 2, respectively. Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.45; H, 5.56.

In similar fashion, *trans*-**5** was converted to *trans*-**7** in 92.4% yield, mp 102−103 °C. $^1$H NMR and $^{13}$C NMR spectra in Tables 1 and 2, respectively. Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27, H, 5.85. Found: C, 66.23; H, 6.00.

(33) Baggett, N.; Brimacombe, J. S.; Foster, A. B.; Stacey, M. M.; Whiffen, D. H. *J. Chem. Soc.* **1960**, 2574.

***cis*-2-Phenyl-5-nitro-1,3-dioxane (*cis*-8)**. According to the procedure of Marei and Raphael,[16] 2-phenyl-5-(hydroxymethyl)-5-nitro-1,3-dioxane, **12**[34] (24.0 g, 0.1 mol), was treated with a solution of lithium in liquid ammonia (1.2 g of lithium and 400 mL of ammonia) to furnish 11.7 g (52.6% yield) of *cis*-**8** as the sole product, mp 127−128 °C (lit.[16] mp 127−129 °C). $^1$H and $^{13}$C NMR spectra in Tables 1 and 2, respectively. The sublimation of *cis*-**8** at 135−140 °C/4 mmHg afforded a 1:1 mixture of *cis*-**8** and *trans*-**8**.

The *trans* isomer was separated by flash chromatography (hexane/ethyl acetate, 9:1), mp 68−69 °C. $^1$H and $^{13}$C NMR spectra in Tables 1 and 2, respectively. Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30. Found: C, 57.36; H, 5.49.

***cis*- and *trans*-2-Phenyl-5-acetamido-1,3-dioxane (*cis*- and *trans*-9)**. A solution of *cis*-2-phenyl-5-nitro-1,3-dioxane (*cis*-**8**) (12.3 g 0.06 mol) in 20 mL of ethanol was added to a suspension of 10% Pd(C) (1.2 g, 1.14 mmol) and then was exposed to hydrogen (800 psi) with stirring and heating (30 °C) during 3 h. The catalyst was removed by filtration (Celite), and the filtrate was concentrated at reduced pressure to afford 9.74 g (92.6%, yield) of *cis*-**13** as a colorless oil. This intermediate, *cis*-**13** (10 g, 0.06 mol), was treated with 50 mL of acetic anhydride and 1 mL of pyridine. The reaction mixture was stirred at rt for 2 h, and then the excess of acetic anhydride was distilled at reduced pressure. The solid residue was crystallized from ethyl acetate to afford 11.5 g (93.5% yield) of the *cis*-**9** as a white solid with mp 153−154 °C. $^1$H and $^{13}$C NMR spectra in Tables 1 and 2, respectively. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.13; H, 6.83. Found: C, 64.77; H, 6.93.

Similarly, *trans*-**8** was converted to *trans*-**9** in 90.1% yield, mp 202−203 °C. $^1$H and $^{13}$C NMR spectra in Tables 1 and 2, respectively. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.13; H, 6.83. Found: C, 64.84, H, 6.98.

**Equilibrations and Analysis**. Equilibrium was approached from both sides; boron trifluoride etherate was the catalyst: ca. 60 mg of dioxane and 1 or 10 equiv of Li salt were placed in a 5 mL ampoule and dissolved in 3 mL of solvent before the addition of two drops of the catalyst. The ampoule was sealed and submerged in a constant-temperature bath until equilibrium was reached. The progress of the equilibration was conveniently monitored by $^1$H NMR spectroscopy. Quenching was effected by pouring the equilibration solution into aqueous 30% sodium bicarbonate. The dioxanes were then extracted with ether, dried over anhydrous $Na_2SO_4$, and evaporated.

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**Supporting Information Available:** Calculated (MOPAC/AM1) heats of formation and structures of minimum energy for axial and equatorial 5-substituted 1,3-dioxanes (color images available only electronically) (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information and for Internet access instructions.

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(34) 2-Phenyl-5-(hydroxymethyl)-5-nitro-1,3-dioxane (**12**) was prepared by condensation of 2-(hydroxymethyl)-2-nitro-1,3-propanediol (15 g, 0.1 mol) and benzaldehyde (10 g, 0.94 mol) according to a published procedure.[19]