# **Conformational Analysis**

# 18\*—Lanthanide-Induced Shift (LIS) Investigation of Some 2-Substituted 1,3-Dioxanes

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A LIS analysis of 2-isopropyl-1,3-dioxane (1) and 2-methyl-2-phenyl-1,3-dioxane (2) is reported. The monodentate complexing model gives good agreement with the observed shifts in both compounds, whereas the bidentate model (lanthanum binding to both oxygens) does not give an acceptable solution. In 1 the lanthanide complexes almost exclusively (90%) with the axial lone pair of the oxygen atom. The four-site binding model gives excellent agreement with the observed shifts ( $R_x$  3.5%). In 2 a similar lanthanide binding is found, and the analysis of the LIS allows both the deduction of the molecular conformation (C-2-methyl equatorial, C-2-phenyl axial) and also the orientation of the phenyl group (perpendicular).

KEY WORDS NMR LIS Conformations 2-Substituted 1,3-dioxanes

#### INTRODUCTION

The 1,3-dioxane system has been the subject of a large number of NMR and conformational investigations in the past,<sup>2,3</sup> partly owing to the ready synthesis of 1,3-dioxanes from aldehydes or ketones and 1,3-diols, and also to their readily interpretable NMR spectra.

The conformational equilibria in 1,3-dioxanes can also be studied conveniently by chemical equilibration, and this was the method used by Eliel and Knoeber<sup>2,4</sup> and Riddell and Robinson<sup>3,5</sup> in their classical investigation of this ring system. They showed very clearly the contrast between the substituent free energy differences in the 1,3-dioxane and cyclohexane rings. For example, the  $-\Delta G^{\circ}$  value of a methyl group on the dioxane ring is 2-Me > 3.6, 4-Me 2.9 and 5-Me 0.8 kcal mol<sup>-1</sup> (1 kcal = 4.184 kJ) compared with 1.7 kcal mol<sup>-1</sup> in cyclohexane.

These authors rationalized these and other data in terms of the shorter C—O vs. C—C bonds, resulting in a flattening of the C-4, C-5, C-6 region and a puckering of the O-1, C-2, O-3 region (Fig. 1), and these suggestions were subsequently confirmed in electron diffraction and x-ray studies of the 1,3-dioxane ring (see later).

The presence of two polar oxygen atoms in the ring also gives rise to large solvent effects on the  $-\Delta G^{\circ}$ values of polar substituents. For example, the  $-\Delta G^{\circ}$ values for 5-chloro-1,3-dioxane range from -1.40 kcal mol<sup>-1</sup> in CCl<sub>4</sub> solvent to 0.25 kcal mol<sup>-1</sup> in acetonitrile. These changes with solvent have explained quanti-

\* For Part 17, see ref. 1.

0749-1581/92/101019-06 \$08.00 © 1992 by John Wiley & Sons, Ltd. tatively in terms of a reaction field model by Abraham  $et al.^{6}$ 

In previous parts of this series,  $^{1,7-9}$  the lanthanideinduced shift (LIS) method was applied in a variety of conformational investigations, including the conformation of substituted cyclohexanones<sup>7</sup> and cyclohexenones<sup>8</sup> and of substituted aromatic aldehydes and ketones.<sup>9</sup> It was felt to be of interest to attempt LIS investigation of the 1,3-dioxane system. This system has not, to our knowledge, been previously investigated by the LIS method, the nearest comparable investigation being that of Peters *et al.*<sup>10</sup> on some 3-oxabicyclo[3.3.1] nonanes, 2-oxaadamantane and 4-methyltetrahydropyran. Their data indicated that in the latter case the lanthanide ion coordinated axially to the oxygen atom.



Figure 1. Bond lengths, valency and torsional angles in the 1,3dioxane ring.

Received 1 May 1992 Accepted (revised) 12 June 1992 In the 1,3-dioxane system it is first necessary to determine the appropriate lanthanide complexation model. There is the possibility of bidentate (using both ring oxygens) or monodentate (only one ring oxygen) complexation; if the latter case applies then there is the question of the relative nucleophilicity of the oxygen lone pairs, i.e. does the lanthanum prefer an axial or equatorial approach?

We follow our previous procedure in these investigations in considering first a molecule of known conformation, in this case 2-isopropyl-1,3-dioxane, to determine the appropriate lanthanide complexation model, and then test this model on a conformational problem. Recently Shea and Dougherty<sup>11</sup> proposed from NMR evidence that 2-methyl-2-phenyl-1,3 dioxane exists in the conformation with an axial phenyl. This seemed an ideal case to test the lanthanide model, and we shall show that indeed the LIS data do confirm unequivocally their findings, and also give us information as to the preferred orientation of the phenyl ring in this compound.

## THEORY

The substrate geometry used (Fig. 1) is derived from electron diffraction studies of Schultz *et al.*<sup>12</sup> on 1,3-dioxanes and x-ray studies of Kok and Romers<sup>13</sup> on 2-*p*-chlorophenyl-1,3-dioxane. These investigations are in good agreement where they overlap, but differ somewhat from the more recent x-ray studies of Shea and Dougherty<sup>11</sup> on some 2-aryl-2-methyl-1,3-dioxanes. For example, the former both record a shorter O—C(O) than O—C(C) bond, 1.393(25) *vs.* 1.439(3) Å<sup>12</sup> and 1.405 *vs.* 1.435 Å,<sup>13</sup> whereas in Shea *et al.*'s work<sup>11</sup> the difference is much smaller, 1.42 *vs.* 1.43 Å. The shorter C—O bond with multiple oxygen substitution on the carbon exactly parallels the analogous well documented C—F bond length: 1.385 Å (CH<sub>3</sub>F), 1.357 Å (CH<sub>2</sub>F<sub>2</sub>) and 1.332 Å (CHF<sub>3</sub>);<sup>14</sup> therefore we used the values shown.

It should also be noted that the dioxane ring is flattened at C-4, C-5, C-6 ( $w_{45}$  55.0°) and puckered at O-1, C-2, O-3 ( $w_{23}$  62.8°), exactly as predicted by Eliel and Knoeber.<sup>4</sup> In the 2-aryl-2-methyl-1,3-dioxanes studied by Shea and Dougherty,<sup>11</sup> a significant flattening of the ring was observed, with values of  $w_{23}$ ,  $w_{34}$  and  $w_{45}$  of 56.2°, 56.2° and 52.5° for *cis*-2-(*p*-chlorophenyl)-2methyl-5-phenyl-1,3-dioxane. This ring flattening could be due to the axial phenyl substituent, and will be considered subsequently.

The C-2 substituents were added using standard bond lengths and angles [C—C 1.53 Å, C(ar)—C 1.50 Å, C(ar)–C(ar) 1.397 Å].

# THE COMPLEXATION MODEL

In previous parts of this series the LIRAS suite of programs (LIRAS3,<sup>15</sup> LIRAS4,<sup>16</sup> HARDER<sup>17</sup>) were developed in order to model satisfactorily the various lanthanum binding modes for different substrates. These have been described elsewhere,<sup>15–17</sup> but it is pertinent to summarize briefly the LIRAS3 model which, although originally developed for carbonyl compounds, can be adapted for this investigation.

The LIRAS3 coordination model for a carbonyl group is shown in Fig. 2(a). The coordinating atom is at the coordinate origin, and the lanthanide position is scanned over the polar coordinates r,  $\phi$ ,  $\psi$  for the best agreement with the observed shifts, the magnetic axis always being along the Ln—O bond.

The program allows reflection of the lanthanide coordinates through the xz plane (the two-site model) or through both the xz and xy planes (the four-site model), but the site populations can only be varied across the xzplane.

Thus, for example, in Fig. 2(a), if the steric environment of the carbonyl lone pairs differed as, for example, in any unsymmetric ketone RCOR', this can be modelled by varying the population of the two sites without introducing a separate set of lanthanide coordinates for each site. This more complex procedure, which is performed with the HARDER program,<sup>17</sup> requires considerably more experimental data and is not needed for the present investigation.



Figure 2. The LIRAS3 complexation model: (a) as used for carbonyl compounds; (b) the bidentate model for 1,3-dioxane; (c) the monodentate model for 1,3-dioxane.

The four-site model gave better agreement for all the compounds considered here, and only these results will be discussed. This is consistent with previous LIS studies involving carbonyl compounds, in which the four-site model gave better agreement factors.<sup>9</sup> It is possible that this model implicitly takes into account the intramolecular motions in these very weak complexes.

The two binding modes we wish to consider for the 1,3-dioxane ring are (a) the bidentate model in which both oxygen atoms coordinate equally to the lanthanide atom and (b) the monodentate model in which only one oxygen (at a time) coordinates (there is, of course, fast exchange on the NMR time scale of the lanthanidesubstrate complexation, but this is easily allowed for by averaging the appropriate nuclei).

The appropriate models are illustrated in Fig. 2(b) and (c). In the bidentate model the lanthanide magnetic axis is directed towards the mid-point of the two oxygens and the lanthanide atom should be situated in the xz plane.

In the monodentate model the axes are changed so that the variation in the percentage population across the xz plane now corresponds to complexation with the axial and equatorial lone pairs on the oxygen. Apart from this rearrangement of the axes, the procedures are identical with those in previous investigations in scanning the lanthanide position for the best solution.

#### RESULTS

Table 1 gives the chemical shifts and the observed LIS  $(\Delta M)$ , i.e. the pseudo-contact shifts, for the 1,3-dioxanes investigated. These pseudo-contact shifts can now be used, ignoring any contact shifts, in the LIS analysis. A good solution can be considered to have an agreement factor  $(R_r)$  of < 5% with all calculated shifts to within 1 ppm of the observed values, and also resulting from a chemically acceptable coordination geometry. Below, each molecule is considered in turn.

#### 2-p-Chlorophenyl-1,3-dioxane

Initially this molecule was used as the conformationally rigid substrate. However, its measured  $\Delta M$  values were always very small (the largest value, that of C-2, was only 4.95), even though repeated experiments gave consistent results, and the LIS analysis gave unreal complexation parameters.

The small observed shifts may be due to the facile ring opening of the 1,3-dioxane ring, as the products of ring opening (p-chlorobenzaldehyde and propane-1,3diol) will complex preferentially to the lanthanide. These very small  $\Delta M$  values also lead to considerable uncertainties in the LIS analysis, in that a large range of possible solutions was consistent with the observed data.

It is possible that there may be competitive binding of the lanthanide with the p-chlorophenyl group. Complexation of lanthanide with the phenyl group of phenylcyclohexane has been noted previously,18 but this did not affect the resultant LIS analysis of the 4phenylcyclohexanone.

#### Table 1. Observed shifts ( $\delta$ , ppm) and LIS values ( $\Delta M$ ) for 2isoproyl-1,3-dioxane (1) and 2-methyl-2-phenyl-1,3dioxane (2)

	Compound 1		Compound 2	
Nucleus	δ*	∆M <sup>b</sup>	б <sup>с</sup>	∆Mª
C-2	105.95	11.38	100.48	17.41
C-4,6	66.81	8.61	61.20	11.37
C-5	25.84	6.88	25.42	8.35
C-2a	32.75	9.61	141.13	8.44
C-0			126.80	5.98
C-m	_		128.65	3.18
С-р	·		127.54	2.72
C-2-Me	_		32.40	14.36
CH <sub>3</sub> (iPr)	16.89	6.89		
H-2	4.227	6.44	1.513 <sup>e</sup>	12.91 <sup>e</sup>
H-4eq	4.112	6.67	3.873	8.75
H-4ax	3.743	4.49	3.809	7.34
H-5eq	1.321	2.60	1.246	4.12
H-5ax	2.058	8.90	2.124	8.97
H-0	_		7.436	7.18
H- <i>m</i>	_		7.400	1.73
Н-р	_		7.306	1.40
CH (iPr)	1.766	8.93		
CH <sub>3</sub> (iPr)	0.926	5.32		

<sup>a</sup> [S]<sub>0</sub> 0.13 mol dm<sup>-3</sup> in CDCl<sub>3</sub>. <sup>b</sup> From three additions of Yb(fod)<sub>3</sub>,  $10^2 p = 3.17$ , 10.90 and 17.84, all correlation coefficients >0.991.

° [S]<sub>o</sub> 0.36 mol dm<sup>-3</sup> in CDCl<sub>3</sub>.

<sup>d</sup> From three additions of Yb(fod)<sub>3</sub>,  $10^2\rho = 2.87$ , 4.30 and 5.42, all correlation coefficients >0.996.

°С-2-СН<sub>3</sub>.

Further, the analysis of 2-methyl-2-phenyl-1,3dioxane (see later) was not affected by any phenyl lanthanide complexation. Hence the results from this molecule were not considered further and are not presented here.

#### 2-Isopropyl-1,3-dioxane

This molecule is conformationally rigid with a chair conformation and an equatorial isopropyl group. The  $-\Delta G^{\circ}$  (ax - eq) value of the C-2 isopropyl group is >4.0 kcal mol<sup>-1,<sup>2</sup></sup> hence no significant amount of the axial conformer is present. The isopropyl group rotates around the C-2-CH bond with the formation of trans and gauche conformers (see later).

We first considered the bidentate model [Fig. 2(b)], particularly as it is easier to visualize, seeking the best solution using all the shifts except the isopropyl CH and methyl <sup>1</sup>H and <sup>13</sup>C atoms as these will be affected by the isopropyl conformation (i.e. gauche or trans). The computational search always produced a solution in which the lanthanide was not in the xz plane, but essentially towards one oxygen, for example r = 4.75 Å,  $\phi = 50^{\circ}$  and  $\psi = 120^{\circ}$  and 100% population on the -yaxis gave  $R_x$  7.6%.

Including the isopropyl nuclei made no real difference to this solution, which is clearly not an acceptable bidentate solution, and this model was not considered further.

The next model considered was that of monodentate complexation [Fig. 2(c)]. The same procedure as that described above was adopted with the computational search, varying both the lanthanide position and also, importantly, the percentage populations about the xz plane. In this case the search converged to an acceptable solution as follows. Using all the dioxane ring nuclei and the isopropyl CH carbon atom gave  $R_x = 3.5\%$ , r = 4.0 Å,  $\phi = 55^{\circ}$  and  $\psi = 120^{\circ}$  with 90% population in the +y orientation. The calculated shifts are shown together with those observed in Table 2 (solution a), and it can be seen that the agreement is well within experimental tolerances with all shifts included in the calculation reproduced to  $\leq 0.6$  ppm with an r.m.s. error of 0.27 ppm.

An attempt was made to see whether altering the conformation of the dioxane ring had any significant affect on the agreement factor. Varying the torsion angles of the OCO fragment did produce a slightly better solution. Reducing the torsional angles from  $63^{\circ}$  (Fig. 1) to  $60^{\circ}$  gave an agreement factor  $R_x$  of 3.36% (cf. 3.5% in Table 2). The difference is not considered to be large enough to be significant.

The complexation geometry is of some interest. The +y orientation is that of the axial oxygen lone pair [Fig. 2(c)], hence the lanthanide occupies almost exclusively the axial position. This may be due to steric effects, as the C-2 isopropyl substituent sterically hinders complexation to the equatorial oxygen lone pair. Alternatively, the nucleophilicity of the axial lone pair may be intrinsically greater than that of the equatorial lone pair, and this is supported by the results of Peters *et al.*<sup>10</sup> on 4-methyltetrahydropyran, in which lanthanide complexation.

Hence in this molecule the LIS data can be explained qualitatively with a chemically reasonable complexation model. The LIS data can also provide information on the conformation of the C-2 isopropyl group, in which the CH—CH dihedral angle may be either *trans* or *gauche*.

Using the calculated values of  $\Delta M$  for the three sets of nuclei affected by this rotation, i.e. the methyl

Table 2. Observed and calculated LIS ( $\Delta M$ ) for 2-isopropyl-1,3-dioxane (1) and 2-methyl-2-phenyl-1,3-dioxane (2)

Compound 1			Compound 2			
Nucleus	Obs.	Calc.*	Nucleus	Obs.	Calc. <sup>b</sup>	
C-2	11.4	11.6	C-2	17.4	16.7	
C-4,6	8.6	8.0	C-4,6	11.4	11.5	
C-5	6.9	7.2	C-5	8.4	9.1	
C-2a	9.6	9.6	C-2a	8.4	8.3	
C-2b	6.9	15.8°	C-0	6.0	5.6	
			C-m	3.2	2.7	
			С-р	2.7	2.2	
			2-Me	14.4	14.5	
H-2	6.4	6.4	H-2(Me)	12.9	12.7	
H₋4eq	6.7	6.7	H-4eq	8.8	9.4	
H-4ax	4.5	4.8	H-4ax	7.3	7.6	
H-5eq	2.6	2.8	H-5eq	4.1	4.8	
H-5ax	8.9	8.7	H-5ax	9.0	9.0	
CH (iPr)	8.9	8.5°	H- <i>o</i>	7.2	6.9	
CH <sub>3</sub> (iPr)	5.3	9.8°	H- <i>m</i>	1.7	1.7	
			H- <i>p</i>	1.4	1.4	

<sup>a</sup>r = 4.00 Å,  $\phi = 55^{\circ}$ ,  $\psi = 120^{\circ}$ , 90% population (+ $\gamma$ ),  $R_x = 3.5\%$ . <sup>b</sup>r = 3.80 Å,  $\phi = 110^{\circ}$ ,  $\psi = 145^{\circ}$ , 80% population (+ $\gamma$ ),  $R_x = 4.7\%$ . <sup>c</sup> Nucleus not included in search procedure. carbons and the CH and CH<sub>3</sub> hydrogens, together with the observed values of  $\Delta M$ , suggests that the isopropyl group orientation is mainly gauche with the CH proton near to the complexing lanthanum atom. This agrees well with the population of ca. 70% gauche estimated from the observed value for the CH–CH coupling of 4.75 Hz.<sup>19</sup>

## 2-Methyl-2-phenyl-1,3-dioxane

The results for 2-isopropyl-1,3-dioxane allow us to consider the conformational equilibrium in this molecule. As in the previous case the bidentate model gave a solution which was essentially a monodentate one, and this was not considered further.

For the monodentate model the computational search was initially performed in a similar fashion to the previous case, considering only the dioxane ring nuclei. This gave a good agreement factor ( $R_x = 2.9\%$ ) and an acceptable solution (r = 3.8 Å,  $\phi = 120^\circ$ ,  $\psi = 120^\circ$ ) and 55% population in the +y axis (not shown in Table 2).

The methyl and phenyl nuclei can now be added, with two possible geometries, methyl (equatorial) and phenyl (axial) or vice versa. In the event the methyl (axial), phenyl (equatorial) conformation did not produce an acceptable solution, and we consider only the alternative conformation. This gave a chemically reasonable solution with  $R_x = 5.4\%$ , although there were some unacceptably large differences (>1 ppm) between the observed and calculated  $\Delta M$  values (not shown in Table 2).

The reason for this was probably due to the molecular geometry used, which was taken directly from the unstrained dioxane ring geometry in Fig. 1. The introduction of the 2-methyl-2-phenyl substituents would be expected to distort the geometry, particularly around the C-2 atom, and indeed Shea and Dougherty<sup>11</sup> observed a significant flattening of this end of the dioxane ring in the crystal (see below).

These observations, plus the use of the molecular mechanics program PCMODEL (Serena Software, Bloomington, IN, USA) to produce an alternative relaxed geometry, allowed a more accurate geometry to be used. The only major difference is that the C—O—C angle is increased to 113.4° and  $w_{23}$  decreased to 57.0°. In addition, the steric strain at C-2 is relieved by relaxing the CH<sub>3</sub>—C—O angles to 105.6°. With these amendments a significantly better solution was obtained ( $R_x = 4.7\%$ ) with no unacceptably large errors (solution b, Table 2).

The complexation geometry obtained is very similar to that for 2-isopropyl-1,3-dioxane (Table 2) and again, as expected, the axial position is strongly preferred by the lanthanide atom. This is easily rationalized because the steric hindrance to complexation with the equatorial oxygen lone pair is severe, with both the C-2 methyl and C-2 phenyl groups in a *gauche* orientation with respect to the equatorial position. Thus again the LIS data give a quantitative and reasonable complexation model.

Further, the model can be used to deduce the conformation of the phenyl ring. The solution given is that for a  $90^{\circ}$  angle between the phenyl plane and the C-2---Me bond, and this is the best solution. Varying the phenyl



Fig. 3 Observed – calculated LIS for H-*ortho vs.* the phenyl ring dihedral angle in 2-methyl-2-phenyl-1,3-dioxane.

dihedral angle produces large changes, particularly for H-ortho, and Fig. 3 shows the calculated shifts at H-ortho vs. the dihedral angle. Thus the LIS method is capable of determining, to some accuracy, both the conformation and particular aspects of the configuration in this molecule.

The result obtained, of methyl equatorial and phenyl axial with an orthogonal phenyl ring, is confirmed by the crystal and NMR studies of Shea and Dougherty<sup>11</sup> for this molecule, and also by previous investigations by Allinger and Tribble<sup>20</sup> in the analogous cyclohexane series, where they found a similar orientation for axial phenyl.

# CONCLUSION

The application of the LIS method to the 1,3-dioxane system shows considerable promise. In 2-isopropyl-1,3-dioxane the LIS data give a quantitative explanation on the basis of the known molecular geometry. The lanthanide complexes to one oxygen (i.e. a monodentate model), with 90% complexation along the axial lone pair of the oxygen atom. In 2-methyl-2-phenyl-1,3-dioxane the method allows the deduction of the precise conformation of the molecule in solution (2-methyl equatorial, 2-phenyl axial) and also the perpendicular orientation of the phenyl group. In this molecule the lanthanide also complexes almost exclusively to the axial lone pair of one oxygen atom.

# **EXPERIMENTAL**

2-p-Chlorophenyl-1,3-dioxane, 2-isopropyl-1,3-dioxane and 2-methyl-2-phenyl-1,3-dioxane were prepared by condensing *p*-chlorobenzaldehyde, isobutyraldehyde and acetophenone with propane-1,3-diol in the presence of toluenesulphonic acid in a Dean–Stark apparatus. In the former case toluene proved to be a satisfactory solvent, the reaction going to completion in ca. 2 h.

The condensation of the latter compounds and propane diol was unsuccessful with toluene as solvent, as the propane-1,3-diol formed an azeotrope with the solvent. The use of benzene or cyclohexane as solvent gave the required products after work-up.

No trace of impurities could be observed in the NMR spectra.

The <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on a Bruker AMX-400 spectrometer with a probe temperature of 20 °C. All spectra were recorded in CDCl<sub>3</sub> which had been stored over molecular sieves (4 Å), with TMS as internal standard. Commercial Yb(fod)<sub>3</sub> was dried *in vacuo* over P<sub>2</sub>O<sub>5</sub> for 24 h prior to use, as were the samples of the dioxanes. The LIS experiments used the incremental weighting method, and the <sup>1</sup>H and <sup>13</sup>C assignments of the spectra followed literature values and additive chemical shift effects.<sup>19,21</sup>

Extreme care was needed to obtain reasonable LIS values, particularly for 2-*p*-chlorophenyl-1,3,-dioxane, as the presence of trace amounts of acid, or even perhaps the lanthanide itself, tended to produce the aldehyde and propane-1,3-diol, both of which complex preferentially to the lanthanide. Perhaps for this reason the absolute values of the induced shifts are smaller than expected.

The experimental plots were all obtained with a molar ratio  $\rho = [L]/[S]$  (L = shift reagent, S = substrate) in the range 0.0–0.10, and all the shifts showed a good correlation and intercept, demonstrating the linearity of the plots.

The estimation of the diamagnetic contribution  $(\Delta D)$  to the LIS was not performed, because it was shown in our previous studies<sup>7</sup> that saturated molecules give no diamagnetic contribution, apart from the carbon of the coordinating carbonyl group. There is no evidence of any diamagnetic or contact contribution in the derived  $\Delta M$  values. The experimental data are given in Table 1.

All the computational work was performed on either a DEC VAX 11/780 or an OPUS PC386 computer.

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