# NMR Spectra, MO Calculations of Spin–Spin Coupling Constants and Conformational Analysis of Substituted 1,3-Dioxolanes

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The NMR spectra of a number of 2,4-disubstituted 1,3-dioxolanes have been recorded and the proton chemical shifts and coupling constants derived from complete spectral analysis. Vicinal coupling constants were found to be dependent on the substituent at C-4 and this effect is more pronounced for J(trans) of the C-4-C-5 fragment. These coupling constants also indicate a homogeneous behaviour within a series with either a cis or trans configuration, although the cis behaviour differs from that of trans isomers. This has been interpreted in terms of definite ring conformations in substituted derivatives, while the unsubstituted 1,3-dioxolane undergoes free pesudorotation. Calculations of coupling constants were performed by semi-empirical MO methods, both for unsubstituted 1,3-dioxolane and for C-4 substituted derivatives in a large number of conformations, in order to compare calculated and experimental values; the correct order of J(cis) and J(trans) for 1,3-dioxolane is obtained only by employing energies from ab-initio MO calculations averaged over the pseudorotation circuit. For the C-4 substituted compounds calculated coupling constants were employed in a 'trial and error' process for the identification of the preferred conformations of these compounds; a set of two torsional angles for each compound was derived which allows a tentative description of the geometry of each molecule. A criticism of these geometries is given according to the evidence available on the structure of substituted 1,3-dioxolanes.

# **INTRODUCTION**

Conformational analysis of six-membered rings represents a relatively simple problem, since the molecules can be described as a function of well defined energy minima. In most cases, the molecular properties of the ground-state can be accounted for by chair conformations. Conformational problems are far more complex for saturated five-membered rings, owing to the presence of several geometries with approximately the same potential energy which interconvert by a pseudorotational mechanism.<sup>1</sup> The cyclopentane ring has been found to be puckered<sup>1</sup> and the puckering displacements move around the ring. This property is not a characteristic limited to cyclopentane but is also<sup>2</sup> common to five-membered rings containing one or more heteroatoms, as shown by the experimental properties of these molecules. Conformations determined for molecules arranged in a crystalline lattice may not be coincident with those statistically favoured in the gas-phase or in solution, and often in this latter situation experimental determinations do not provide direct evidence for a conclusive description of either a single conformation or of a set of conformations which can better represent the molecule. When substituents are present in the ring it seems that the molecule is confined<sup>3</sup> to certain definite energy minima of the pseudorotation circuit; the

number and the size of the substituents have definite control<sup>4</sup> over the energy minima of the pseudorotation circuit assumed by the ring.

For the study of the molecular conformation of saturated rings the method offering the greatest possibilities<sup>5</sup> is that based on the analysis of vicinal proton-proton coupling constants. For six-membered rings these constants enable the dihedral angle between vicinal protons to be determined by the Karplus equation<sup>6</sup> or the R value expression:<sup>7</sup> the averaged J(cis) and J(trans) values of one of the methylene fragments are employed to derive the torsional angle corresponding to that part of the molecule. Torsional angles obtained from the R method in six- and sevenmembered rings are usually in satisfactory agreement<sup>7</sup> with the results obtained by the direct methods of measurement of these quantities. For five-membered rings the application of these methods does not allow<sup>5,8</sup> the same degree of confidence and the results obtained are often far removed from the experimental estimates. This failure has been attributed<sup>5</sup> to the lack of three-fold projection symmetry along the carboncarbon bond as a consequence of ring-strain. Attempts<sup>8</sup> to introduce explicitly the deformation from trigonal symmetry of the projection angle in the Karplus equation or R value expression did not allow definite conclusions on the conformational analysis of these systems. Even so, the results show clearly<sup>8</sup> that to reproduce the experimental values of the coupling constants, a weight-averaging procedure over the whole pseudorotational circuit must be performed.

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Substituents can confine the ring to definite minima due to their own steric requirements.<sup>5</sup> For a number of substituted 1,3-dioxolanes9 the relative isomer stability, determined experimentally, seems to indicate that the preferred conformation or the limited number of preferred conformations for isomers of the same type, namely cis or trans derivatives, should be very similar, even though they may differ in the cis and trans isomers. Attempts to describe these derivatives in terms of definite conformations can be performed, bearing in mind that further difficulties arise in this description since substituents destroy the symmetry properties of the unsubstituted compound, and stabilise effective conformations which do not necessarily coincide with the energy minima of the original pseudorotational circuit. The rigorous procedure for the geometrical definition of the conformations of puckered five-membered rings involves the amplitude (q) and phase  $(\phi)$  coordinates of a pseudorotational When the physical properties of these circuit. molecules are known as a function of q and  $\phi$ , values relative to one definite conformation can be derived. This type of information is at present not obtainable by experimental procedures. A description of molecular properties as a function of the torsional angle,  $\omega$ , of one particular fragment, leaving the remaining part of the molecule undetermined, is feasible even if it represents an oversimplification of the problem. This can apply to the vicinal proton-proton coupling constant of the fragment being considered, provided that changes in the geometry of the remainder of the molecule have no significant effect on this value. Alternatively, a system can be chosen where it may be reasonably assumed that conformational changes are mainly localised in the torsional angle of one carboncarbon fragment, the geometrical properties of the remainder of the molecule being constant. This may be the case in a series of cis and trans isomers where substitution occurs only at the particular fragment under consideration; 1,3-dioxolanes which differ in substitution at C-4 and C-5 (the torsional angle referring to the corresponding C-C bond) should properly represent such a class of compounds.

We have devoted our attention to a number of substituted 1,3-dioxolanes in order to gain information on their conformational properties. The 1,3-dioxolane nucleus serves as the basic structure for a number of potent agonists and antagonists of the muscarinic acetylcholine receptors of smooth muscle,<sup>10</sup> Studies<sup>10-12</sup> on derivatives of 1,3-dioxolane have demonstrated that correlations exist between the activity of these compounds and their molecular arrangement. The knowledge of their conformational properties, therefore, may well help in understanding the pharmacological behaviour of these molecules. The compounds examined here, 4-p-toluenesulphonyloxymethyl- and 4-chloromethyl-2-alkyl-1,3-dioxolanes, are precursors of 4-dimethylaminomethyl methiodide derivatives, employed at cholinergic receptor level.<sup>12</sup> We report here the proton NMR spectra of these derivatives and the assignments. The vicinal proton-proton coupling constants will be employed in an attempt at conformational analysis of substituted 1,3-dioxolanes, also employing the values calculated by MO methods.

#### NMR spectra

The compounds examined are those represented in the following scheme,



where the 'envelope' conformation has been arbitrarily adopted for representative purposes. The proton magnetic resonance spectral parameters obtained at 60 MHz are collected in Table 1. Chemical shifts and coupling constants referring to the five protons on C-4, C-5 and to the methylene side-chain were derived by iterative analysis employing the LAOCOON 3 program.<sup>14</sup> For compounds **1** in the *cis* and *trans* configuration the assignments given by Inch and Williams<sup>15</sup> agree with our results but seem to be reversed compared to that of a previous report,<sup>13</sup> as deduced by a comparison of the resonances of H-6 and the methyl

Table 1. Chemical shifts (& units) and coupling constants (Hz) for substituted 1,3-dioxolanes

Compound		Solvent	H-1	H-2	H-3	H-4	H-5	H-6	6-CH3	J(12)	J(13)	J(14)	J(15)	J(23)	J(45)	J (H-6, CH <sub>3</sub> )	J(34)
1	cis	CDCI <sub>3</sub>	4.247	3.982	3. <del>9</del> 82	3.857	3.857	4.970	1.302	4.99	4.99	6.37	6.37	_		4.86	
	trans	CDCl <sub>3</sub>	4.285	4.064	4.064	3.617	4.122	5.005	1.302	5.10	5.10	6.60	6.65		-8.73	4.82	
	cis	C <sub>6</sub> H <sub>6</sub>	3.848	3.825	3.825	3.337	3.484	4.697	1.147	5.73	5.73	7.29	3.60		-8.90	4.81	
	trans	C <sub>6</sub> H <sub>6</sub>	3.886	3.783	3.783	3.226	3.616	4.786	1.148	4.89	4.89	6.89	6.91		8.91	4.80	
2a	cis		4.266	3.551	3.431	3.927	3.975	5.056	1.396	4.12	8.30	6.33	3.94	-10.87	~8.58	4.86	0.73
	trans	CDCl <sub>3</sub>	4.323	3.625	3.501	3.730	4.219	5.172	1.365	4.91	7.49	6.47	6.44	-10.93	-8.97	4.92	
	cis	C <sub>6</sub> H <sub>6</sub>	3.810	3.140	3.012	3.423	3.624	4.767	1.224	4.40	7.69	7.02	3.84	-10.91	-8.81	4.76	0.70
	trans	C <sub>6</sub> H <sub>6</sub>	3.915	3.104	2.976	3.335	3.786	4.901	1.210	4.84	6.82	6.49	6.65	-11.13	-8.72	4.85	
2b	cis	$CDCI_3$	4.268	3.546	3.423	3.920	3.974	4.897		4.06	8.55	5.86	4.38	-10.85	-8.81	4.51 J(H-6, CH <sub>2</sub> )	0.66
2c	cis	CDCl <sub>3</sub>	4.257	3.543	3.411	3.914	3.967	4.923		4.13	8.55	6.01	4.24	-10.80	-8.70	4.44 J(H-6, CH <sub>2</sub> )	0.64
	cis	C₅H <sub>6</sub> ັ	3.856	3.175	3.046	3.461	3.648	4.706		4.39	7.73	7.27	3.84	-10.87	-8.99	4.35 J(H-6, CH <sub>2</sub> )	0.63
2d	cis	$\text{CDCl}_3$	4.251	3.541	3.406	3.913	3.965	4.916		4.10	8.62	6.16	4.05	-10.78	-8.53	4.38 J(H-6, CH <sub>2</sub> )	0.56

group on C-2. On changing the substituent T the most obvious differences in the spectra are found in the side-chain methylene group; the two protons are apparently equivalent when T is the O-tosyl group, while they differ considerably both in chemical shift and in their coupling to H-1 when T is a chlorine atom. This is true both in the cis and trans isomers and in the two solvents employed, chloroform and benzene. The vicinal coupling constants relative to the molecular fragment C-4-C-5 are also influenced by the different T substituents, since results in CDCl<sub>3</sub> solution show that in derivative cis-1 J(14) and J(15) are equal while in cis-2a J(14) is greater than J(15). In benzene solution these two coupling constants assume the same order of magnitude for cis-1 and cis-2a. Different preferred conformations of the methylene group relative to the bond joining this substituent to the dioxolane ring, and of the ring itself, are likely to be responsible for this effect. Only minor differences are effected in the spectra by changes of the substituent R, at least as regards the cis derivatives examined here.

The solvent effect of benzene relative to chloroform indicates that the shift of H-4 in the *cis* series and H-5 in the *trans* series are those most affected. This is likely to be related to the different ability for removing solvent interactions by these two protons, depending on the molecular conformations assumed by the compounds.

# Conformational analysis of substituted 1,3-dioxolanes

In order to employ the vicinal spin-spin coupling constants for the conformational analysis of these molecules, we first set up a scheme by which calculated coupling constants for a large number of conformations can be compared with the experimental values, and conformational information derived accordingly. The procedure was initially tested on the unsubstituted 1,3-dioxolane. The full conformational behaviour of this molecule may be described<sup>2</sup> by employing the pseudorotational potential function on the variables q and  $\phi$ . Energy calculations have been performed by Cremer and Pople<sup>2</sup> in the 4-31G *ab* initio MO approach with geometry optimisation. Since we are concerned with molecules having a larger number of heavy atoms, employment of the ab initio MO methods, and especially of the 4-31G basis expansion, becomes almost impossible. Therefore, we tried to obtain energy values for 1,3-dioxolane from various semi-empirical MO methods in order to compare the pseudorotational potential functions given by the different approaches. Bond lengths and bond angles for the dioxolane ring are those employed previously.<sup>2</sup> The energy values corresponding to a certain number of conformations of known q and  $\phi$  were thus derived from the Extended Hückel<sup>16</sup> (EHM), INDO<sup>17</sup> and MINDO<sup>18</sup> semi-empirical MO methods, and the corresponding potential function  $V(q, \phi)$  interpolated with the procedure of Ref. 2. Geometry optimisation was not performed in the approaches employed here. The results obtained can be compared in Fig. 1 by observing the pseudorotation V(q) and inversion (for



**Figure 1.** Potential energy function (in KJ mol<sup>-1</sup>) of 1,3dioxolane calculated by different MO methods as a function of the q and  $\phi$  coordinates: the definition of the numbers is as follows ① 4-31G, ② STO-3G, ③ EHM, ④ INDO, ⑤ MINDO. (a) Plot of the potential energy as a function of  $\phi$  in the different approximations; the constant q corresponds to ① 0.265, ② 0.265, ③ 0.196, ④ 0.177, ⑤ 0.265. (b) Behaviour of the potential energy in the inversion process at  $\phi = 0^{\circ}$ . (c) Behaviour of the potential energy in the inversion process at  $\phi = 90^{\circ}$ .

 $C_s$  at  $\phi = 0^\circ$  and  $C_2$  at  $\phi = 90^\circ$ ) diagrams; those for the STO-3G and 4-31G *ab initio* approaches were derived from Ref. 2. All the methods indicate a low barrier for the pseudorotation process. In Fig. 1a the EHM, INDO and STO-3G approaches provide a qualitatively similar trend, while this is reversed in the 4-31G

and MINDO schemes. As regards the order of the stability of the conformers, INDO, EHM and STO-3G show the C<sub>s</sub> form as being more stable, MINDO the planar  $C_{2V}$  form and 4-31G the  $C_2$  form. For the inversion processes, Figs. 1b and 1c, the barrier calculated by EHM is the highest, whereas MINDO does not predict inversion, especially for the C<sub>s</sub> form. Pople and Cremer<sup>2</sup> have pointed out that the results from 4-31G are to be preferred to those from the STO-3G approach: in particular, the ring puckering amplitude, q, is in reasonable agreement with the experimental value (0.27 Å) found from the crystal structure of 2,2'-bisdioxolane. The EHM and INDO methods provide a description of the pseudorotation and inversion processes which, from a qualitative point of view, may appear acceptable but they fail in quantitative predictions of the small differences in the stability order of the  $C_s$  and  $C_2$  forms, correctly predicted only by the 4-31G basis set. Moreover, these methods fail to reproduce a constant value of the amplitude q for the values of  $\phi$  corresponding to the C<sub>s</sub> and C<sub>2</sub> forms, as can be seen in Fig. 1(b and c); only by employing the 4-31G approach<sup>2</sup> can one obtain correctly both this result and the corresponding q value which more nearly approaches the experimental value.

The proton-proton coupling constants for 1,3dioxolanes were evaluated in the one-electron MO approximation of the contact contribution<sup>19</sup> by employing EHM wave-functions derived from atomic Clementi orbitals<sup>20</sup> according to a procedure previously reported<sup>21</sup> (method A), and in the INDO finite perturbation scheme<sup>22</sup> (method B). Method A has been employed<sup>21</sup> by us to evaluate the spin-spin coupling constants in a wide series of organic compounds, and the satisfactory trend of the results with respect to those from other semi-empirical procedures was assessed. Vicinal coupling constants J(14)cis, J(15)transand geminal coupling constants for protons on C-2 and C-5 were calculated by both methods A and B for several conformations corresponding to known q and  $\phi$  values. The values of J(gem) relative to C-4 calculated by methods A and B, respectively, are negative and positive, the result from method A being consistent with experiment. Both methods indicate that the range of J(cis) as a function of q and  $\phi$  is restricted to a small interval (2-4 Hz) while J(trans) spans a larger interval (10-20 Hz), in agreement with the experimental results of substituted 1,3-dioxolanes.

If calculated and experimental coupling constants are to be compared in systems where pseudorotation has a low energy barrier, the calculated value should refer to a mean quantity averaged over a large number of conformations rather than to that corresponding to a definite minimum.<sup>23</sup> With this aim, expression (1) was employed, where summation extends over the whole pseudorotational circuit (q = constant) and  $\Delta E_i$  refers

$$\langle J \rangle = \frac{\sum_{i} J_{i} \exp(-\Delta E_{i}/RT)}{\sum_{i} \exp(-\Delta E_{i}/RT)}$$
(1)

to the most stable conformation. The  $\Delta E_i$  values employed in (1) are internal energies, while, more correctly, free-energy differences should be correlated<sup>24</sup> to the fractional populations of conformers; we believe, however, that this simplification is within the limit of the accuracy given by the other approximations introduced in the description of coupling constants reported here. The averaging procedure was applied on coupling constants both from methods A and B and by employing energy values from INDO. EHM and ab initio 4-31G, where the last values were derived from Ref. 2. The energy values from MINDO were not considered, since this method fails to describe the inversion process, as pointed out above. The results obtained are shown in Table 2; owing to the molecular symmetry and to the fact that the coupling constants are averaged over the whole pseudorotational circuit, only one cis and one trans vicinal coupling constant need to be evaluated. The order of J(cis)and J(trans) is reversed with respect to the experimental values when the energy values are from semiempirical methods, while the correct trend is obtained when more accurate energy values are employed such as those from the ab initio 4-31G approach. This result most probably originates from the improper description of the relative energy of the Cs and C2 conformations given by the semi-empirical methods, owing to the weighting introduced in the averaging process: vicinal coupling constants obtained both by methods A and B are in the order J(cis) < J(trans) in the C<sub>s</sub> conformation and opposite for the C<sub>2</sub> conformer. These results indicate that in the process of averaging coupling constants over a set of conformations only energy values from accurate ab initio methods should be employed; this applies even though coupling constants may be safely computed by semiempirical MO methods in order to have a reasonable comparison with experimental values both in sign and

Table 2. Calculated mean values for proton-proton coupling constants in 1,3-dioxolane†

Energy values from EHM	<sub>J(cis)</sub> ^ 9.55 <sup>d</sup> ; 10.85 <sup>e</sup>	<sup>J(trans)<sup>A</sup> 14.58<sup>d</sup>; 12.52<sup>e</sup></sup>	J(cis) <sup>B</sup>	J(trans) <sup>B</sup>	J(gem) <sup>A*</sup>	J(gem) <sup>B*</sup>	Experime J(cis) <b>7.3</b> ª	ental values J(trans) 6.0 <sup>a</sup>	J(gem)* 7 <sup>b</sup> ; 0 to +1 <sup>b</sup>
INDO	0.51	0.00	6.63 <sup>d</sup> ; 7.79 <sup>e</sup>	11.00 <sup>d</sup> ; 9.92 <sup>e</sup>	0.40 4.05				+0.8 <sup>c</sup>
4.310	9.51	6.68	6.34	5.72	-6.19; -1.65	0.90; 8.92			

<sup>†</sup> The superscripts A and B refer to the methods employed for calculating coupling constants (see text).

The first and second entry are referred to in the order of protons on C-4 and C-2.

<sup>d</sup> Calculated by employing the q value corresponding to the C<sub>s</sub> conformation.

<sup>e</sup> Calculated by employing the q value corresponding to the C<sub>2</sub> conformation.

<sup>&</sup>lt;sup>a</sup> From Ref. 25.

<sup>&</sup>lt;sup>b</sup> Ref. 26. <sup>c</sup> Ref. 27.

magnitude. This constriction is particularly important when averaging is to be carried out over a number of conformations not differing greatly in energy content. The use of semi-empirical methods for conformational analysis and ring puckering has been adversely criticized.<sup>28</sup> Geminal coupling constants averaged taking into account 4-31G energies are in agreement with experimental values when associated with method A where the coupling constants were calculated by the EMH approach.

The experimental results reported in Table 1 show that vicinal coupling constants, and more significantly J(trans), are affected by substitution on the dioxolane ring; the pseudorotation circuit is thus perturbed with respect to the unsubstituted compound. For substituted derivatives we therefore approached the problem by restricting the analysis to a number of definite conformations, in view, also, of the fact that for these molecules *ab initio* 4-31G energy calculations are prohibitive. Calculations of coupling constants were performed on a compound of type **2** having a CH<sub>2</sub>Cl



substituent on C-4 both by methods A and B, covering a pseudorotational and inversion path (different q and  $\phi$  values) and rotating the substituent around the C-4-C-6 bond (different  $\alpha$  values). The conformation with the C-6-H-2 bond lying in the plane defined by atoms C-6-C-4-C-5 and with the chlorine atom pointing outside the ring, was assumed as having  $\theta = zero$ , as shown in A. The coupling constants calculated for this compound do not differ greatly (within 1-2 Hz) from those corresponding to the same q and  $\phi$  values of the unsubstituted compound. (In substituted compounds this condition is limited to the coordinates of the atoms composing the ring.) Furthermore, J(14) and J(15) values are not greatly affected by the rotation of the CH<sub>2</sub>Cl group, suggesting that substituents of this type have no 'direct' influence on these coupling constants but, rather, perturb the conformational behaviour of the ring. Assuming free pseudorotation and applying Eqn (1), the calculated values of the vicinal coupling constants do not differ greatly from those of the unsubstituted compound. A solution should thus be found in terms of preferred definite energy minima. A practical difficulty in employing the q and  $\phi$  coordinates is due to the loss of a direct envisagement of the conformation involved, and we thus preferred to calculate first the torsional angles,  $\omega$ , and then to express the atom positions in terms of q and  $\phi$  coordinates. For defining five-membered rings two puckering coordinates are necessary,<sup>29</sup> q and  $\phi$ ; if torsional angles are employed at least two of them must be specified.<sup>30</sup> Accordingly, conformations with different values of  $\omega_1$ , the torsional angle relative to the C-4-C-5 bond and ranging within  $+30^{\circ}$  and  $-30^{\circ}$  are exp-



**Scheme 1.** Set of conformations of 4-chloromethyl-1,3dioxolane corresponding to different values of the torsional angles  $\omega_1$  and  $\omega_2$ .

licitly considered for the two opposite situations of  $\omega_2$ , the torsional angle relative to the C-4-O-3 bond, near to +30° and -30° and corresponding to the apex, C-2, lying above and below the mean plane of the remaining four atoms of the ring (depicted in Scheme 1 for conformations B to E). Calculations of the vicinal coupling constants J(12), J(13) and the long-range J(43), observed experimentally, were also performed. Since the values calculated by method A show a general behaviour closer to that found experimentally, only this set of values has been taken into account in the discussion of the conformational properties of substituted dioxolanes.

No account of the calculated energies can be taken. since, as pointed out above, the semi-empirical methods fail to describe these systems. The conformational analysis will thus be carried out by a 'trial and error' procedure, matching the calculated and experimental coupling constants of each molecule and noting the  $\theta$  and  $\omega_1$  angles which correspond to the smallest deviation. This process starts by analysing the calculated J(12) and J(13) values as a function of  $\theta$ , noting that these constants have a small dependence on  $\omega_1$ . By examining one of the two-dimensional diagrams of J(12) and J(13) as a function of  $\theta$ , for example corresponding to  $\omega_1 = 0^\circ$  and  $\omega_2(+)$ , shown in Fig. 2, we see that the correct experimental behaviour corresponding to J(13) > J(12) is found for values of  $\theta$  in the regions around 140° and 310°, corresponding to the dashed portions. Molecular models show that for  $\theta$ values near  $140^{\circ}(\pm 20^{\circ})$  the chlorine atom points above the dioxolane ring, while for values in the region of  $310^{\circ}(\pm 40^{\circ})$  the chlorine atom points outside the ring; the latter situation should be the one which better satisfies the energy requirements, and we have therefore fixed the preferred conformations of the CH<sub>2</sub>Cl group in this region. J(14) and J(15) show a similar behaviour in both regions. Coupling constants calculated by method A are usually higher<sup>21</sup> than experimental values, and a scaling factor can tentatively be introduced to bring the calculated and experimental quantities close to each other: for J(12) and J(13) this can be sought in the region of  $\theta$  values between 260°



**Figure 2.** Diagram of calculated vicinal coupling constants J(12) and J(13) (method A) as a function of the angle of rotation,  $\theta$ , of the CH<sub>2</sub>Cl group at  $\omega_1 = 0^\circ$  and  $\omega_2(-)$ .

and 270° and a scaling factor of 1.96 for the experimental values in CDCl<sub>3</sub>. In Fig. 3 we have plotted typical examples of the calculated coupling constants J(12), J(13), J(14), J(15), J(24) and J(34) as a function of the variables  $\theta$ ,  $\omega_1$  and for the two limiting conditions of  $\omega_2$  near +30° and -30°. Figure 3b shows that J(14), the vicinal *cis* coupling, changes only within a small interval as a function of  $\omega_1$  while greater changes are found for J(15), the vicinal *trans* coupling. Figure 3c shows that the long-range coupling constant having the higher values is J(34), and in view of the scaling factor of approximately 2 only this long-range interaction is likely to be clearly observed experimentally.

Starting from these general considerations, we have taken for each compound of Table 1 (only experimental values in  $CDCl_3$  have been used) the difference

between J(14) and J(15) multiplied by 1.96, and derived from Fig. 3b the value of  $\omega_1$  for which this difference occurs (both in sign and magnitude) in the region of  $\omega_2$  both positive and negative. All the other coupling constants are interpolated from the appropriate diagrams at these values of  $\omega_1$  and  $\omega_2$ , then scaled and compared with the experimental values. An example of the procedure is reported in Table 3 for compound 2a in the cis and trans configuration; agreement between calculated and experimental values is, in general, satisfactory, the mean deviation  $\Delta$  being smaller when  $\omega_2$  is negative. This has also been verified for the other derivatives subjected to this process and reported in Table 4. The scaled values of the coupling constants and the deviations from experimental values, reported in parentheses, show that the reproducibility is, in general, satisfactory for the whole set of calculated values. The torsional angle around the C-4–C-5 bond is thus in the range of  $0^{\circ}$  and can be positive or negative. From the values reported in Table 4, the largest distortion from 0° is found for the trans compounds, showing values of  $\omega_1$  near +10° and thus corresponding to conformation F.



The solvent effects of benzene relative to chloroform can now be interpreted in the light of the preferred conformations derived. In the *cis* compounds H-4 is relatively freer to interact with the benzene solvent, while in the *trans* compounds the arrangement of the apex C-2, and, consequently, of R prevents the solvent approaching this proton. H-5 should now be more available for solvent interactions,



**Figure 3.** Behaviour of calculated vicinal and long-range coupling constants in substituted dioxolanes as a function of  $\theta$ ,  $\omega_1$  and  $\omega_2$  angles; (a) plot of J(12) and J(13) against  $\omega_1$  for three values of  $\theta$  and in the two limiting cases of  $\omega_2(\pm)$ ; (b) plot of J(14) and J(15) as a function of  $\omega_1$  for the two limiting cases of  $\omega_2(\pm)$  and for  $\theta = 260^\circ$  (dashed line) and 270°; (c) plot of J(24) (full line) and J(34) (dashed line) as a function of  $\omega_1$  for the two limiting cases of  $\omega_2(\pm)$  and for  $\theta = 260^\circ$  and 270°.

Compound 2a cis	J(14)	J(15)	J(12)	J(13)	J(34)		Compound 2a trans	J(14)	J(15)	J(12)	J(13)	J( <b>34</b> )	
ω <sub>2</sub> : +	9.25	4.50	8.41	16.50	1.25	calculated	ω <sub>2</sub> : +	10.70	10.62	9.82	14.12	0.74	calculated
$\omega_{1}^{-} = -7.3^{\circ}$	4.71	2.29	4.28	8.40	0.64	scaled	$\omega_1 = +1.3^{\circ}$	5.45	5.41	5.00	7.19	0.38	scaled
	6.33	3.94	4.12	8.30	0.73	experimental		6.47	6.44	4.91	7.49	~0	experimental
	1.62	1.65	-0.12	-0.10	0.09	Δ		1.02	1.03	-0.09	0.30	-0.38	Δ
$\widehat{\Delta} = \pm 0.72$							$\overline{\Delta} = \pm 0$	.56					
ω2: -	13.00	8.30	8.00	16.75	1.16	calculated	ω2: -	13.50	13.38	8.96	14.02	0.80	calculated
$\omega_{1}^{-} = -5.5^{\circ}$	6.62	4.23	4.07	8.53	0.5 <b>9</b>	scaled	$\omega_{1}^{-} = +8.67^{\circ}$	6.87	6.81	4.56	7.14	0.41	scaled
	6.33	3.94	4.12	8.30	0.73	experimental		6.47	6.44	4.91	7.49	0	experimental
	-0.29 $\widehat{\Delta} = \pm 0.$	0.29 2	0.05	-0.23	0.14	Δ		-0.40 $\vec{\Delta} = \pm 0$	-0.37 .37	0.35	0.35	-0.41	Δ

Table 3. Calculation scheme and comparison with experimental values for the coupling constants in compounds 2a

also owing to the outward distortion of the  $CH_2T$  substituent ( $\omega_1$  positive) relative to the dioxolane ring.

Lacking direct tests for assessing the reliability of the conformations derived here for substituted dioxolanes, we have tried a comparison with the 'philosophy' of the R method<sup>7</sup> in six- and fivemembered rings. In six-membered rings torsional angles are well predicted by the R value expression<sup>7</sup> when the full set of trans and cis coupling constants relative to the same molecular fragment is known. In fivemembered rings qualitative information can be derived,<sup>5</sup> but the torsional angles determined<sup>5</sup> from R values are overestimated. The Karplus equation,<sup>6</sup> also, could not be employed, since the presence of strong electronegative groups on the ring makes problematical<sup>31</sup> the determination of the series of coefficients which enter into the equation.<sup>6</sup> Furthermore, both the R value method and the simplified Karplus equation establish a quadratic cosine relationship between coupling constants and torsional angles which limits the application to symmetric situations, and precludes sign determinations which are particularly useful when the

Table 4. Calculated coupling constants (Hz) and torsional angles  $\omega_1$ , for a number of substituted 1,3-dioxolanes (the deviations from experimental values are reported in parentheses)

Compound	J(14)	J(15)	J(12)	J (13)	J(34)	ω1
2b cis	6.80	5.37	4.00	8.35	0.49	+0.3°
	(-0.94)	(-0.99)	(0.06)	(0.20)	(0.17)	
2c cis	6.72	4.91	4.07	8.38	0.52	−1.7°
	(-0.71)	(~-0.67)	(0.06)	(0.17)	(0.12)	
<b>2d</b> cis	6.70	4.58	4.07	8.48	0.55	-3.35°
	(0.54)	(-0.53)	(0.03)	(0.14)	(0.01)	
1 cis	6.70	6.70	5.71ª			+7.5°
	(-0.33)	(-0.33)	(-0.72)			
1 trans	6.82	6.92	5.84ª			+ <b>8.67</b> °
	(-0.22)	(0.27)	(-0.74)			
2,4-diphenyi-	6.70	6.59				+7.17°
cisb	(0.34)	(0.34)				
2,4-diphenyl-	6.62	7.74				+13.3°
trans	(-0.23)	(0.07)				

\* Mean value of J(12) and J(13).

<sup>b</sup> Ref. 9: experimental values of J(45) are -7.72 and -8.14 Hz for the *cis* and *trans* compound respectively.

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torsional angles range around 0°, as seems to be the case for  $\omega_1$  in substituted dioxolanes. On the other hand, implementation of these expressions with sine terms introduces a new series of undetermined parameters. The calculated R value for 1,3-dioxolane as a function of  $\omega_1$  is reported in Fig. 4; it can be seen that its behaviour is symmetrical, since interchange within the pairs of cis-type and trans-type coupling constants occurs for opposite signs of  $\omega_1$ . The experimental value of R for 1,3-dioxolane, from coupling constants reported in Table 2, is 0.82 and from Fig. 4  $\omega_1$  may be derived as  $\pm 2.5^\circ$ . This can be compared with a value of  $-0.46^\circ$ , obtained by averaging  $\omega_1$  over the whole pseudorotational circuit by employing an equation equivalent to (1), with  $\omega_1$  in the place of J, and 4-31G energies. If we apply the same procedure to 2,2'-bis-1,3-dioxolane, for which vicinal coupling constants have been reported,<sup>32</sup>  $\omega_1$  derived from the plot of Fig. 4 amounts to  $\pm 17.5^{\circ}$ ; the experimental value<sup>32</sup> for the solid amounts to  $-20.7^{\circ}$ . Apart from the difference in the physical states for these two estimates, their agreement seems, at least, interesting.



Figure 4. Plot of the calculated R value in 1,3-dioxolane as a function of the  $\omega_1$  torsional angle.

The presence of a relatively large substituent at C-2 probably confines this molecule in a defined energy minimum.

In 2-substituted alkoxy derivatives Altona<sup>32</sup> concluded that the  $\omega_1$  values should be higher in compounds having a predominantly exocyclic *anti* conformation (the 2-OMe substituted compound) than those having a predominantly gauche form (the 2-OBu' substituted compound) of the exocyclic CO bond. R values from Altona's work<sup>32</sup> enable  $\omega_1$  angles for both these compounds to be obtained from the plot of Fig. 4; these are in the correct order (±17.1 and ±14.2 in benzene solution) even if their difference is rather small. These torsional angles probably refer to an averaged situation, and further studies will aim at obtaining greater insight into the manipulation of calculated R values for obtaining torsional angles in five-membered rings.

The R value cannot be obtained for 1,3-dioxolanes mono-substituted at C-4 or C-5, whereas the ratio between one *cis*-type and one *trans*-type coupling constant, denoted as R', is still available. This experimental quantity, which should still be independent of the electronegativity of groups bonded to the C-4–C-5 fragment and related to the molecular conformation, can probably be employed to obtain structural information. Examination of these values reveals their linear dependence on the  $\omega_1$  angles calculated in this paper, and Eqn (2) can then be formulated by a least-square treatment. Equation (2) thus enables the torsional angle  $\omega_1$  to be determined (probably an averaged value) in 1,3-dioxolanes

$$\omega_1 = 33.321 \ R' - 25.323 \tag{2}$$

substituted at C-4 or C-5 from the experimental R' value. The determination of  $\omega_1$  is also linked with the constancy of the  $\omega_2$  torsional angle as a function of the substituents at C-4 or C-5. Knowledge of these two torsional angles enables a full description of the conformation of the ring, in particular as a function of q and  $\phi$  coordinates. Equation (2) cannot be extended in general to five-membered rings since, even though R' is a quantity which should normally be free from electronegativity effects, it should be affected by strain effects which are characteristic of the different five-membered heterocyclic compounds.

In conclusion, we feel that the results reported in this paper represent an encouraging attempt to determine the conformation of five-membered rings by employing experimental vicinal proton-proton coupling constants, even if several aspects need to be investigated more deeply. The results indicate that the procedure seems to be valid both for substituted 1,3dioxolanes having definite energy minima and when an average situation gives a better description of the molecular properties.

### EXPERIMENTAL

The NMR spectra were recorded on a JEOL JNM-C60-HL spectrometer by employing 0.5 M solutions in choloroform- $d_1$  and benzene. All the calculations were performed on a CYBER 76 CDC computer.

The syntheses and properties of the *cis*- and *trans*-4-chloromethyl-2-alkyl-1,3-dioxolanes have been reported elsewhere.<sup>12</sup>

cis- and trans-2-Methyl-4-p-toluenesulphonyloxymethyl-1,3-dioxolanes were prepared as follows. Equimolecular amounts (1 mole) of pure glycerine and paraldehyde, acidified with 5 mls of 50%  $H_2SO_4$ , were heated at 100°C for 10 h with stirring. The reaction mixture was made alkaline with a 20% aqueous solution of Na<sub>2</sub>CO<sub>3</sub> and then extracted with diethyl ether. The ether solution, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, was evaporated and the residue distilled. The fraction collected at 80-90°C, 11 mm, (yield 63%) composed of cis- and trans-2-methyl-4was hydroxymethyl-1,3-dioxolane and of cis- and trans-2methyl-5-hydroxy-1,3-dioxane. This mixture was separated using a Fractovap model P gas chromatograph with a 10 mm diameter and 4 metres long column filled with 20% Carbowax M on Chromosorb A 30-40 mesh, using the following operating conditions: column oven temperature 140°C, injection port temperature 240°C, temperature of the filament detector 240°C, helium flow-rate 200 ml/minute, quantity of sample 0.5 ml of a 1/1 solution in diethyl ether. In agreement with the literature,<sup>33</sup> the chromatogram shows 4 peaks; A, B, C and D. Peak A is identified as cis-2-methyl-5-hydroxy-1,3-dioxane and peak D as trans-2-methyl-5-hydroxy-1,3-dioxane. Peaks B and C are identified as cis-2-methyl-4-hydroxymethyl-1,3-dioxolane and its trans isomer. Toluene-psulphonates were prepared by reaction overnight with toluene-p-sulphonyl chloride in pyridine at room temperature; cis-tosylate m.p. 53° (from ethanol), trans-tosylate m.p. 73° (from ethanol), in agreement with the values reported in Ref. 15.

## REFERENCES

- J. E. Kilpatrick, K. S. Pitzer and R. Spitzer, J. Am. Chem. Soc. 69, 2483 (1957).
- 2. D. Cremer and J. A. Pople, J. Am. Chem. Soc. 97, 1358 (1975) and references quoted therein.
- 3. R. Keskinen, A. Nikkila, K. Pihlaja and F. G. Riddell, J. Chem. Soc. Perkin Trans. 2, 466 (1974).
- 4. C. Altona, H. R. Buys and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 973 (1966).
- J. B. Lambert, J. F. Papay, S. A. Khan, K. A. Kappauf and E. S. Magyar, J. Am. Chem. Soc. 96, 6112 (1974) and references guoted therein.
- M. Karplus, J. Chem. Phys. 30, 11 (1959); J. Am. Chem. Soc. 85, 2870 (1973).
- (a) J. B. Lambert, J. Am. Chem. Soc. 89, 1836 (1967); (b)
  J. B. Lambert, Acc. Chem. Res. 4, 87 (1971); (c) H. R. Buys, Recl. Trav. Chim. Pays-Bas, 88, 1003 (1969).

- 8. B. Fuchs and P. S. Wechsler, Tetrahedron, 33, 57 (1977).
- 9. W. E. Willy, G. Binsch and E. L. Eliel, J. Am. Chem. Soc. 92, 5394 (1970).
- 10. D. J. Triggle, Neurotransmitter-Receptor Interaction, Academic Press, New York (1971). Chapt. IV.
- 11. B. Belleau and J. Puranen, J. Med. Pharm. Chem. 6, 325 (1963).
- 12. L. Villa, V. Ferri and E. Grana, Il Farmaco, Ed. Sci. 29, 167 (1974)
- 13. D. R. Garrison, M. May, H. F. Ridley and D. J. Triggle, J. Med. Pharm. Chem. 12, 130 (1969).
- 14. S. Castellano and A. A. Bothner-By, J. Chem. Phys. 41, 3863 (1964).
- 15. T. D. Inch and N. Williams, J. Chem. Soc. (C), 264 (1970).
- 16. R. Hoffmann, J. Chem. Phys. 39, 1397 (1963).
- J. A. Pople and D. L. Beveridge, Approximate Molecular Orbital Theory, McGraw-Hill, New York (1970).
- 18. Quantum Chemistry Program Exchange, Indiana University, Chemistry Department. QCPE Program No. 288. See also: N. C. Baird and M. J. S. Dewar, J. Chem. Phys. 50, 1262 (1969); M. J. S. Dewar and E. Haselbach, J. Am. Chem. Soc. 92, 950 (1970); N. Bodor, M. J. S. Dewar and D. H. Lo, J. Am. Chem. Soc. 94, 5303 (1972).
- 19. J. A. Pople and D. P. Santry, Mol. Phys. 8, 1 (1964).
- E. Clementi, *IBM J. Res. Dev.* 9, 2 Suppl. (1965).
  G. Barbieri, R. Benassi, P. Lazzeretti and F. Taddei, *Org.* Mag. Reson. 7, 563 (1975).

- 22. J. A. Pople, J. McIver and N. S. Ostlund, Chem. Phys. Lett. 1, 465 (1967); J. Chem. Phys. 49, 2960, 2965 (1968).
- 23. V. Tabacik, Tetrahedron Lett. 555, 561 (1968).
- 24. T. Schaefer and W. J. E. Parr, J. Chem. Phys. 65, 1197 (1976)
- 25. N. Sheppard and J. J. Turner, Proc. R. Soc. London Ser. A, 252, 506 (1959).
- 26. M. Anteunis, G. Swaelens and J. Gelan, Tetrahedron, 27, 1917 (1971).
- 27. S. L. Smith and R. H. Cox, J. Chem. Phys. 45, 2848 (1966).
- 28. L. L. Combs and M. Holloman, J. Phys. Chem. 79, 512 (1975).
- 29. D. Cremer and J. A. Pople, J. Am. Chem. Soc. 97, 1354 (1975).
- 30. C. Altona, H. J. Geise and G. Romers, Tetrahedron, 24, 13 (1968).
- 31. K. G. R. Pachler, Tetrahedron, 27, 187 (1971).
- 32. C. Altona and A. P. M. Van der Veek, Tetrahedron, 24, 4377 (1968).
- 33. G. Aksnes, P. Albriktsen and P. Juvvik, Acta Chem. Scand. 19, 920 (1965).

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