

Conformational Analysis. XX.* 2-Alkyl-2-methyl- and 2-Alkyl-2,4-dimethyl-1,3-dioxanes. V.** A Variable Temperature ^1H NMR Study

KALEVI PIHLAJA ^{a,b} and TIMO HÄRKÖNEN ^a

^a Department of Chemistry, University of Turku, SF-20500 Turku 50, Finland and ^b Department of Chemistry, State University College at Potsdam, Potsdam, New York 13676, U.S.A.

The equatorial-axial preferences in various 2-alkyl-2-methyl-1,3-dioxanes ($R = \text{Et, Pr, i-Pr, i-Bu, and } \textit{sec}\text{-Bu}$) are determined from the methyl ^1H chemical shifts at different temperatures. The corresponding chemical shifts of *r*-2-alkyl-2,*c*-4- and *r*-2-alkyl-2,*t*-4-dimethyl-1,3-dioxanes are used as models for the $\nu(2a\text{-Me})$ and $\nu(2e\text{-Me})$ values in the conformationally labile derivatives. In all cases 2-alkyl-2-methyl-1,3-dioxanes prefer the chair form where the methyl group is axial. In the case of Et, i-Pr, and i-Bu the present results are in close agreement with the values determined earlier by chemical equilibration of the diastereoisomeric 2-alkyl-2,4-dimethyl derivatives. Comparison of the experimental results with those based on the assumption that the interaction energies are additive reveals that the deviation between observed and calculated free energy differences increases with the increasing crowding of the substituent and the magnitude of this deviation correlates closely with the polar substituent constants of the alkyl groups. Accordingly, an estimate based on the additivity principle can be used to obtain a good approximation for the free energy difference in question.

Conformational preferences in some 2-alkyl-2-methyl substituted 1,3-dioxanes have been studied previously by ^1H NMR chemical shifts ^{3,4} and by chemical equilibration. ^{5,6} In general, the chair form where the methyl group at position 2 is axial has been found to be the preferred conformation, ^{3,5-7} although in one case ⁴ an erroneous assignment of the methyl chemical shift has led to a contradictory result

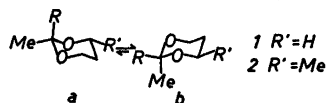


Fig. 1. Conformational ($R' = \text{H}$) and configurational equilibria ($R' = \text{Me}$) for 2-alkyl-2-methyl-substituted 1,3-dioxanes.

which has, however, been reconsidered by the authors. ⁸

Some questions of general interest are still to be answered. (1) Does the methyl substitution ^{5,6} at position 4/6 alter the observed enthalpy and entropy differences significantly from those directly obtainable for the conformationally labile 2-alkyl-2-methyl-1,3-dioxanes? (2) Do the experimental enthalpy, entropy and/or free energy differences correlate with those obtained by assuming additivity and taking into account all interactions resulting from the rotation of the $\alpha\text{-C-C}$ and/or $\beta\text{-C-C}$ bonds of the alkyl groups? To answer these questions we determined the values of the conformational equilibrium constants of several 2-alkyl-2-methyl-1,3-dioxanes ($R = \text{Et, Pr, i-Pr, i-Bu, and } \textit{sec}\text{-Bu}$) at several temperatures and from them the values of the thermodynamic parameters (Fig. 1; $R' = \text{H}$).

RESULTS

The values of $\nu(2e\text{-Me})$ and $\nu(2a\text{-Me})$ for *1a* and *1b*, respectively, can be derived from the model values as follows. ⁹ Comparison of the

* Part XIX, see Ref. 1.

** Part IV, see Ref. 2.

Table 1. The methyl ¹H chemical shifts (Hz) of 2-alkyl-2-methyl-1,3-dioxanes at different temperatures.

R	T=253	T=268	T=288	T=306	T=318	T=333	T=348
Et	—	76.84(12) ^a	76.81(12)	76.80(11)	76.80(8)	76.79(8)	76.79(7)
Pr	—	76.79(13)	76.87(14)	76.92(11)	77.00(9)	77.03(10)	77.08(12)
i-Pr	73.18(10)	73.26(5)	73.31(12)	73.43(6)	73.45(16)	73.49(7)	73.53(16)
i-Bu	79.65(15)	—	79.50(18)	79.44(10)	79.41(14)	79.37(13)	79.34(8)
sec-Bu	71.27(9)	71.41(11)	71.76(8)	71.91(10)	72.07(17)	72.28(12)	72.50(7)

^a 100 × Standard error of the mean. ^b For 2,2-dimethyl-1,3-dioxane $\nu_{\text{Me}} = 0.5(\nu_{\text{a}} + \nu_{\text{e}}) = 79.35 \pm 0.06$ Hz at all temperatures. ^c For 2-*t*-butyl-2-methyl-1,3-dioxane $\nu_{\text{Me}} = \nu_{\text{a}} = 79.22 \pm 0.05$ Hz throughout the temperature range.

Table 2. The chemical shifts (Hz) of the 2-methyl groups of diastereoisomeric 2-alkyl-2,4-dimethyl-1,3-dioxanes (2a and 2b) in the temperature range from 253 to 348 K.

R	Configu- ration	$\nu_{2\text{e-Me}}$	$\nu_{2\text{a-Me}}$	No. of exp.
Me	2a≡2b	76.23(7) ^a	82.42(8)	36, 41
Et	2a	71.34(7)		36
	2b		79.51(7)	37
Pr	2a	71.41(8)		82
	2b		79.64(8)	36
i-Pr	2a	63.73(9)		37
	2b		76.67(8)	37
i-Bu	2a	74.32(8)		84
	2b		80.64(6)	42
sec-Bu	2a	63.28(6)		33
	2b		75.85(10)	34
<i>t</i> -Bu	2b		78.09(7)	42

^a 100 × Standard error of the mean.

Table 3. The Values of the conformational equilibrium constants ($K = [Ib]/[Ia]$) at different temperatures.

R	T						
	253	268	288	306	318	333	348
Et	—	1.73	1.71	1.70	1.70	1.70	1.70
Pr	—	1.62	1.68	1.71	1.77	1.79	1.83
i-Pr	2.28	2.34	2.37	2.47	2.48	2.51	2.55
i-Bu	3.02	—	2.76	2.66	2.61	2.55	2.51
sec-Bu	1.59	1.65	1.83	1.91	2.01	2.15	2.30

$\nu(2\text{a-Me})$ values of the anancomeric 2-*t*-butyl-2-methyl-1,3-dioxanes (2b) and *r*-2-*t*-butyl-2-*cis*-4-dimethyl-1,3-dioxanes (2b) gives the following relation

$$\nu_{2\text{a}}(2\text{-R}, 2\text{-Me}) = \nu_{2\text{a}}(r\text{-2-R-2}, c\text{-4-Me}_2) + 1.13 \text{ Hz} \quad (1)$$

From (1) and the methyl chemical shifts of 2,2-dimethyl- and 2,2,4-trimethyl-1,3-dioxanes we obtain

$$\nu_{2\text{e}}(2\text{-R}, 2\text{-Me}) = \nu_{2\text{e}}(r\text{-2-R-2}, t\text{-4-Me}_2) - 1.08 \text{ Hz} \quad (2)$$

With the aid of eqns. (1), (2), and

$$K = \frac{\nu_{\text{obs}} - \nu_{\text{e}}}{\nu_{\text{a}} - \nu_{\text{obs}}} \quad (3)$$

the conformational equilibrium constants are readily calculated (Table 3) and from them the values of enthalpy, entropy, and free energy differences (Table 4).

DISCUSSION

If we accept the value 3.6 kJ mol⁻¹ for the *gauche* interaction between two methyl groups,^{3,9} the value 1.9 kJ mol⁻¹ for this interaction between a methyl group and an oxygen atom,^{3,6} the value 15.5 kJ mol⁻¹ for the *trans*-annular Me-Me interaction,¹⁰ and the value 10.0 kJ mol⁻¹ for the latter interaction between a methyl group and an oxygen atom,¹⁰ the relative enthalpies (H_i) of different rotational isomers (Fig. 2 and Table 5) and from them their mol fractions (n_i) are easy

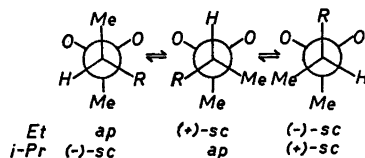


Fig. 2. Ethyl (R=H) and isopropyl (R=Me) rotamers for 2-alkyl-2-methyl-1,3-dioxanes; *ap* = antiperiplanar, *sc* = synclinal.

to evaluate. Using the following approach³ described also by Eliel and Enanoza¹¹

$$H^{\circ}_{\text{confo}}(1a \text{ or } 1b) = \sum_i n_i H_i \quad (4)$$

$$S^{\circ}_{\text{mix}} = -R \sum_i n_i \ln n_i \quad (5)$$

$$\Delta H^{\circ} = H^{\circ}_{\text{confo}}(1b) - H^{\circ}_{\text{confo}}(1a) \quad (6)$$

$$\Delta S^{\circ} = S^{\circ}_{\text{mix}}(1b) - S^{\circ}_{\text{mix}}(1a) \quad (7)$$

$$\Delta G^{\circ} = \Delta H^{\circ} - T \Delta S^{\circ} \quad (8)$$

it is estimated that 1a is an equimolar mixture of (+)-*sc* and (-)-*sc* forms (Fig. 2; For the nomenclature, see Ref. 12) when R=Et, whereas an axial isopropyl group can attain the *ap* form only because the methyl-(or Et)-in-the-ring rotamers are so crowded that they have to be excluded. Correspondingly, 1b should include 50% of *ap* and 25% of both (+)-*sc* and (-)-*sc* forms when R=Et and 20% of *ap* and 40% of both (+)-*sc* and (-)-*sc* forms when R=i-Pr. Summary of the rotameric contributions and the respective interaction energies is given in Table 5 which together with eqns. (5)–(7) provides the estimated thermodynamic quantities (Table 4).

Consider the possible answers to our introductory questions.

The influence of the conformation holding

group. In the case of Et, i-Pr, and i-Bu substituents the thermodynamic quantities for the configurational equilibrium $2a \rightleftharpoons 2b$ have been measured by chemical equilibration^{5,6} (Table 4). Comparison of these results with those obtained in this work for the conformational equilibrium $1a \rightleftharpoons 1b$ (Fig. 1) points out that the difference is small and sometimes even within the limits of experimental accuracy (all values for Et, ΔG° for *i-Pr*, and ΔS° for *i-Bu*). Moreover, the increased conformational enthalpy of 1b (R=i-Pr) is counterbalanced by the entropy increase, which, on the other hand, points out that the mixing entropy alone is not necessarily enough to explain the total entropy difference [cf. eqn. (7)] although the other factors are responsible for about 1.6 J mol⁻¹K⁻¹ only. 2-Isobutyl-2-methyl-1,3-dioxane shows a clearly higher preference for the equatorial isobutyl group than the corresponding 4-methyl derivatives [$\Delta(\Delta G^{\circ})$ ca. 0.6 kJ mol⁻¹]. This is at least partly due to the relatively high experimental errors in both sets of measurements since the standard deviation shown in Table 4 does not include the contribution from the inaccuracies of the chemical shift measurements (Table 1 and 2) which in the case of the isobutyl derivative (Table 1) were rather high. On the other hand, it is probably an indication of the different buttressing effects of the methyl

Table 4. The values of ΔH° , ΔS° , and $\Delta G^{\circ}(298)$ for the studied conformer equilibria in comparison with chemical equilibration (CE)^{5,6} and estimated results. The free energy difference favors always the chair form where the methyl group is axial.

Compound	Method	$-\Delta H^{\circ}/\text{kJ mol}^{-1}$	$\Delta S^{\circ}/\text{J mol}^{-1} \text{K}^{-1}$	$-\Delta G^{\circ}(298)/\text{kJ mol}^{-1}$
2-Et,2-Me	¹ H NMR	0.19 ± 0.04^a	3.8 ± 0.1	1.3
	CE ⁵	0.2 ± 0.2	3.3 ± 0.5	1.2 (1.3; ⁶ 1.5 ¹⁷)
	Estd	0.8	2.9	1.7
2-Pr,2-Me	¹ H NMR	-1.17 ± 0.08	8.4 ± 0.25	1.3
	Estd	0.6	3.5	1.7
2- <i>i</i> -Pr,2-Me	¹ H NMR	-0.86 ± 0.04	10.3 ± 0.1	2.2
	CE ⁵	-0.38 ± 0.06	8.9 ± 0.2	2.3 (2.6; ⁶ 2.9 ¹⁷)
	Estd	1.4	8.7	3.9
2- <i>i</i> -Bu,2-Me	¹ H NMR	1.41 ± 0.04	3.6 ± 0.1	2.5
	CE ⁵	0.8 ± 0.2	3.9 ± 0.65	1.9
	Estd	1.6	3.2	2.6
2- <i>sec</i> -Bu,2-Me	¹ H NMR	-2.9 ± 0.2	15.0 ± 0.6	1.6
	Estd	1.3	8.6	3.9

^a Standard deviation

group at position 4 in *2a* and *2b*. As observed, a weaker buttressing influence may be expected when the isobutyl group is axial.^{6,13}

At any rate, the deviations discussed above do not remove the usefulness of the equatorial 4/6 methyl substitution as a conformation holding group since in most cases they do not alter the observed thermodynamic quantities significantly^{9,13} but allow frequently a less tedious and more reasonable possibility to observe conformational energy differences. Of course, this conclusion is not limited to 1,3-dioxanes, but applies to other related compounds as well.^{9,14,15}

Comparison with the estimated thermodynamic quantities. The calculated parameters (see also Table 5) are shown in Table 4 together with the experimental results obtained in this work and by chemical equilibration.⁵ Comparison of the experimental free energy differences

with the estimated ones points out that the deviation between them increases with the increasing crowding of the alkyl group (especially so if we choose the CE value for *i*-Bu). Moreover, these rather small deviations between calculated and experimental values correlate with the polar substituent constants of the alkyl groups^{2,18} [$\Delta(\Delta G^\circ) = -17.4\sigma^* - 1.5 \text{ kJ mol}^{-1}$ ($r = 0.989$)] and hence support the view that the alterations from the additivity are due to a minor decrease in the super-chair character of the O(1)-C(2)-O(3) moiety of *1a* and not to the values selected to the different interaction energies. In other words the contribution to the conformational energy of an axial alkyl group originating from the *syn*-axial 2,4- and 2,6-interactions¹⁸ decreases slightly in the order Me > Et ~ Pr > *i*-Bu > *i*-Pr > *sec*-Bu instead of the assumed constancy. At least qualitatively the above conclusions fit also into

Table 5. Rotameric contributions to the conformational status of 2-alkyl-2-methyl-1,3-dioxanes (*1*).^a

Group	Orien- tation	Contributing β,α -rotamers	(H_i)/kJ mol ⁻¹)	Mol fractions	$H^\circ_{\text{conf}}/\text{kJ}$ mol ⁻¹	$S^\circ_{\text{mix}}/\text{J}$ mol ⁻¹ K ⁻¹		
Et	e	- , <i>ap</i>	(3.8)	0.50	4.6	8.7		
	e	- , (+)- <i>sc</i> and - , (-)- <i>sc</i>	(5.5)	0.25				
	a	- , (+)- <i>sc</i> and - , (-)- <i>sc</i>	(5.5)	0.50			5.5	5.8
<i>i</i> -Pr	e	- , <i>ap</i>	(11.0)	0.20	9.6	8.7		
	e	- , (+)- <i>sc</i> and - , (-)- <i>sc</i>	(9.3)	0.40				
	a	- , <i>ap</i>	(11.0)	1.00			11.0	—
Pr	e	<i>ap, ap</i>	(3.8)	0.47	5.2	10.7		
	e	(-)- <i>sc, ap</i> and (+)- <i>sc, ap</i>	(11.9)	0.02				
	e	<i>ap, (+)-sc</i> and <i>ap, (-)-sc</i>	(5.5)	0.24				
	e	(+)- <i>sc, (+)-sc</i> and (-)- <i>sc, (-)-sc</i>	(13.6)	0.01				
	a	<i>ap, (+)-sc</i> and <i>ap, (-)-sc</i>	(5.5)	0.48				
	a	(+)- <i>sc, (+)-sc</i> and (-)- <i>sc, (-)-sc</i>	(13.6)	0.02			5.8	7.2
<i>i</i> -Bu	e	<i>ap, ap</i>	(20.0)	0.01	12.7	12.9		
	e	(+)- <i>sc, ap</i> and (-)- <i>sc, ap</i>	(11.9)	0.31				
	e	(+)- <i>sc, (-)-sc</i> and (-)- <i>sc, (+)-sc</i>	(13.6)	0.15				
	e	(+)- <i>sc, (+)-sc</i> and (-)- <i>sc, (-)-sc</i>	(17.4)	0.03				
	a	(+)- <i>sc, (-)-sc</i> and (-)- <i>sc, (+)-sc</i>	(13.6)	0.41				
	a	(+)- <i>sc, (+)-sc</i> and (-)- <i>sc, (-)-sc</i>	(17.4)	0.09			14.3	9.7
<i>sec</i> -Bu	e	<i>ap, (+)-sc</i> and <i>ap, (-)-sc</i>	(21.0)	0.02	14.0	12.4		
	e	(+)- <i>sc, ap</i>	(14.6)	0.17				
	e	(-)- <i>sc, ap</i>	(19.1)	0.03				
	e	(-)- <i>sc, (-)-sc</i>	(17.4)	0.05				
	e	(+)- <i>sc, (+)-sc</i> and (+)- <i>sc, (-)-sc</i>	(12.9)	0.35				
	e	(-)- <i>sc, (+)-sc</i>	(21.2)	0.01				
	a	<i>ap, ap</i>	(26.5)	0.01				
	a	(+)- <i>sc, ap</i>	(14.6)	0.85			15.3	3.8
	a	(-)- <i>sc, ap</i>	(19.1)	0.14				

^a Alkyl-in-the-ring rotamers for the axial orientations have been neglected.

the data available for some other corresponding ring systems.^{9,14}

The deviations in enthalpy and entropy differences vary less regularly with the size of the alkyl group although the calculated values do not differ appreciably from the experimental results when R=Et, i-Pr or i-Bu. In addition, the deviations in enthalpy and entropy differences seem to counterbalance each other and lead to the above-mentioned correlation in the case of ΔG° . Consequently, the calculated values serve at least as a good first approximation, although only the free energy differences may be predicted quite precisely.

EXPERIMENTAL

All of the studied compounds were prepared previously.³

The ¹H NMR spectra were recorded using a 60 MHz Perkin-Elmer R 10 spectrometer at 253, 268, 288, 306, 318, 333, and 348 (± 1) K. The solutions contained 10 % v/v of the substrate, 89 % v/v of the solvent CCl₄, and 1 % of the internal standard, TMS. The reported shifts are means of at least ten measurements for 2-alkyl-2-methyl-1,3-dioxanes (1). The methyl chemical shifts of 2,2-dimethyl-, 2-*tert*-butyl-2-methyl-, 2,2,4-trimethyl-, and diastereomeric 2-alkyl-2,4-dimethyl-1,3-dioxanes (2) did not change significantly within the temperature range in question. Hence the model values were calculated by averaging the chemical shifts observed for them at all of the above temperatures. The methyl chemical shifts are shown in Table 1 (1) and in Table 2 (2).

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- This is, of course, excluding alkyl-in-the-ring rotamers.

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