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CONFORMATIONAL EFFECTS IN COMPOUNDS WITH SIX-MEMBERED RINGS—III

CONFORMATIONAL EQUILIBRIA IN 2- AND 4-METHYLCYCLOHEXANONE: THE "2-ALKYLKETONE EFFECT"

W. D. Cotterill and M. J. T. Robinson
The Robert Robinson Laboratories, The University of Liverpool

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Abstract—The *cis* to *trans* isomerization of four epimeric pairs of dialkylcyclohexanones have been studied quantitatively as models of the conformational equilibria in 2- and 4-methylcyclohexanone. The conformational equilibrium in 2-methylcyclohexanone is only consistent with those in 4-methylcyclohexanone and acyclic ketones and aldehydes if the 2,6-diaxial repulsion between the methyl group and a hydrogen atom in a 2(ax)-methylcyclohexanone is less than analogous interactions in (ax)-methylcyclohexane. The methyl-oxygen repulsion ("2-alkylketone effect") in 2(eq)-methylcyclohexanone can not be determined from studies of the conformational equilibrium in 2-methylcyclohexanone but it has been shown to be small.

Robins and Walker found that the observed relative stabilities of several 1,4-dioxoperhydrophenanthrenes[1] differ from the predicted relative stabilities of the parent hydrocarbons,[2] and showed[3,4] that the results could be rationalized if there are differences between steric interactions in alkylcyclohexanones and in alkylcyclohexanes. They supposed that there is a significant repulsion between an equatorial 2-alkyl group and the carbonyl oxygen atom ("2-alkylketone effect")[5] in a 2-alkylcyclohexanone,[3] and that an axial 3-alkyl group is less hindered in a cyclohexanone than in the parent hydrocarbon[4] ("3-alkylketone effect").[5] Klyne,[5] explicitly taking no account of differences in bond angles and bond lengths between ketones and hydrocarbons, which now appears to be a rather poor approximation (see below), showed that these two alkylketone effects could explain a variety of qualitative and semi-quantitative observations about cyclic ketones if each effect was about 1 kcal mole^{-1}. Several authors[6–9] have doubted whether the "2-alkylketone effect" is important, but failure to recognize the special stabilization due to axial α-carbon-hydrogen bonds[10] has invalidated previous discussions of the "2-alkylketone effect", which fails to account for conformational equilibria in acyclic ketones and aldehydes [10] Because the original hypothesis of the "2-alkylketone effect" appears to have been

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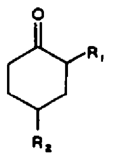
[1] P. A. Robins and J. Walker, *J. Chem. Soc.* 1789 (1955).
[2] W. S. Johnson, *J. Amer. Chem. Soc.* **76**, 1498 (1954).
[3] P. A. Robins and J. Walker, *J. Chem. Soc.* 3960 (1954).
[4] P. A. Robins and J. Walker, *Chem. & Ind.* 772 (1955).
[5] W. Klyne, *Experientia* **12**, 119 (1956).
[6] L. F. Fieser and M. Fieser, *Steroids* p. 213. Reinhold, New York (1959).
[7] N. L. Allinger and H. M. Blatter, *J. Amer. Chem. Soc.* **83**, 994 (1961).
[8] B. Rickborn, *J. Amer. Chem. Soc.* **84**, 2414 (1962).
[9] C. Beard, C. Djerassi, J. Sicher, F. Šipoš and M. Tichy, *Tetrahedron* **19**, 919 (1963).
[10] W. D. Cotterill and M. J. T. Robinson, *Tetrahedron Letters* 1833 (1963).

mistaken and was, indeed, based largely on misleading data, and because conformational equilibria in alkylcyclohexanones result from the interplay of several factors, we shall, in general, use the term alkylketone effect for the quantities

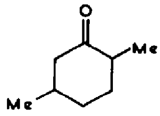
$$\Delta H_{(e\to a)}\ (\text{alkylcyclohexanone}) - \Delta H_{(e\to a)}\ (\text{methylcyclohexane})^{11}$$

without implication as to the origin of the differences. We prefer to use methylcyclohexane as the standard for comparison because other alkylcyclohexanes are sometimes anomalous[11] and it seems useful to define alkylketone effects so that the numerical values are representative of special features in the ketones alone.

Our original purpose in the research to be described in this and later papers was to determine the quantitative importance of the 2- and 3-alkylketone effects for methyl groups and to find out if there was any anomaly in 4-methylcyclohexanone. We intended to do this by measuring epimerization equilibria for the ketones (I; R_1 = Me, R_2 = t-Bu; I; R_1 = t-Bu, R_2 = Me and II), using the pairs of stereoisomers as models for the chair conformations of the methylcyclohexanones. The scope of the work was extended, however, when we found that the 2-alkylketone effect as originally conceived is probably small for a methyl group and is obscured by other interactions, and that there were important experimental difficulties to be overcome. In preliminary experiments the ketones were epimerized at temperatures between 0° and 78° with an alcoholic sodium alkoxide and the equilibrium mixtures of ketones were isolated by conventional methods and analysed by gas chromatography. Since the resulting enthalpy differences were higher than we had expected, showed rather poor reproducibility, and for 2-methyl-4-t-butylcyclohexanone differed substantially from that published shortly afterwards by Allinger and Blatter,[7] the experimental method was changed in order to eliminate as many sources of error as possible. By using a strongly basic ion exchange resin suspended in a propanol solution of a ketone the isolation procedure was reduced to the filtration of a small sample of the solution which was injected directly into the gas chromatograph. A single solution could be followed to equilibrium at each chosen temperature in turn and then returned to the first temperature to check the reproducibility of the results and the absence of side reactions.



I



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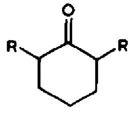

III

Another difficulty was recognized when we found that a 2-t-butyl group in a cyclohexanone can not be relied on to act simply as a conformation locking group. Allinger and Blatter's results for the ketones (I; R_1 = Me, R_2 = t-Bu and I; R_1 = R_2 = t-Bu)[7] are self-contradictory unless repulsions between the 2-t-butyl group and the oxygen atom in the latter are taken into account. More dramatically, *cis*- and *trans*-4,6-di-t-butylcyclohexane-1,3-dione show large differences in properties and the *cis* isomer is converted almost quantitatively into the *trans* by aqueous alkali.[12]

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[11] B. J. Armitage, G. W. Kenner and M. J. T. Robinson, *Tetrahedron* **20**, 747 (1964).

[12] N. J. W. Pumphrey and M. J. T. Robinson, *Tetrahedron Letters* 741 (1963).

In addition to the three methyl-t-butylcyclohexanones, therefore, we have studied dimethylcyclohexanones, taking into account the conformational equilibrium in each stereoisomer, to remove any uncertainty arising from the use of t-butyl groups as conformation locking groups, and decalones, to determine whether conclusions drawn from alkylcyclohexanones may be applied to polycyclic compounds. In this paper we consider the conformational equilibria in 2- and 4-methylcyclohexanone.

EXPERIMENTAL

Ketones. All the ketones studied here have been described previously and were prepared by methods chosen or modified to minimize the formation of isomeric ketones or of other compounds known to have similar gas chromatographic characteristics. Whenever possible the more stable stereoisomer of each pair was purified by low temperature crystallization from light petroleum (b.p. 40–60°). This was found to be far the most efficient method for those ketones which could be induced to solidify.

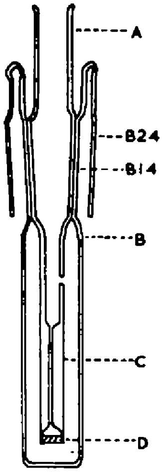


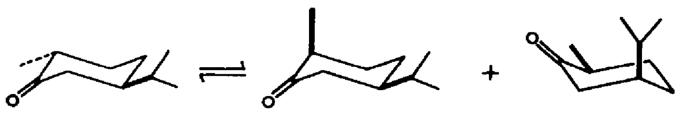
FIG. 1

Epimerization equilibria. A solution of a ketone (about 40–60 mg) in propanol (purified by fractional distillation, 2-3 ml) and the methoxide form of Amberlite CG 400 (washed free of "fines", soaked in 5% methanolic sodium methoxide, washed with dry methanol and, finally, with purified propanol; 100 mg) were placed in the tube B (Fig. 1) which was then closed with the filter-stick A. It was essential to grease the ground glass joints carefully, otherwise excessive evaporation of the solvent occurred. The tube B was then put into a vapour bath and when it had heated to the required temp the filter-stick was closed with a small rubber bung. From time to time the liquid in the filter-stick was forced back through the filter by pumping air into the thick-walled capillary C, from which freshly filtered solution could be removed with a 10 μl. Hamilton microsyringe. The dimensions of the filter-stick were such that the syringe needle reached to within 1–2 mm of the sintered glass plate D, which had to be fused rather than cemented on to the capillary tube. With this apparatus it was possible to extend a series of measurements over a period of up to 4 weeks, although this was unnecessary with any of the ketones described in this paper. Usually equilibria were reached very slowly at 0° and were studied with separate solutions.

Gas chromatography. The apparatus and methods were similar to those described earlier.[11] Most analyses of alkylcyclohexanones were carried out at 78° with a column (170 × 0·4 cm) packed with deactivated celite (G-CEL, Gas Chromatography Ltd., 100–110 mesh) coated with 1% by weight of 1,2,3-tri-(2-cyanoethoxy)-propane (distilled 3 times in a molecular still at 200°). Analyses were based on peak areas and are not corrected for differences in detector response; equilibrium constants for a given pair of stereoisomers are therefore in error by a constant factor which alters the entropy difference but not the enthalpy difference.

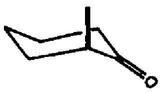
RESULTS AND DISCUSSION

Although higher than those previously reported[7,8] the enthalpy differences (Table 1) for the epimerization of 2,6-dimethyl- and 2-methyl-4-t-butyl-cyclohexanone are in good agreement and are supported by results for other ketones to be reported in a later paper in this series. Because Allinger and Blatter[7] and Rickborn[8] used alcoholic sodium alkoxides to epimerize these ketones, while we have found this method to be inferior to the use of an ion exchange resin, we believe that our results are more accurate. One other recent study of a derivative of 2-methylcyclohexanone must be considered. The free energy difference for the isomerization of carvomenthone (IV) to isocarvomethone (V), $\Delta F = +1{\cdot}4$ kcal mole^{-1}, was interpreted as a measure of the difference in stability of the two chair conformations of 2-methylcyclohexanone by Rickborn,[8] who supposed that the preferred conformation of isocarvomethone is Va with the methyl group axial. As was reasonable when early and rather inaccurate estimates only were available for the free energy differences for the conformational equilibrium in isopropylcyclohexane ($\Delta F_{(e\to a)} = +3{\cdot}3$ kcalmole^{-1})[13] and the epimerization of carvomenthone ($\Delta F_{(e\to a)} = +0{\cdot}8$ kcalmole^{-1}),[14,5] Klyne[5] also assumed that the methyl group rather than the isopropyl group would be axial in isocarvomenthone. It now seems far more likely that the preferred conformation of isocarvomenthone is Vb and that this free energy difference is relevant to the 3-alkylketone effect for isopropyl rather than to the 2-alkylketone effect for methyl so that there is no conflict with our results. The conformational equilibrium in 4-methylcyclohexanone was studied primarily to provide a model for skew interactions between axial 2- and 4-substituents in a cyclohexanone to assist in interpreting the conformational equilibrium in 2-methylcyclohexanone. There is good agreement between the results for the ketones (I; R_1 = t-Bu, R_2 = Me) and (I; $R_1 = R_2$ = Me) when allowance has been made in the latter for the conformational equilibrium in the *trans* isomer. Since the enthalpy differences, $\Delta H_{(e\to a)}$, are so similar for



IV Va Vb

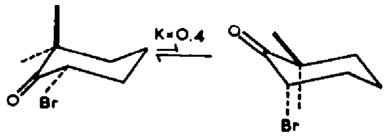
VIa



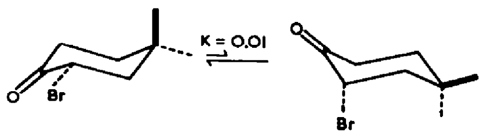
VIb

VII

VIII



IXa IXb



Xa Xb

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[13] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.* 77, 5562 (1955).

[14] R. G. Johnston and J. Read, *J. Chem. Soc.* 1138 (1935).

4-methylcyclohexanone ($\Delta H_{(e\rightarrow a)} = +1{\cdot}90$ kcalmole^{-1}) and methylcyclohexane ($\Delta H_{(e\rightarrow a)} \simeq +1{\cdot}7$ kcalmole^{-1})^{11} it is probable that *cis*-2,4-diaxial interactions in cyclohexanone are similar to *cis*-1,3-diaxial interactions in cyclohexane (see below).

TABLE 1. EQUILIBRIUM CONSTANTS,[a] AND ENTROPY[a] AND ENTHALPY DIFFERENCES FOR THE EPIMERIZATION[b] (*CIS* → *TRANS*) OF DIALKYLCYCLOHEXANONES

Ketone	K(°C)	ΔH kcalmole^{-1}	ΔS cal deg^{-1} mole^{-1}
I; R_1 = Me,	0·0317 (0)		
R_2 = t-Bu	0·0514 (34·5)		
	0·0645 (56·2)		
	0·0793 (78·5)	+2·16 ± 0·11	+0·8 ± 0·2
		(+2·1 ± 0·3)[c]	
		(+2·2 ± 0·3)[d]	
I; R_1 = t-Bu,	0·0375 (0)		
R_2 = Me	0·0550 (34·5)		
	0·0685 (56·2)		
	0·0835 (78·5)	+1·89 ± 0·09	+0·4 ± 0·2
I; R_1 = R_2 = Me	0·0551 (0)		
	0·0840 (34·5)		
	0·127 (78·5)	+2·02 ± 0·10	−1·6 ± 0·2
III; R_1 = R_2 = Me	0·0473 (0)		
	0·0762 (34·5)		
	0·0962 (56·2)		
	0·118 (78·5)	+2·18 ± 0·11	+1·8 ± 0·2

[a] Uncorrected for differences in detector response.
[b] Catalysed by a basic ion exchange resin unless otherwise stated.
[c] Preliminary experiments using methanolic sodium methoxide as the basic catalyst (0–56°).
[d] Preliminary experiments using ethanolic sodium ethoxide as the basic catalyst (0–78°).

The enthalpy difference for the conformational equilibrium in 2-methylcyclohexanone ($\Delta H_{(e\rightarrow a)} = +2{\cdot}17$ kcalmole^{-1}) is higher rather than lower than for that in methylcyclohexane (Table 2) so that the observed 2-alkylketone effect for a methyl group is apparently qualitatively different from that expected for a methyl-carbonyl repulsion in 2(eq)-methylcyclohexanone. Before considering intramolecular interactions we point out that this anomaly is not due to differential solvation. For all the epimeric pairs of 2-methylcyclohexanones we have studied, the isomer with the 2-methyl group axial has the longer gas chromatographic retention time on a polar stationary phase, as would be expected from considerations of steric hindrance to solvation of the carbonyl group. It follows, therefore, that solvation decreases $\Delta F_{(e\rightarrow a)}$ (2-methylcyclohexanone) and almost certainly decreases $\Delta H_{(e\rightarrow a)}$ (2-methylcyclohexanone), although the temperature dependence of the retention times has not been measured. If the apparent retention times for the epimers with the methyl group axial and equatorial are t_a and t_e, then the effect of solvation on the epimerization equilibrium is given by

$$\begin{aligned}\Delta\Delta F_{351^\circ} &= \Delta F(\text{solution}) - \Delta F(\text{vapour})\\ &= -RT \ln(\text{ratio of partition coefficients})\\ &= -RT \ln t_a/t_e\end{aligned}$$

For 1,2,3-tri(2-cyanoethoxy)-propane at 78° the ratio $t_a/t_e = 1{\cdot}20 \pm 0{\cdot}01$ for the ketones (I; R_1 = Me, R_2 = t-Bu and III; $R_1 = R_2$ = Me) so that $\Delta\Delta F_{351°} = -0{\cdot}13$ kcalmole^{-1} for this solvent and it may be larger in propanol.

TABLE 2. ENTHALPY DIFFERENCES FOR THE CONFORMATIONAL EQUILIBRIA IN 2- AND 4-METHYLCYCLOHEXANONE

Ketone used as model	$\Delta H_{e\rightarrow a}$ (kcalmole^{-1})	Reference
2-Methylcyclohexanone:		
I; R_1 = Me, R_2 = t-Bu	$+2{\cdot}1_6$	This paper
	$+1{\cdot}5_7$	7
III; $R_1 = R_2$ = Me	$+2{\cdot}1_8$	This paper
	$+1{\cdot}9_5$	8
4-Methylcyclohexanone:		
I; R_1 = t-Bu, R_2 = Me	$+1{\cdot}8_9$	This paper
I; $R_1 = R_2$ = Me	$-1{\cdot}9_0$	This paper

An indirect estimate of the difference in enthalpy of the two chair conformations of 2-methylcyclohexanone can be obtained by considering the enthalpy, H_a^0 and H_e^0, of each conformation relative to a hypothetical model free from skew interactions and methyl-oxygen repulsions, and with the same number of axial α-carbon-hydrogen bonds as cyclohexanone.* Thus the relative enthalpy of 2(ax)-methylcyclohexanone, H_a^0, is given by

$$H_a^0 = H[2(ax)\text{—}Me:6(ax)\text{—}H] + H[2(ax)\text{—}Me:4(ax)\text{—}H] + H[\text{loss of 1 axial } \alpha\text{-C—H bond}].$$

The first two terms represent the repulsions due to (modified) skew interactions between the 2(ax)-methyl group and the 4(ax)- and 6(ax)-hydrogen atoms, while the third term relates to the loss in stability of ketones or aldehydes when an axial or analogously situated α-carbon-hydrogen bond is replaced by a carbon-carbon bond.[10] Similarly the relative enthalpy of 2(eq)-methylcyclohexanone, H_e^0, is given by

$$H_e^0 = H[2(eq)\text{—}Me:O{=}C]$$

where a positive value of the right hand side implies a methyl-oxygen repulsion qualitatively in agreement with Klyne's "2-alkylketone effect", so that

$$\begin{aligned}\Delta H_{(e\rightarrow a)} &= H_a^0 \text{—} H_e^0\\ &= H[2(ax)\text{—}Me:6(ax)\text{—}H] + H[2(ax)\text{—}Me:4(ax)\text{—}H] +\\ &\quad H[\text{loss of axial } \alpha\text{-C—H bond}] - H[2(eq)\text{—}Me:O{=}C].\end{aligned}$$

The four terms will be discussed in succession.

The first term depends upon the relative orientation of the 2- and 6-axial bonds. The precise shape of the chair conformation of cyclohexanone has not been determined

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* This is analogous to Allinger and Hu's[15] treatment of the conformational equilibrium in ethylcyclohexane but the hypothetical "strain-free" model for an alkylcyclohexanone must be chosen differently.

[15] N. L. Allinger and S-E. Hu, *J. Amer. Chem. Soc.* **84**, 370 (1962).

by direct physical methods* but there seems no reason to suppose that the 2- and 6-axial bonds lean inwards with a consequent increase in repulsion between the 2- and 6-axial groups compared with an analogous derivative of cyclohexane. The evidence provided by calculation[17,18] and by application of the Octant Rule[18] is interrelated and must be considered in some detail. Corey and Sneen's original calculation[17] of the geometry of the cyclohexylidene ring, assuming ideal trigonal (120°) and tetrahedral (109° 28′) bond angles, has been claimed to conflict with the Octant Rule because it leads to the prediction that an equatorial 2- or 6-methyl substituent in an optically active cyclohexanone will make a significant contribution to the amplitude of the Cotton effect, whereas virtually no effect is observed in 2-α-methyl-3-oxo-5α-steroids.[18] Prompted by this result Corey (quoted in Ref. 18) has recalculated the shape of the cyclohexylidene ring, using a bond length and bond angle found for acetone[19] for the trigonal carbon atom but apparently retaining the ideal tetrahedral angle (109° 28′) for the methylene groups. In this model the axial 2- and 6-bonds are nearly parallel and the dihedral angle between the carbonyl group and the equatorial 2- and 6-bonds (4° 3′) was considered small enough to be consistent with the effect of a 2α-methyl substituent in a 3-oxo-5α-steroid. Very recently, however, Djerassi and Sicher *et al.*[9] have found that an equatorial 2-methyl substituent in a simple alkylcyclohexanone *does* contribute significantly to the Cotton effect in contrast to the evidence from steroids. Nevertheless the magnitude of this effect was considered small enough to be consistent with Corey's second calculation. We suggest that there may be a small difference in shape between simple cyclohexanones and the A-ring of a 3-oxo-5α-steroid which results from strain in the latter caused by the *trans*-fusion of the A- and B-rings. Such strain is commonly neglected but it appears to influence the reactivity of 3-oxo-5α-steroids[20] and is to be expected since carbon bond angles in normal[21] and branched paraffins[22] are about 112–113° rather than 109° as is assumed in most conformational analysis. The exact magnitude of the contribution of an equatorial 2-methyl substituent to the Cotton effect in a cyclohexanone is still in doubt. If allowance is made for the small concentration ($\simeq 5\%$) of (+)2(ax)-methylcyclohexanone (VIb; $a \simeq +67$)[9] in (+)2-methylcyclohexanone ($a = +12$)[9] then the amplitude calculated for +2(eq)-methylcyclohexanone (VIa) is $a = +8{\cdot}5$. A larger amplitude has been found for (−)*cis*-2,4-dimethyl- ($a = -16{\cdot}5$)[9] and (+)*cis*-2-methyl-4-t-butyl- ($a = +17{\cdot}5$)[9] cyclohexanone which should be locked in the conformations (VII and VIII) with no contribution from the 4-alkyl-substituents. Djerassi and Sicher have suggested that the *cis*-2,4-dialkylcyclohexanones are anomalous but since the chemical and optical purity of these ketones is beyond doubt[9] whereas there is no check at present on the optical purity of

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* Romers' electron diffraction study of cyclohexanone established the chair conformation of the ring[16] but not the directions of the carbon-hydrogen bonds.

[16] C. Romers, *Rec. Trav. Chim.* **75**, 331 (1956).

[17] E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.* **77**, 2505 (1955).

[18] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Amer. Chem. Soc.* **83**, 4013 (1961).

[19] J. D. Swalen and C. C. Costain, *J. chem. Phys.* **31**, 1562 (1960).

[20] M. J. T. Robinson and W. B. Whalley, *Tetrahedron* **19**, 2123 (1963).

[21] R. A. Bonham and L. S. Bartell, *J. Amer. Chem. Soc.* **81**, 3491 (1959); R. A. Bonham, L. S. Bartell and D. A. Kohl, *Ibid.* p. 4765.

[22] D. R. Lide, *J. chem. Phys.* **33**, 1519 (1960).

(+)2-methylcyclohexanone, which was available in very small amount only, we believe that a = +17 is at least as likely as a = +8·5 to be the true molecular rotation amplitude of (+)2(eq)-methylcyclohexanone. The balance of evidence from molecular rotation amplitudes seems to be that there is an appreciable dihedral angle between an equatorial 2-bond and the carbonyl group in a cyclohexanone, which implies that the axial 2- and 6-bonds diverge.

Other evidence also suggests that the 2- and 6-bonds in cyclohexanone either lean outwards or are more easily distorted than axial bonds in cyclohexane, or both. For example, the carbonyl group stretching frequency of cyclohexanone, 1718 cm^{-1}, is lower than that of adamantanone, 1732 cm^{-1},[23] in which the axial bonds of cyclohexanone have become part of another ring and are thereby constrained to be nearly parallel. Similarly there is a far higher proportion of the conformation (IXb) with the bromine axial in 2-bromo-6,6-dimethylcyclohexanone (IX) than in 2-bromo-4,4-dimethylcyclohexanone(X)[24]; since our determination of the conformational equilibrium in 4-methylcyclohexanone indicates that *cis*-2,4-diaxial interactions in cyclohexanone, are quantitatively very similar to *cis*-1,3-diaxial interactions in cyclohexanes (see above), *cis*-2,6-diaxial interactions in cyclohexanones must be relatively small. It appears certain, therefore, that the repulsion between the methyl group and the 6(ax)-hydrogen atom in the conformation (VIa) will be less than a diaxial 1,3-interaction between a methyl group and a single hydrogen atom in (ax)-methylcyclohexane, i.e.,

$$\begin{aligned} H[2(ax)\text{—}Me:6(ax)\text{—}H] &< \tfrac{1}{2}\Delta H_{(e\rightarrow a)}\ (\text{methylcyclohexane}) \\ &< +0{\cdot}85 \pm 0{\cdot}1\ \text{kcalmole}^{-1}.^{11} \end{aligned}$$

Models of methylcyclohexanones show that the distance between a 2(ax)-methyl group and a 4(ax)-hydrogen atom is only very slightly longer (by 0·06 ± 0·02A)* than the distance between a 2(ax)-hydrogen atom and a 4(ax)-methyl group so that the repulsion should be similar, i.e., H[2(ax)—Me:4(ax)—H] should be equal to, or slightly less than, $\tfrac{1}{2}\Delta H_{(e\rightarrow a)}$ (4-methylcyclohexanone) = +0·95 $kcalmole^{-1}$, and it will be taken to be +0·85 ± 0·1 $kcalmole^{-1}$. A similar conclusion might be made from a comparison of distances between axial methyl and hydrogen substituents in 2-methylcyclohexanone and methylcyclohexane if it was assumed that the flexibility of the hydrocarbon and ketone rings were the same but such an assumption is obviously uncertain. The third term, H[loss of axial α-C—H bond], takes account of the stabilizing factor, with stereochemical requirements similar to those expected for hyperconjugation, which can correlate a variety of observations about ketones and aldehydes,[10] and the fourth term is qualitatively the 2-alkylketone effect as postulated by Robins and Walker[3] and by Klyne.[5] At present these last two terms can not be evaluated separately with any accuracy (see below) but their algebraic sum is given by the difference in stability of the conformations of propionaldehyde (1·0 $kcalmole^{-1}$)[25]

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* An average of measurements on Dreiding models; if the shape of the cyclohexanone ring is that calculated by Corey[18] the difference will be even smaller.

[23] P. von R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.* **83**, 182 (1961).

[24] E. J. Corey, *J. Amer. Chem. Soc.* **75**, 2301 (1953); E. J. Corey, T. H. Topie and W. A. Wozniak, *Ibid.* **77**, 5415 (1955).

[25] R. J. Abraham and J. A. Pople, *Mol. Phys.* **3**, 609 (1960).

or of isobutyraldehyde (1·2 kcalmole^{-1}),[26] and we will assume a value +1·1 ± 0·2 kcalmole^{-1} to be the best estimate at present. The calculated value of the difference in heat content for the two chair conformations of 2-methylcyclohexanone is therefore given by:

$$\begin{aligned}&\Delta H_{(e\rightarrow a)}\ \text{(2-methylcyclohexanone)}\\ &= (+0{\cdot}85 \pm 0{\cdot}1) + (<0{\cdot}85 \pm 0{\cdot}1) + (1{\cdot}1 \pm 0{\cdot}2)\\ &= < +2{\cdot}8 \pm 0{\cdot}3\ \text{kcalmole}^{-1}\end{aligned}$$

Since the experimental value for propyl alcohol solutions, $\Delta H_{(e\rightarrow a)} = +2{\cdot}1_7 \pm 0{\cdot}2$ kcalmole^{-1}, is significantly less than the calculated, even allowing for the possible effects of differential solvation, it appears that our supposition that the repulsion between axial 2- and 6-substituents in a cyclohexanone are appreciably less than similar repulsions in a cyclohexane is correct and that the 2- and 6-axial bonds either lean apart or are more easily distorted than axial bonds in cyclohexane, or both. This greater ease of distortion is to be expected for two reasons. Firstly a small increase in the internal angle at a carbonyl group has a larger effect in flattening that end of the ring than does a similar increase in bond angle at a tetrahedral carbon atom. Secondly torsional strain which results from changes in dihedral angles accompanying flattening of the end of the ring will be less for the ketone because the barrier to rotation about a single bond is much lower if the bond is adjacent to a carbonyl group than if it is between two tetrahedral carbon atoms.

There is considerable interest in attempting to evaluate the energy terms H[2(eq)—Me:O=C] and H[loss of axial α-C—H bond] separately even though this is not necessary in order to calculate an upper limit for $\Delta H_{(e\rightarrow a)}$ (2-methylcyclohexanone). The observation by Cubberley and Mueller[27] that the heats ($\Delta H_{298°} = -15{\cdot}1 \pm 0{\cdot}1$ kcalmole^{-1}) and free energies ($\Delta F_{298°} = -6{\cdot}75 \pm 0{\cdot}1$ kcalmole^{-1}) of hydrogenation to equilibrium mixtures of the alcohols are identical for cyclohexanone and its 2- and 3-methyl derivatives implies that the inductive and steric effects of the 2-methyl group cancel so that the methyl-carbonyl repulsion in 2-methylcyclohexanone is given by

$$H[2(eq)\text{—Me:O=C}] \simeq H[2\text{—Me:OH}] - H[2\text{—Me inductive effect}].$$

The first term of the right hand side is the weighted average of the repulsions between methyl and hydroxyl groups in an equilibrium mixture of 2-methylcyclohexanols and the second term is the differential inductive effect of the 2-methyl group. As the methyl groups will be mainly equatorial and therefore skew to the hydroxyl group in the stereoisomeric 2-methylcyclohexanols the average methyl-hydroxyl repulsion will be approximately equal to the interaction in the skew conformation of propyl alcohol, which has not been studied, or, less exactly, to one of the methylene-hydroxyl skew interactions in cyclohexanol when the hydroxyl group is axial, i.e., to $\frac{1}{2}\Delta H_{(e\rightarrow a)}$ (cyclohexanol) in the gas phase; unfortunately the only available data are free energy differences for solutions. The lowest published value of $\Delta F_{(e\rightarrow a)}$ (cyclohexanol), +0·3 — +0·4 kcalmole^{-1} for very dilute solutions in a non-polar solvent,[28] may not

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[26] R. J. Abraham, personal communication.

[27] A. H. Cubberley and M. B. Mueller, *J. Amer. Chem. Soc.* **69,** 1535 (1947).

[28] R. A. Pickering and C. C. Price, *J. Amer. Chem. Soc.* **80,** 4931 (1958).

be very accurate and more recent values[29–31] are higher, rather discordant (varying between +0·66, 25% solution in carbon disulphide,[29] and +1·25 kcalmole^{-1}, 5% solution in water[29]), and have not been measured at sufficiently low concentrations in non-polar solvents to eliminate intermolecular hydrogen bonding. The stable conformations of the propyl halides, furthermore, are the skew[32] in contrast to the greater stability of conformations with halogen atoms equatorial rather than axial cyclohexyl halides.[33] Thus even the lowest value of $\frac{1}{2}\Delta H_{(e\to a)}$ (cyclohexanol) is likely to overestimate the methyl-hydroxyl repulsion in 2-methylcyclohexanol, which seems likely to be in the range 0 ± 0·3 kcalmole^{-1}. If it is assumed that free energy and enthalpy differences are approximately equal in reactions without a change in the number of molecules and that there is no important difference between equilibria in the gas phase and in dilute toluene solutions, then the differential inductive effect of the 2-methyl should be obtainable from the difference between Taft's polar substituent constants for ethyl and isopropyl, and the polar reaction constant for the free energy differences of equilibria[34] supposed[35] to be

$$R_1R_2CHOH + Me_2CO \rightleftharpoons R_1R_2CO + Me_2CHOH$$

The alcohols, however, must have been mainly in the form of aluminium alkoxides because Adkins *et al.* used an excess of aluminium t-butoxide as a catalyst[34] and this probably accounts for the magnitude of the polar reaction constant, $\rho^* = -6{\cdot}4$, which is very large as Kreevoy and Taft commented.* This reaction constant probably results from the cumulative effect of several factors. Kreevoy and Taft assumed that steric effects would be unimportant in most simple alcohols and ketones but this is most unlikely to be true in aluminium alkoxides. The oxygen atom in an aluminium alkoxide, furthermore, will bear a much larger negative charge than in an alcohol. Both these effects will increase the apparent stabilization of carbonyl compounds by alkyl groups and qualitatively they explain the large magnitude of the reaction constant, which is, for example, larger rather than smaller than the reaction constant, $\rho^* = -3{\cdot}5$, found for the rates of acid catalysed hydrolysis of acetals and ketals:[37]

$$R_1R_2C(OEt)_2 + \overset{+}{H} \rightarrow R_1R_2C = \overset{+}{O}Et + EtOH \rightarrow \text{products.}$$

The transition state in these reactions is, presumably, virtually the fully formed oxonium ion and so should be much more and not less electron demanding relative to the acetal or ketal than is a ketone relative to an alcohol. We believe, therefore, that the magnitude of the reaction constant for the heats or free energies of hydrogenation of ketones should be much less than 3·5, perhaps about 2. Since the inductive effect of a 2-methyl substituent in a cyclohexane should be very similar to

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* The mistaken interpretation of the experimental data also invalidates the hyperconjugation parameters h_H and h_C for aldehydes and ketones.[36]

[29] F. A. L. Anet, *J. Amer. Chem. Soc.* **84**, 1053 (1962).

[30] E. L. Eliel and M. H. Gianni, *Tetrahedron Letters* 97 (1962); E. L. Eliel, M. H. Gianni and T. H. Williams, *Ibid.* 741 (1962).

[31] A. H. Lewin and S. Winstein, *J. Amer. Chem. Soc.* **84**, 2464 (1962).

[32] E. Hirota, *J. Chem. Phys.* **37**, 283 (1962), and references quoted therein.

[33] O. Hassel and H. Viervall, *Acta Chem. Scand.* **1**, 149 (1947).

[34] H. Adkins, R. M. Elofson, A. G. Rossow and C. C. Robinson, *J. Amer. Chem. Soc.* **71**, 3622 (1949).

[35] R. W. Taft and M. M. Kreevoy, *J. Amer. Chem. Soc.* **79**, 401 (1957).

[36] R. W. Taft and I. C. Lewis, *Tetrahedron* **5**, 210 (1959).

[37] M. M. Kreevoy and R. W. Taft, *J. Amer. Chem. Soc.* **77**, 5590 (1955).

the difference between ethyl ($\sigma^* = -0{\cdot}1$)[38] and isopropyl ($\sigma^* = -0{\cdot}2$)[38] the differential inductive effect of the 2-methyl substituent, H[2-Me inductive effect], is probably about $-0{\cdot}2$ kcalmole^{-1}. Thus the calculated value of

$$H[2(eq)\text{—}Me:O\!=\!C] = 0{\cdot}0 \pm 0{\cdot}3 - (-0{\cdot}2) \simeq +0{\cdot}2 \text{ kcalmole}^{-1}$$

suggests that the "2-alkylketone effect" for methyl is at most small and may be negligible as was first suggested by Fieser and Fieser.[6] Consequently the loss in stability caused by replacing an axial α-carbon-hydrogen bond by a carbon-carbon bond[10] in a ketone or aldehyde may be little, if at all, greater than $+1{\cdot}1 \pm 0{\cdot}2$ kcalmole^{-1}.

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[38] R. W. Taft, *J. Amer. Chem. Soc.* **75**, 4231 (1953).