Tetrahedron, 1964, Vol. 20, pp. 777 to 790. Pergamon Press Ltd. Printed in Northern Ireland

CONFORMATIONAL EFFECTS IN COMPOUNDS WITH SIX-MEMBERED RINGS—IV

CONFORMATIONAL EQUILIBRIA IN 2- AND 3-ALKYLCYCLOHEXANONES AND SKEW INTERACTIONS BETWEEN METHYL AND CARBONYL GROUPS

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

(*Received* 22 *October* 1963)

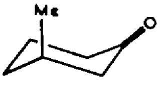
Abstract—The 2- and 3-akylketone effects for alkylcyclohexanones other than 2-methylcyclohexanone are shown to be closely related in their origins. An analysis of the conformational equilibria in 2-ethyl- and 2-isopropyl-cyclohexanone provides estimates of the interactions between the methyl and carbonyl groups in the skew conformations of butyraldehyde. The numerical values of these interactions are used in an interpretation of conformational equilibria in other cyclic ketones and in aliphatic aldehydes.

THE 2- and 3-alkylketone effects were considered by Robins and Walker[1] and by Klyne[2] to result from two distinct causes and accordingly the terms "2- and 3-alkylketone effects" were used for both the experimental observations and the causes proposed to explain them. The 2-alkylketone effect was thought to result from repulsion between an equatorial 2-methyl (or methylene or methine) group and the carbonyl group in a 2-alkylcyclohexane, but such repulsion now appears to be quite small. The 3-alkylketone effect was defined as the extent to which the sum of the skew interactions between an axial 3-methyl (or methylene or methine) group and the carbonyl and $C_{(5)}$-methylene groups in, e.g., 3(ax)-methylcyclohexanone (I), are less than the sum of the skew interactions between the axial methyl group and the $C_{(3)}$- and $C_{(5)}$-methylene groups in the parent hydrocarbon (II). As an approximation it was supposed[1,2] that the decrease in the sum of the repulsions was simply due to the virtual elimination of one of the skew interactions in the alkylcyclohexane with no significant change in the other.

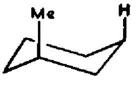
The 2- and 3-alkylketones effects, however, are not physically distinct. The observed difference between the conformational equilibria in 2-methyl- and 2-ethylcyclohexanone is mainly due to *decreased* hindrance to the axial ethyl group in the preferred conformation (III) of 2(ax)-ethylcyclohexanone compared with (ax)-ethylcyclohexane (IV), in the same way that the ketone (I) differs from the hydrocarbon (II), as was recognized by Allinger and Blatter.[3] In 2-isopropylcylohexanone there is not only decreased repulsion when the isopropyl group is axial, but also *increased* repulsion, compared with the corresponding conformations of isopropylcyclohexane, when the isopropyl group is equatorial, as in the conformations V and VI. It is preferable, therefore, to use the terms 2- and 3-alkylketone effect for the observed differences between conformational equilibria in 2- and 3-alkylcyclohexanones

[1] P. A. Robins and J. Walker, *J. Chem. Soc.* 1789 (1955); *Chem. & Ind.* 772 (1955).
[2] W. Klyne, *Experientia* **15**, 119 (1956).
[3] N. L. Allinger and H. M. Blatter, *J. Amer. Chem. Soc.* **83**, 944 (1961).

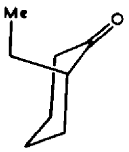
and in methylcyclohexane,[4] and for differences in analogous chemical equilibria. It also appears to be appropriate to use enthalpy differences rather than free energy differences, even though the latter are more readily available, when discussing the 2- and 3-alkylketone effects. The free energy differences for the equilibria between sets of conformation in 2-ethyl- and 2-isopropyl-cyclohexanones involve changes of entropy. These entropy changes which we will discuss briefly later in this paper, are mainly entropies of mixing and are not relevant to the interactions in particular conformations.



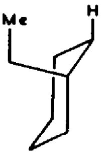
I



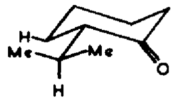
II



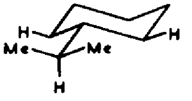
III



IV



V



VI

Using the technique described in Part III we have measured epimerization equilibria for the ketones (VII; R = Et, VIII; $R_1 = R_2 =$ Me, VIII; $R_1 =$ t-Bu, $R_2 =$ Me and IX; $R_1 = R_2 =$ Me). We also began a study of the epimerization of the ketone (VII; R = i-Pr) but this was discontinued at an early stage when Rickborn published results for the ketones (VII; R = Me, Et, i-Pr, or t-Bu)[5] because our preliminary results agreed with Rickborn's* and were consistent with Allinger and Blatter's for the ketone (X; R = i-Pr).[3] In all the ketones which we will discuss in this paper the more stable stereoisomer has one strongly preferred conformation but in some cases the less stable stereoisomers have two conformations of comparable stability. The ketones (VII) are straightforward because the *cis* isomers are *meso* compounds virtually locked in the conformation (VIIa) with both alkyl groups equatorial while the *trans* isomers are racemic mixtures with only one conformation, (VIIb) or its mirror image, for each enantiomer. We believe that the t-butyl groups in the ketone (VIII; $R_1 =$ t-Bu) and in the ketones (X; R = Et or i-Pr) determine the conformation of each stereoisomer, but in the *cis* isomer of the ketone (VIII; $R_1 = R_2 =$ Me) both chair conformations are present in appreciable amount. We assume that the equilibrium (VIIIa; $R_1 = R_2 =$ Me) $\rightleftharpoons$ (VIIIb $R_1 = R_2 =$ Me) is quantitatively similar to the conformational equilibrium in 2-methylcyclohexanone[4] so that the equilibrium constants for the reaction (VIIIa; $R_1 = R_2 =$ Me) $\rightleftharpoons$ (VIIIc; $R_1 = R_2 =$ Me) may be obtained by difference. Similarly the free energy difference for epimerization of carvomenthone *trans*-(VIII; $R_1 =$ Me, $R_2 =$ i-Pr) to isocarvomenthone *cis*-(VIII; $R_1 =$ Me, $R_2 =$ i-Pr)[5] may be corrected for the conformational equilibrium in the latter.[4] The epimeric ketones (IX; $R_1 =$ Me, $R_2 = \alpha$Me or βMe)

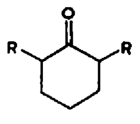
---

* There is an obvious discrepancy in Rickborn's paper between the experimental data for the ketone (VII; R = i-Pr) and the derived enthalpy and entropy differences, which we have recalculated for inclusion in Table 3.

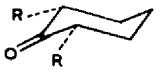
[4] W. D. Cotterill and M. J. T. Robinson, Part III.

[5] B. Rickborn, *J. Amer. Chem. Soc.* **84**, 2414 (1962).

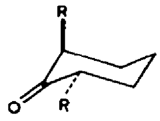
each have one strongly preferred conformation with the 3-methyl group equatorial, because in the alternative two-chair conformations with the 3-methyl group axial there are severe 1,3-diaxial interactions between the 3-methyl group and either the 10-methyl or the $C_{(5)}$-methylene group. The ketones (IX; R_1 = Me, R_2 = αMe or βMe) are, therefore, excellent models for the two-chair conformations (IXa; R_1 = Me, R_2 = H and IXb; R_1 = Me, R_2 = H) of 10-methyl-*cis*-2-decalone. As yet we have been unable to separate the ketones (IX; R_1 = Me, R_2 = αMe or βMe) and prove their configurations, which have been assigned provisionally from gas chromatographic retention times. Since 6,6-dimethyl-*cis*-2-decalone, which has the preferred conformation (XI), is less readily eluted than 7,7-dimethyl-*cis*-2-decalone, which has the preferred conformation (XII), although the *trans* isomers have almost identical retention times,[8] we conclude that the less readily eluted of the ketones (IX; R_1 = Me, R_2 = αMe or βMe) has the preferred conformation (IXa; R_1 = R_2 = Me). This is the expected result if the differences in retention times for stereoisomers depend on the extent to which the carbonyl group is shielded from solvation by the polar stationary phase as appears to be the case with simple alkylcyclohexanones.



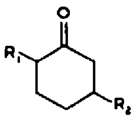
VII



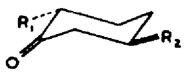
VIIa



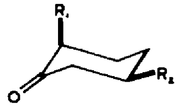
VIIb



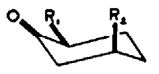
VIII



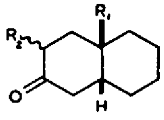
VIIIa



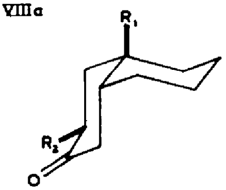
VIIIb



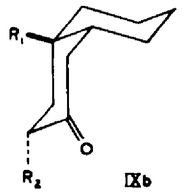
VIIIc



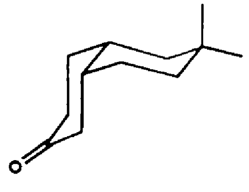
IX



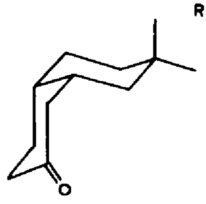
IXa



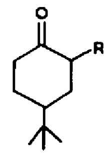
IXb



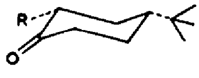
XI



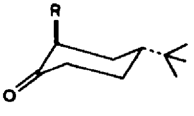
XII



X



Xa



Xb

TABLE 1. APPARENT RETENTION TIMES OF ALKYLCYCLOHEXANONES RELATIVE TO CYCLOHEXANONE ON GLYCEROL TRI-2-CYANOETHYL ETHER AT 78°

Substituents in cyclohexanone	Relative apparent retention time	Ratios of relative apparent retention times
None	1·00	
2-Methyl	0·88	
3-Methyl	1·16 (A)	
4-Methyl	1·20 (B)	
3,3-Dimethyl	1·29 (C)	A:C – 1:1·11
4,4-Dimethyl	1·54 (D)	B:D = 1:1·28

For example, the ratios of apparent retention times for alkylcyclohexanones (Table 1) show that a single, mainly equatorial, 3- or 4-methyl substituent increases the apparent retention time by a factor 1·18 ± 0·02, although a 2-methyl substituent decreases the apparent retention time by a factor 0·88, presumably by strongly hindering solvation of the carbonyl group. The second, axial methyl substituents in 3,3- and 4,4-dimethylcyclohexanone increase the retention times by 1·11 and 1·28, compared with the monomethyl ketones, the difference reflecting the shielding of the carbonyl group in 3,3-dimethylcyclohexanone.

EXPERIMENTAL

Ketones. The dialkylcyclohexanones studied here have all been described previously. The preparation of 3,10-dimethyl-*cis*-2-decalone from 10-methyl-*cis*-2-decalone will be described in a later paper on the synthesis of decalin derivatives[8] required for this and other investigations.

Epimerization equilibria. The ion exchange resin method used previously[4] was used without modification.

Gas chromatography. The apparatus and methods were similar to those described earlier.[4,9] The stationary phases used were glycerol tri-2-cyanoethyl ether at 78° for alkylcyclohexanones and at 110° for decalones, and mannitol hexa-2-cyanoethyl ether at 110° and at 132° for decalones.

RESULTS AND DISCUSSION

Our experimental enthalpy differences for epimerization equilibria in dialkylcyclohexanones (Table 2) and the derived values for conformational equilibria in alkylcyclohexanones (Table 3) are in good agreement with recently published data for 2-ethylcyclohexanone but there are serious discrepancies for the 3-alkylketone effect in 3-methylcyclohexanone. Rickborn[5] has suggested that the 3-alkylketone effect is insignificant. This conclusion was based on an analysis of an equilibrium constant, for which no source was given, for the epimerization of menthone (*trans*-VIII; R_1 = i-Pr, R_2 = Me) to isomenthone (*cis*-VIII; R_1 = i-Pr, R_2 = Me). In effect Rickborn used the 2-isopropyl substituent as a conformation locking group, for which it is unsuitable. At the other extreme Djerassi *et al.*,[10] in agreement with Klyne,[2] found the 3-alkylketone effect to be about $-0{\cdot}9$ kcal mole^{-1}. This was based

---

[6] A. S. Dreiding, *Chem. & Ind.* 1419 (1954).

[7] D. J. Millen, *Progress in Stereochemistry* (Edited by P. B. D. de la Mare and W. Klyne) Vol. III; p. 138 *et seq.* Butterworths, London (1962).

[8] W. D. Cotterill, D. W. Elliott and M. J. T. Robinson, to be published.

[9] B. J. Armitage, G. W. Kenner and M. J. T. Robinson, Part II

[10] C. Djerassi, E. J. Warawa, J. M. Berdahl and E. J. Eisenbraun, *J. Amer. Chem. Soc.* **83**, 3334 (1961).

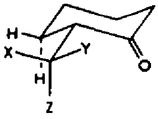
TABLE 2. EQUILIBRIUM CONSTANTS,[a] AND ENTROPY[a] AND ENTHALPY DIFFERENCES FOR THE EPIMERIZATION (CIS → TRANS) OF DIALKYLCYCLOHEXANONES AND 3,10-DIMETHYL-CIS-2-DECALONE

Ketone	K(°C)	ΔH (kcal mole^{-1})	ΔS (cal deg^{-1} mole^{-1})
VII; R = Et	0·128 (0)		
	0·166 (34·5)		
	0·193 (56·2)		
	0·216 (78·5)	−1·26 ± 0·07	+0·6 ± 0·2
VIII; R_1 = R_2 = Me	9·71 (0)		
	7·04 (34·5)		
	5·95 (56·2)		
	5·29 (78·5)	−1·50 ± 0·1	−1·0 ± 0·2
VIII; R_1 = t-Bu	22·0 (0)		
	16·3 (34·5)		
	13·8 (56·2)		
	11·8 (78·5)	−1·54 ± 0·1	+0·5 ± 0·2
IX; R_1 = R_2 = Me	2·01 (0)		
	1·83 (34·5)		
	1·70 (78·5)	−0·40 ± 0·05	+0·1 ± 0·1

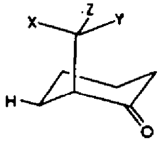
[a] Uncorrected for differences in detector response.

on a free energy difference, $\Delta F_{298} = +0{\cdot}8$ kcal mole^{-1} for the *trans* to *cis* isomerization of the ketone (VIII; R_1 = t-Bu, R_2 = Me), estimated from optical rotation measurements. For the same reaction we have found $\Delta H = +1{\cdot}54$ kcal mole^{-1}, and we believe that this result, based on gas chromatographic analysis and agreeing with other measurements by ourselves and by Allinger and Freiberg (Table 3), is certain to be more accurate. We will discuss first the 2-alkylketone effects.

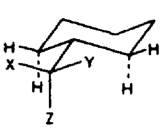
The 2-alkylketone effects for 2-ethyl- and 2-isopropylcyclohexanone may most conveniently be considered by taking the conformations of 2-methylcyclohexanone and methylcyclohexane as starting points. If we assume that the conformations resulting from replacing the hydrogen atoms Z in XIVa and XVIa by methyl groups may be neglected because they have high energies resulting from interactions analogous to those which would be present in (ax)-t-butylcyclohexane, then the permissible conformations of 2-ethyl- and 2-isopropyl-cyclohexanone and of ethyl- and isopropylcyclohexane may be obtained hypothetically from the conformations XIIIa to XVIa by replacing hydrogen atoms X, Y and Z by methyl groups without altering, as a



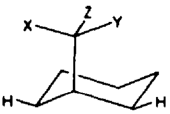
XIII



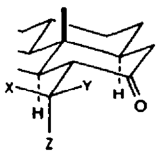
XIV



XV



XVI



XXIV

	2-Methyl	2-Ethyl			2-Isopropyl		
	a:	b:	c:	d:	e:	f:	g:
X =	H	Me	H	H	Me	Me	H
Y =	H	H	Me	H	Me	H	Me
Z =	H	H	H	Me	H	Me	Me

TABLE 3. ENTHALPY AND ENTROPY DIFFERENCES, FOR CONFORMATIONAL EQUILIBRIA AND INTERACTIONS IN CARBONYL COMPOUNDS

Ketone used as model	$\Delta H_{(e\to a)}$ (kcal mole^{-1})	$\Delta S_{(e\to a)}{}^{a}$ (cal deg^{-1} mole^{-1})	Alkylketone effect[b] or interaction[c] (kcal mole^{-1})	Reference
	2-Ethylcyclohexanone:			
VII; R = Et	$+1\cdot2_{8}{}^{d}$	($-0\cdot8$)	$-0\cdot5$	This paper
R = Et	$+1\cdot2_{8}{}^{d}$	$-0\cdot2$		5
X; R = Et	$+1\cdot0_{6}{}^{d}$	(0 assumed)		3
	2-Isopropylcyclohexanone:			
VII; R = i-Pr	$+0\cdot3_{2}{}^{d,e}$	$-0\cdot8^{e}$	$-1\cdot4$	5
X; R = i-Pr	$+0\cdot4_{4}{}^{d}$	$-0\cdot5$		3
	3-Methylcyclohexanone:			
VIII; $R_1 = R_2 =$ Me	$+1\cdot3_{1}{}^{d}$	($-0\cdot2$)	$-0\cdot5$	This paper
f	$+1\cdot3_{5}{}^{d,f}$	(0 assumed)[f]		3
VIII; $R_1 =$ t-Bu, $R_2 =$ Me	$+1\cdot5_{4}$	($-0\cdot5$)		This paper
	$\Delta F = +0\cdot8$			10
VIII; $R_1 =$ i-Pr, $R_2 =$ Me	$\Delta F > +1\cdot8$			5
	3-Isopropylcyclohexanone:			
VIII; $R_1 =$ Me, $R_2 =$ i-Pr	$\Delta F = -1\cdot6$			5
	cf. 2-Methylcyclohexanone:			
	$+2\cdot1_{7}$		$+0\cdot4$	4
	Skew butanal interactions,		$\pi = +0\cdot1$	This paper
			$n = -1\cdot6$	This paper
	Skew butane interaction,		$h = +0\cdot9$ (assumed)	

---

[a] Derived from the values found for epimerization equilibria by allowing for conformational equilibria in the model ketones.

[b] Alkylketone effect = $\Delta H_{(e\to a)}$ (alkylcyclohexanone) − $\Delta H_{(e\to a)}$ (methylcyclohexane), assuming $\Delta H_{(e\to a)} = +1\cdot8$ kcal mole^{-1} for methylcyclohexane.

[c] Enthalpy.

[d] Selected for calculation of alkylketone effects and of skew butanal interactions.

[e] Derived from the experimental results reported by Rickborn,[5] who gave $\Delta H = +0\cdot03$ kcal mole^{-1} and $\Delta S = +0\cdot6$ cal deg^{-1} for the *trans* to *cis* isomerization of 2,6-diisopropylcyclohexanone, for which we calculate $\Delta H = -0\cdot32$ kcal mole^{-1} and $\Delta S = -0\cdot6$ cal deg^{-1} mole^{-1}.

[f] 3,5-Dimethylcyclohexanone: Allinger and Freiberg found $\Delta F_{498} = +0\cdot67$ kcal mole^{-1} for the *cis* to *trans* isomerization of this ketone and assumed $\Delta S = R \ln 2$, i.e., no entropy change except that due to the entropy of mixing of the racemic *trans* isomer.

first approximation, the principal destabilizing interactions already present. It should be noted that this depends on the absence from XIIIa of significant methyl–oxygen interactions, which we showed to be very probable in the preceding paper. This is advantageous because we thereby avoid separating the factors which combine to destabilize XIVa relative to XIIIa and we may simply use the experimental value of $\Delta H_{(e\to a)}$ (2-methylcyclohexanone) = $+2\cdot1_7$ kcal mole^{-1}, and add to or substract from this the extra interactions present in the conformations of 2-ethyl- and 2-isopropyl-cyclohexanone in order to obtain their relative enthalpies H°. H° is here the enthalpy of a conformation relative to a hypothetical conformation free of skew interactions and with the same number of axial α-carbon-hydrogen bonds as cyclohexanone.

The extra interactions in 2-ethyl- and 2-isopropyl-cyclohexanone compared with 2-methylcyclohexanone are analogous to the interactions in the set of conformations of butyraldehyde with a skew chain of carbon atoms ('skew butanal')* and various orientations of the aldehyde group. If two hydrogen atoms of a methyl group of butane in the skew conformation (XVII) are replaced by an oxygen atom then three conformations of butyraldehyde result.† The hydrogen-hydrogen interaction (h kcal mole^{-1}), which is probably the main cause of the instability of the skew conformation of butane, is either left substantially unchanged, as in XVIIIa, or is replaced by an interaction between the methyl group and the π-electrons of the carbonyl group ('π-skew butanal interaction', π kcal mole^{-1}), as in XVIIIb, or is replaced by an interaction between the methyl group and an unshared pair of electrons on the oxygen atom ('*n*-skew butanal interaction', *n* kcal mole^{-1}), as in XVIIIc. The conformation (XVIIIa), of course, has no relevance to the behaviour of ketones but the interactions in XVIIIb and XVIIIc are related to the alkylketone effects as conceived by Klyne. Although the rather severe methyl-oxygen repulsion in XVIIIc could be relieved considerably by partial rotation of the aldehyde group without much torsional strain developing, the analogous conformation of a 2(eq)-alkylcyclohexanone is more rigid because rotation is then limited to bonds between tetrahedral carbon atoms, for which barriers to rotation are much higher than for a bond to an aldehyde group.[7]

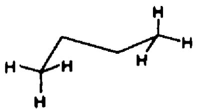
Replacement of a hydrogen atom X by a methyl group introduces one skew butane interaction ($h = +0{\cdot}9$ kcal mole^{-1} seems to be the best value for cyclic systems) into each of the conformations XIIIa to XVIa. In contrast, the replacement of the hydrogen atoms Y by methyl groups introduces an *n*-skew butanal interaction into XIIIa, a π-skew butanal interaction into XIVa, and skew butane interactions into XVa and XVIa, while replacement of hydrogen atoms Z by methyl groups causes two skew butane interactions in XVa and one skew butane and one *n*-skew butanal interaction in XIIIa. Because the carbonyl group and the $C_{(2)}$-equatorial bond in cyclohexanone are not quite coplanar, the oxygen atom in XIII is rather closer to a methyl group at Y than to one at Z, so that the methyl-oxygen repulsion in XIIIc will be slightly greater than the repulsion in the conformation XIIId. These interactions will be further modified by slight rotations of the 2-alkyl substituents to minimize the total strain. This rotation is both easier and more important for relieving strain when the methyl group is at Y than when it is at Z, because in the latter position the methyl group moves nearer the axial 3-hydrogen atom as it moves away from the oxygen atom. As a first approximation, therefore, we will assume that methyl groups at Y and Z in XIII are equally hindered by the oxygen atom. In order to analyse the 2-alkylketone effects for ethyl and isopropyl it is necessary to have a rough estimate of how the *n*- and π-skew butanal and skew butane interactions compare. From the 3-alkylketone effects for 3-methyl- and 3-isopropyl-cyclohexanone (Table 3) it is clear that the π-skew butanal interaction is likely to be less than 0·9 kcal mole^{-1}. An approximate value of the *n*-skew butanal interaction is given directly by the free

---

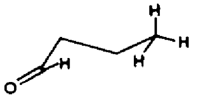
* This seems a rather more appropriate terminology than "1-butanone" interactions.[8]

† Since the carbonyl group eclipses a carbon-hydrogen or carbon-carbon bond these are true conformations.[7]

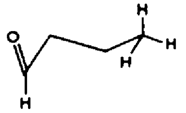
energy difference, $\Delta F_{298} = +2{\cdot}1$ kcal mole^{-1}, for the isomerization of 5α- to 5β-cholestan-4-one. If the interaction between the $C_{(19)}$-methyl group and the carbonyl group and the 2β-hydrogen atom in XIX are taken to be equivalent to the interactions between the $C_{(9)}$-methine group and the carbonyl group and the 2α-hydrogen atom in XX, then the difference in stability found for the two ketones is a measure of the *n*-skew butanal interaction between the carbonyl group and the 7α-hydrogen atom. Although appreciable entropy differences have been found for the isomerization of *trans-* to *cis*-decalin derivatives, it still seems certain that the enthalpy difference associated with an *n*-skew butanal interaction is considerably greater than $+0{\cdot}9$ kcal mole^{-1}, and we will assume initially that it is $+2{\cdot}0 \pm 0{\cdot}5$ kcal mole^{-1}. It is worth noting that Klyne[2] assumed that the *n*-skew butanal and skew butane were similar and Rickborn[5] implied this in his discussion of the 2-alkylketone effect. Allinger *et al.*[13] furthermore, claimed that the free energy difference found for the isomerization of 5α- to 5β-cholesten-4-one agreed with the difference in stability calculated by applying Hill's equation[15] to the repulsion between the carbonyl group and the 7α-hydrogen atom in XX ($-0{\cdot}88$ kcal mole^{-1}) and adding this to the difference in stability ($+0{\cdot}9$ kcal mole^{-1}) expected for the parent hydrocarbons, 5α- and 5β-cholestane (XXI and XXII). Since the relative stabilities of the hydrocarbons (XXI and XXII), making the usual assumptions about the equivalence of skew interactions, differ only by the presence of the skew interaction between the 4α- and 7α-hydrogen atoms in



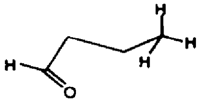
XVII



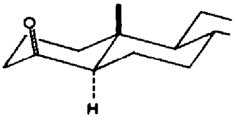
XVIIIa



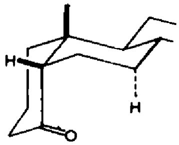
XVIIIb



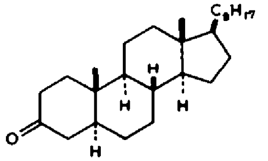
XVIIIc



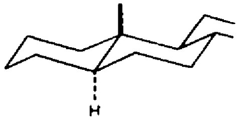
XIX



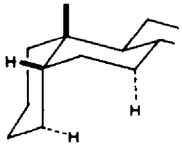
XX



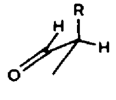
XXIII



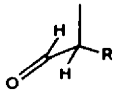
XXI



XXII



XXV



XXVI

---

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

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

[13] N. L. Allinger, M. A. Darooge and R. B. Hermann, *J. Org. Chem.* **26**, 3626 (1961).

[14] N. L. Allinger and J. L. Coke, *J. Org. Chem.* **26**, 2096 (1961).

[15] T. L. Hill, *J. Chem. Phys.* **16**, 399 (1948).

XXII which is not present in the ketone (XX), it is clear that the Allinger *et al.* calculation is mistaken and that there is a large discrepancy between the calculated and experimental values for the n-skew butanal repulsion in XX.

Using π ($< +0{\cdot}9$ kcal mole^{-1}) for the π-skew butanal interaction and n ($+2{\cdot}0 \pm 0{\cdot}5$ kcal mole^{-1}) for the n-skew butanal interaction, and assuming that the enthalpy difference between the two chair conformations of 2-methylcyclohexanone is $+2{\cdot}1_7$ kcal mole^{-1}, the relative enthalpies of the conformations of 2-ethylcyclohexanone are as follows.

$H^\circ(\text{XIIIb}) = +0{\cdot}9$ kcal mole^{-1}
$H^\circ(\text{XIIIc}) = n$ kcal mole^{-1}
$H^\circ(\text{XIIId}) = n + 0{\cdot}9$ kcal mole^{-1}
$H^\circ(\text{XIVb}) = +2{\cdot}1_7 - 0{\cdot}9$ kcal mole^{-1}
$H^\circ(\text{XIVc}) = +2{\cdot}1_7 + \pi$ kcal mole^{-1}
(Conformation XIVd is neglected)

If it is assumed that these conformations have the same entropy then the relative enthalpies, $H_e(t^\circ)$ and $H_a(t^\circ)$, and the entropies of mixing, $S_e(t^\circ)$ and $S_a(t^\circ)$, of the sets of conformations with the ethyl group equatorial or axial may be calculated for any temperature t° and for various assumed values of π, in order to determine the value of π consistent with the observed enthalpy difference for the conformational equilibrium in 2-ethylcyclohexanone. The resulting range of values for π, $+0{\cdot}07 \pm 0{\cdot}05$ kcal mole^{-1} if n is assumed to be $+2{\cdot}0 \pm 0{\cdot}5$ kcal mole^{-1}, is so insensitive to the value assumed for the n-skew butanal interaction that it is unnecessary to recalculate π for the more precise value of n obtained from the 2-alkylketone effect for 2-isopropylcyclohexanone.

The relative enthalpies of the conformations of 2-isopropylcyclohexanone, following the method outlined above for 2-ethylcyclohexanone, are:

$H^\circ(\text{XIIIe}) = +0{\cdot}9 + n$ kcal mole^{-1}
$H^\circ(\text{XIIIf}) = +1{\cdot}8 + n$ kcal mole^{-1}
$H^\circ(\text{XIIIg}) = +0{\cdot}9 + 2n$ kcal mole^{-1}
$H^\circ(\text{XIVe}) = +2{\cdot}1_7 + \pi + 0{\cdot}9$ kcal mole^{-1}
(Conformations XIVf and XIVg are neglected).

If we again assume that the various conformations have the same entropy then the calculation follows the same course as for 2-ethylcyclohexanone. In the present case, however, there is good reason to suppose that the entropy of the conformation (XIIIg) will be relatively low because the carbonyl oxygen atom will greatly hinder the libration of the isopropyl group in the same way that the t-butyl group is hindered in 2-t-butylcyclohexanone. Since this restriction of rotation of the isopropyl group will also diminish the extent to which the oxygen methyl repulsions can be relieved compared with the other conformations, $+0{\cdot}9 + 2n$ kcal mole^{-1} probably under-estimates the strain energy in the conformation (XIIIg). For these reasons the calculations have been carried out assuming either that the entropies of the conformations are equal and using the relative enthalpies given above or that the conformation (XIIIg) may be neglected completely. The latter assumption appears likely to be nearer the truth and on this basis $n = +1{\cdot}6$ kcal mole^{-1} if $\Delta H_{(e\to a)}$ (2-isopropylcyclohexanone) $= +0{\cdot}3_7$ kcal mole^{-1}. As inclusion of the conformation (XIIIg) only changes the value of n by $+0{\cdot}08$ kcal mole^{-1} the choice is unimportant for these enthalpy calculations. At present it is not worth while considering the probable errors in the values of π and n given in Table 3 because we hope to study other ketones in the near future.

The entropy differences for the conformational equilibria in 2-ethyl- and 2-isopropyl-cyclohexanone may be calculated from the enthalpies of the individual conformations if we assume that the conformations to be included all have the same entropy. This assumption has already been made in the analysis of the 2-alkylketone effects but the entropy differences are more sensitive to errors in it. The entropies of mixing of the sets of conformations (XIIIb, c or d and XIVb, c or d) are $S_{e(298)} = +1{\cdot}0_6$ and $S_{a(298)} = 0{\cdot}9_9$ cal deg^{-1} mole^{-1} so that $\Delta S_{(e\rightarrow a)}$ (2-ethylcyclohexanone) $= -0{\cdot}0_7$ cal deg^{-1} mole^{-1} in agreement with Rickborn's experimental value. As we have assumed that in 2(ax)-isopropylcyclohexanone only the conformation (XIVe) need be considered, $\Delta S_{(e\rightarrow a)}$ (2-isopropylcyclohexanone) $= -S_{e(298)} = -1{\cdot}3_5$ or $-0{\cdot}9_4$ cal deg^{-1} mole^{-1} depending on whether the conformation (XIIIg) is or is not included. Since the observed entropy differences are $-0{\cdot}8$ and $-0{\cdot}5$ cal deg^{-1} mole^{-1} it appears better to neglect the conformation (XIIIg) as was suggested above. The agreement between the observed and calculated entropy differences indicates that the assumptions we have made in the enthalpy calculations, which are not very sensitive to small entropy differences, are valid.

Our analysis of the conformational equilibrium in 2-isopropylcyclohexanone leads to the prediction that the relative stabilities of the conformations of 2(eq)-isopropylcyclohexanone are in the order

$$(\text{XIIIe}) > (\text{XIIIf}) > (\text{XIIIg})$$

and this order would only be altered by rather large changes in the interactions assumed. When our work had been completed, Djerassi *et al.* reported that the circular dichroism of 2α-isopropyl-5α-cholestan-3-one (XXIII; R = i-Pr), unlike the 2α-methyl analogue (XXIII; R = Me), is temperature dependent.[16] The change to more positive values at low temperatures was intrepreted as due to an increase in the proportion of the conformation (XXIVf), "which seems reasonable since it (conformation XXIVf) does not exhibit the eclipsing between one of the methyl groups and the carbonyl function" present in the conformations XXIVe and XXIVg.[16] This conclusion seems to be questionable on two grounds. Firstly, the sign of the observed change of circular dichroism is only consistent with an increase in the proportion of conformation (XXIVf) at low temperatures if methyl groups at Y and Z are in front octants.[12] This appears to be excluded by the negative contribution made by the 2-t-butyl group in (−)-*trans*-2-t-butyl-5-methylcyclohexanone [absolute configuration as in VIIIa (R_1 = t-Bu, R_2 = Me)].[10] Secondly, neither Y nor Z *eclipse* the carbonyl group in XXIV if the 2α-substituent takes up the normal staggered orientation relative to the other groups attached to the 2-carbon atom. The main difference between methyl groups at Y and at Z in (XXIV) is the additional skew interaction with the $C_{(1)}$-methlyene group when the methyl group is at Z. We believe, therefore, that the temperature dependence of the circular dichroism of 2α-isopropyl-5α-cholestan-3-one is consistent with the relative stabilities of its conformations being

---

[16] K. H. Wellman, E. Bunnenberg and C. Djerassi, *J. Amer. Chem. Soc.* **85**, 1870 (1963).

in the order (XXIVe) > (XXIVf) > (XXIVg), which is analogous to the order we predict for the conformations of 2-iospropylcyclohexanone.

The enthalpy differences for the conformational equilibrium in 3-methylcyclohexanone (Table 3) calculated from the epimerization of 2,5-dimethyl- and of 2-t-butyl-5-methyl-cyclohexanone differ slightly and since the use of a 2-t-butyl substituent to lock conformations is suspect[17] the lower value is more reliable. The value reported by Allinger and Freiberg was obtained from the free energy difference for the *cis* to *trans* isomerization of 3,5-dimethylcyclohexanone ($\Delta F_{493} = +0{\cdot}67 \pm 0{\cdot}15$ kcal mole^{-1}) and an assumed entropy difference, so that the very good agreement with our result is partly fortuitous. The 3-alkylketone effect in 3-methylcyclohexanone is only about $-0{\cdot}5$ kcal mole^{-1}. This is less than Klyne estimated[2] and apparently significantly less than would be expected from the low value we have found for the π-skew butanal interaction ($\pi \simeq +0{\cdot}1$ kcal mole^{-1}). It appears that the skew interaction between the methyl group and the $C_{(5)}$-methylene group in 3(ax)-methylcyclohexanone ($\simeq +1{\cdot}2$ kcal mole^{-1}) may be slightly greater than a single skew interaction ($\simeq -0{\cdot}9$ kcal mole^{-1}) in (ax)-methylcyclohexane, a difference which may be due to differences in interatomic distances or in flexibility, or both.[4]

The conformational equilibrium in 10-methyl-*cis*-2-decalone (IX; R_1 = Me, R_2 = H) was studied because this ketone should provide a simple example of a 3-alkylketone effect in a multicyclic system. With the usual assumptions about skew interactions in cyclohexane rings it has been predicted[2,6,18] that the preferred conformation of *cis*-2-decalone and its 10-methyl derivative should be IXb, which should be more stable than the other two-chair conformation (IXa) by approximately the magnitude of the 3-alkylketone effect in 3-methylcyclohexanone, i.e., $-0{\cdot}5$ kcal mole^{-1}. A contrary conclusion has been reached from a study of the Cotton effect in (−)-10-methyl-*cis* 2-decalone (IX; R_1 = Me, R_2 = H).[12,19] The sign of the molecular rotation amplitude (a = −11) indicates that the conformation (IXa; R_1 = Me, R_2 = H), for which the octant rule predicts a negative effect, makes a greater contribution than the conformation (IXb; R_1 = Me, R_2 = H), for which a positive Cotton effect is predicted. This has been interpreted as evidence for the existence of a new and unexplained conformational effect outweighing the 3-alkylketone effect and making the conformation (IXa; R_1 = Me, R_2 = H) more stable than IXb (R_1 = Me, R_2 = H). In the absence of a method for estimating the magnitude of the molecular rotation amplitude as well as its sign for each conformation, however, the observed sign of the rotation amplitude of the mixture is not a sure guide to the relative stabilities, which are expected to be similar, of the individual conformations. The enthalpy difference, $\Delta H = -0{\cdot}4$ kcal mole^{-1}, for the reaction (IX; R_1 = Me, R_2 = βMe) → (IX; R_1 = Me. R_2 = αMe) agrees well with the 3-alkylketone effect in 3-methyl cyclohexanone. The entropy difference, uncorrected for selectivity in the gas chromatography detector, is negligible and unless the ionization detector used is at least as sensitive to the ketone IX (R_1 = Me, R_2 = αMe) as to the ketone IX (R_1 = Me, R_2 = βMe), which appears to be most improbable, the free energy and enthalpy differences will have the same sign. If our assignment of the configurations of the epimeric

---

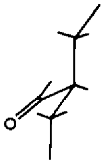
[17] N. W. J. Pumphrey and M. J. T. Robinson, *Tetrahedron Letters* 741 (1963).

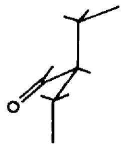
[18] D. A. H. Taylor, *Chem & Ind.* 250 (1954).

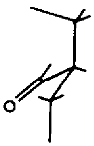
[19] C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.* **80**, 3986 (1958).

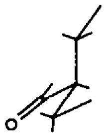
3,10-dimethyl-*cis*-2-decalones, which appear to be based upon sound analogies, are nevertheless incorrect then there is a discrepancy of $2 \times 0{\cdot}4 = 0{\cdot}8$ kcal mole^{-1} between the predicted and observed enthalpy differences.

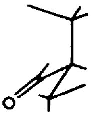
The isomerization of carvomenthone to isocarvomenthone[5] provides a model for the conformational equilibrium in 3-isopropylcyclohexanone.[4] The correction for the conformational equilibrium in isocarvomenthone, (VIIIb; R_1 = Me, R_2 = i-Pr) $\rightleftharpoons$ (VIIIc; R_1 = Me, R_2 = i-Pr), can not be made accurately because we have to assume, for lack of experimental evidence, that entropy changes may be neglected. On this basis we find $\Delta F_{(e\rightarrow a)} = \Delta H_{(e\rightarrow a)} \simeq +1{\cdot}6$ kcal mole^{-1} for 3-isopropylcyclohexanone. Since $\Delta F_{(e\rightarrow a)}$ and $\Delta H_{(e\rightarrow a)}$ are higher for isopropylcyclohexane than for methylcyclohexane, it is not surprizing that the 3-alkylketone effect is smaller in 3-isopropylcyclohexanone than in 3-methylcyclohexanone, but a detailed discussion must await more accurate experimental evidence.

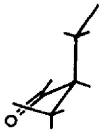

XXVIIa

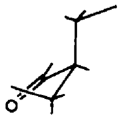

XXVIIb

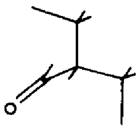

XXVIIc

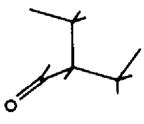

XXVIId

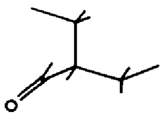

XXVIIe

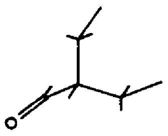

XXVIIf


XXVIIg


XXVIIIa


XXVIIIb/c


XXVIIId/e


XXVIIIf/g

The conformational equilibria in some simple aldehydes provide an interesting example of the operation of skew butanal interactions. Abraham[20,21] has studied the conformational equilibria in propionaldehyde,[20] isobutyraldehyde[21] and 2-ethylbutyraldehyde[21] by measuring the temperature dependence of the spin-spin coupling constants for the aldehydic and α-protons. The conformation (XXV) has a lower enthalpy than the conformation (XXVI) by $1{\cdot}0$ kcal mole^{-1} in propionaldehyde

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

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

(R = H) and by 1·2 kcal mole^{-1} in isobutyraldehyde (R = Me). These enthalpy differences are consistent with the properties of ketones with differing numbers of axial or similarly situated α-carbon-hydrogen bonds.[22] In 2-ethylbutyraldehyde, however, the set of conformations XXVII has a barely significantly higher enthalpy than the set XXVIII. Following the method used for 2-ethyl- and 2-isopropylcyclohexanone the sets of conformations (XXVII and XXVIII) may be derived hypothetically from the conformations, (XXV; R = Me and XXVI; R = Me), of isobutyraldehyde by replacing two hydrogen atoms in the latter by methyl groups. Each set has nine conformations of which two have severe methyl-methyl repulsions and may be neglected. The relative enthalpies of the remaining conformations may be estimated in terms of the skew butane interaction (h), the n- and π-skew butanal interactions (n and π) and the difference in stability, X, of XXV and XXVI. In this way it is found that all the permissible conformations of set XXVII have at least two of the larger skew interactions, and may have one π-skew butanal interaction as well:

H° (XXVIIa or b) $= h + n$ kcal mole^{-1}
H° (XXVIIc) $= \pi + h + n$ kcal mole^{-1}
H° (XXVIId) $= 2h$ kcal mole^{-1}
H° (XXVIIe) $= \pi + 2h$ kcal mole^{-1}
H° (XXVIIf or g) $= 2h + n$ kcal mole^{-1}
(Two conformations are neglected).

The conformations in the set XXVIII,* however, have only π-skew butanal and skew butane interactions:

H° (XXVIIIa) $= 2\pi + X$ kcal mole^{-1}
H° (XXVIIIb or c) $= \pi + 2h + X$ kcal mole^{-1}
H° (XXVIIId or e) $= \pi + h + X$ kcal mole^{-1}
H° (XXVIIIf of g) $= 2h + X$ kcal mole^{-1}
(Two conformations are neglected).

If we compare only the most stable conformations of each set then the observation that the enthalpy of the set XXVIII is equal to or slightly less than that of the set XXVII requires that $2\pi + X < 2h$ provided $h < n$, which agrees with the values of π, h and n used earlier. The values appropriate to a flexible aliphatic aldehyde, however, will be considerably lower than those found for cyclohexanones and the less stable conformations must be allowed for. We have, therefore, calculated the relative enthalpies of sets XXVII and XXVIII at 25°, assuming equal entropies for the individual conformations, for various assumed values of π, h and n to find those consistent with the observed enthalpy difference between the sets XXVII and XXVIII. The results are shown in Fig. 1, in which the regions to the right of the curves are consistent with the observed enthalpy difference. Two conclusions may readily be made from inspection of Fig. 1. Firstly, the results are not very sensitive to changes in the value of n in the range +0·8 to +1·4 kcal mole^{-1} which seems likely to include the correct average value. Secondly, only low values for the π-skew butane

---

* Six conformations of set XXVIII occur as mirror image pairs (b and c, d and e, f and g), of which only one enantiomorph from each pair is explicitly shown in the formulae.

[22] W. D. Cotterill and M. J. T. Robinson, *Tetrahedron Letters* 1833 (1963).

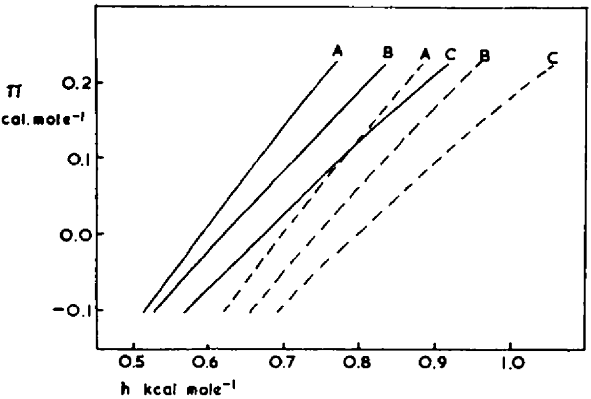


Fig. 1. Relationships between π-skew butanal and skew butane interactions satisfying the equation H°(XXVII) $\simeq$ H°(XXVIII) for various values of the n-skew butanal interaction (A, $n = 1{\cdot}4$; B, $n = 1{\cdot}0$; C, $n = 0{\cdot}8$ kcal mole^{-1}) and of X (Solid lines, $X = 1{\cdot}0$ kcal mole^{-1}, broken lines, $X = 1{\cdot}2$ kcal mole^{-1}).

interaction, $\pi < +0{\cdot}2$ kcal mole^{-1}, are consistent with the probable values of a skew butane interaction, $h = +0{\cdot}6$ to $+0{\cdot}8$ kcal mole^{-1}, if $X = +1{\cdot}0$ kcal mole^{-1} (from propionaldehyde) and even lower values of π are required if $X = +1{\cdot}2$ kcal mole^{-1} (from isobutyraldehyde).

Acknowledgements—We thank Dr. R. J. Abraham for communicating results prior to publication and D.S.I.R. for a maintenance grant (to W. D. C.).