Conformations of 1,1-Dimethyl-*trans*-decalin-10-carboxylic Acids[1a,b]

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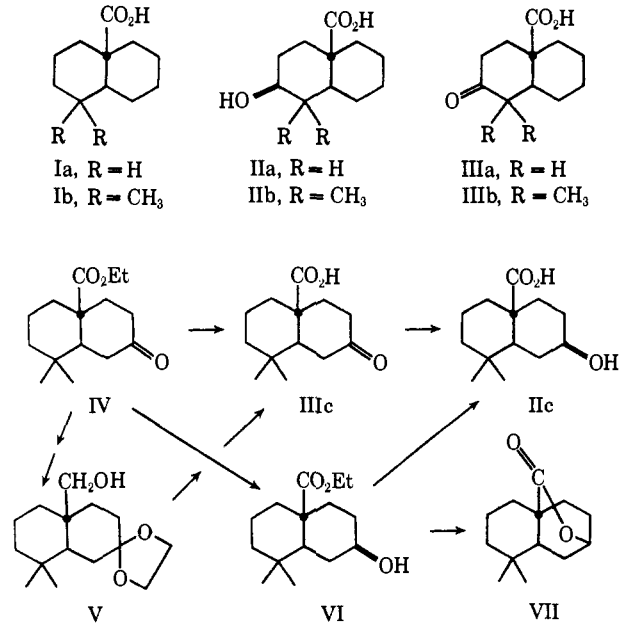
Abstract: Apparent acidity constants (pK_{MCS}*) were determined for *trans*-decalin-10-carboxylic acid, 1,1-dimethyl-*trans*-decalin-10-carboxylic acid, and their 2β- and 7β-hydroxy and 2- and 7-keto derivatives. The acid-strengthening effects of a 2β- and a 7β-hydroxyl group are identical, ΔpK_{MCS}* = 0.23, and the same in both the methylated and unmethylated series of acids, as is expected for all-chair decalin systems. The effect of a 2-keto group in the desmethyl series (ΔpK_{MCS}* = 1.00) is substantially greater than that of either a 2- or 7-keto group in the 1,1-dimethyl series (ΔpK_{MCS}* = 0.83 and 0.67, respectively), indicating that the ketonic rings of the methylated keto acids are not in chair conformations. Kirkwood–Westheimer calculations of the magnitudes of the pK* increments expected from field effects of hydroxyl and carbonyl groups in chair and nonchair forms support these conclusions. It is further found that in 95% ethanol and chloroform both methylated keto acids are in equilibrium with their pseudoacid forms, as is also the case for the 1,1-dimethyl-2-keto acid in 80% methyl Cellosolve, whereas no significant amount of the pseudoacid tautomer of the desmethyl keto acid is present in any of these solvents.

Some time ago we reported ^1H nmr data which indicated that the ketonic ring of a 1,1-dimethyl-10-carbethoxy-*trans*-2-decalone[2] occupies a nonchair conformation in preference to the chair which exists when C-2 is tetrahedrally substituted or the geminate methyl groups are absent.[3] The nmr technique which was employed in that study, *viz.*, observation of nonequivalence of the ethoxy *O*-methylene protons which is induced by their proximity to the axial 1β-methyl, was incapable of detecting conformational distortions in the unmethylated ring of the decalin system. In order to gain further insight into the conformational relationship between 1,1-dimethyl 10-substituted *trans*-decalins and their analogs which lack the geminate dimethyl substituents, we have now examined the acidities of a series of angular carboxylic acids. Changes in the conformation of either ring will result in changes in the proximity to the angular carboxyl of a polar substituent on that ring, and thus may be reflected by changes in acidity of the carboxyl group.

The group of acids whose ionization constants we wished to compare was *trans*-decalin-10-carboxylic acid (Ia)[4–6] and its 1,1-dimethyl derivative Ib,[7] together with their 2β- and 7β-hydroxy (IIa,[4,5] IIb,[8] and IIc) and 2- and 7-keto counterparts (IIIa,[8] IIIb,[8] and IIIc). Of this series, only 1,1-dimethyl-7β-hydroxy-*trans*-decalin-10-carboxylic acid (IIc) and its 7-keto analog IIIc have not been described previously. The keto acid IIIc was prepared by saponification of its known[7] ethyl ester IV, or by Jones oxidation and hydrolysis of the hydroxy ketal V, which was obtained by lithium aluminum hydride reduction of the ketal of keto ester IV. The hydroxy acid IIc was produced either by borohydride reduction of keto acid IIIc or by borohydride reduction of keto ester IV followed by saponification of the resulting hydroxy ester VI. Exposure of the hydroxy ester to more dilute alcoholic alkali afforded the lactone VII, which could also be obtained by heating the hydroxy acid. This confirms the assignment of a β con-



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(2) For convenience all decalins discussed herein are numbered with the bridgehead holding the carboxyl as C-10 and the methylated position as C-1. The configurational notations α and β are used to indicate a trans or cis relation to the angular group, respectively. All compounds were examined as racemates, although the prefix *dl* is omitted and only one enantiomer is depicted.

(3) W. L. Meyer, D. L. Davis, L. Foster, A. S. Levinson, V. L. Sawin, D. C. Shew, and R. F. Weddleton, *J. Amer. Chem. Soc.*, 87, 1573 (1965).

(4) A. S. Hussey, H. P. Liao, and R. H. Baker, *ibid.*, 75, 4727 (1953).

(5) W. G. Dauben, R. C. Tweit, and R. L. MacLean, *ibid.*, 77, 48 (1955).

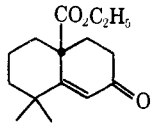
(6) P. D. Bartlett, R. E. Pincock, J. H. Rolston, W. G. Schindel, and L. A. Singer, *ibid.*, 87, 2590 (1965); R. E. Pincock, E. Grigat, and P. D. Bartlett, *ibid.*, 81, 6332 (1959).

(7) W. L. Meyer and A. S. Levinson, *J. Org. Chem.*, 28, 2184 (1963).

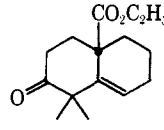
(8) A. S. Dreiding and A. J. Tomasewski, *J. Amer. Chem. Soc.*, 77, 411 (1955).

figuration to the hydroxyl group. It is interesting to note that the hydroxy ester VI can be isolated from borohydride reduction of the corresponding keto ester, in light of the fact that the same reduction of keto ester IX leads directly to lactone. Clearly the geminate dimethyl substitution sterically enhances lactonization in the latter case,[7] undoubtedly through destabilization of the chair–chair conformer of the hydroxy ester.

All of the geminate dimethylated acids have now been interrelated synthetically,[3,7] and consequently all have the same ring-fusion configuration. Assignment of this as trans rests on several lines of evidence. This is the exclusive stereoisomeric system produced by palladium-catalyzed hydrogenation of the unsaturated keto ester VIII in ethanol[7] or platinum-catalyzed hydrogenation of the unsaturated keto ester IX in acetic acid,[3,7] reactions which should involve approach of the catalyst to the less-hindered α face of the molecule. The acid Ib is a weaker acid than its ring-fusion epimer,[9] which is expected for the more hindered trans system. Finally the keto ester IV has been converted into *dl*-carnosic acid dimethyl ether and *dl*-carnosol by sequences which should not perturb the ring-fusion configurations.[10] These natural products are known to possess the trans A/B fusion.[11]



VIII



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The configuration of the desmethyl acids Ia, IIa, and IIIa has been well documented in the earlier literature.[4,5,12,13] For our work the hydroxy acid was prepared by hydrogenation of 10-carbethoxy-$\Delta^{1,9}$-2-octalone over platinum in ethanol,[4] sodium borohydride reduction of the resulting saturated keto ester, and saponification of the hydroxy ester. The hydroxy acid so obtained agreed in physical properties with those reported by Dauben,[5] and on Jones oxidation this acid was converted to the keto acid IIIa which has the same melting point as Dreiding and Tomasewski[8] report for the authentic trans keto acid.

Apparent dissociation constants for the eight acids were determined by titration in 80% methyl Cellosolve,[14] with the pH at half-neutralization being taken as pK_{MCS}*[14] (Table I). In the desmethyl series of acids a 2β-hydroxy substituent increases the acidity of the angular carboxyl by 0.24 pK_{MCS}* unit, while the 2-keto group produces a 1.00-unit increase. These increments are taken as the field effects of these polar substituents in an all-chair *trans*-decalin, for with four carbons between the carboxyl and the oxygen substituent any bond-polarization inductive effect is negligible. The assumption that these molecules have chair conformations seems justified by the absence of substituents whose nonbonded interactions would destabilize such

(9) R. F. C. Brown, *Aust. J. Chem.*, 17, 47 (1964).
(10) W. L. Meyer and E. Schindler, *Tetrahedron Lett.*, 4261 (1966); W. L. Meyer and D. C. Shew, *ibid.*, 2963 (1968).
(11) C. H. Brieskorn, A. Fuchs, J. B. Bredenberg, J. D. McChesney, and E. Wenkert, *J. Org. Chem.*, 29, 2293 (1964).
(12) W. G. Dauben, J. B. Rogan, and E. J. Blanz, Jr., *J. Amer. Chem. Soc.*, 76, 6384 (1954).
(13) A. S. Dreiding and A. J. Tomasewski, *ibid.*, 77, 168 (1955).
(14) W. Simon, *Angew. Chem., Int. Ed. Engl.*, 3, 661 (1964), and references therein.

Table I. pK_{MCS}* Values for Selected *trans*-Decalin-10-carboxylic Acids

Acid	pK_{MCS}*	ΔpK_{MCS}*[a]
Desmethyl series		
Ia	8.60[b]	
IIa (2β-OH)	8.36	0.24
IIIa (2-keto)	7.60[c]	1.00[c]
	(7.60)[d]	(1.00)[d]
1,1-Dimethyl series		
Ib	8.99[e]	
IIb (2β-OH)	8.78	0.21
IIc (7β-OH)	8.76	0.23
IIIb (2-keto)	8.16[c]	0.83[c]
	(8.38)[d]	(0.61)[d]
IIIc (7-keto)	8.32[c]	0.67[c]
	(8.35)[d]	(0.64)[d]

[a] pK_{MCS}* difference between the acid and its monofunctional parent Ia or Ib. [b] Reported 8.58 in ref 18. [c] Corrected for the pseudoacid–keto acid equilibrium; see text. [d] Uncorrected for the pseudoacid–keto acid equilibrium. [e] Reported 8.86 in ref 9 and 18.

forms.[15,16] The Kirkwood–Westheimer calculations discussed below support this premise.

Owing to the additional steric hindrance to solvation which the carboxyls of the 1,1-dimethyl acids experience, they are appreciably weaker than their unmethylated counterparts. For example, 1,1-dimethyl-*trans*-decalin-10-carboxylic acid (Ib) has pK_{MCS}* 8.99[17] compared to 8.60 for its desmethyl homolog Ia. The dimethyl acid Ib is substantially weaker than the Simon correlation[18] predicts (calcd 8.66), undoubtedly a reflection of the fact that a 1,3-methyl–carboxyl interaction cannot be equated with a 1,3-hydrogen–carboxyl interaction in all cases.[18] So long as the conformation of the bicyclic system and the nature of the axial substituents which hinder the carboxyl do not change, however, this hindrance to solvation should remain constant, and introduction of a polar group should produce a change in acidity which is related only to the dipolar nature of the substituent and its position with respect to the carboxyl group. Thus, if the conformations of the desmethyl and dimethyl systems are the same, introduction of a polar group at a given position should produce the same relative effect on the acidity of each. That this is in fact the case can be seen from the acidities of the three hydroxy acids. A β-oriented hydroxyl group in either the 2 or 7 position of the dimethyl acid strengthens the acid by 0.22 ± 0.01 pK_{MCS}* unit, as should be the case since the two locations are equivalent in distance and direction from the carboxyl. This is identical with the effect of the 2β-hydroxyl on the desmethyl acid, where again the distance involved is identical when all the compounds have chair conformations. The identity of these pK_{MCS}* increments consequently supports assignment of chair conformations to the

(15) N. L. Allinger, J. Allinger, and M. A. DaRooge, *J. Amer. Chem. Soc.*, 86, 4061 (1964).
(16) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 469–486, and references therein.
(17) Brown[9] and Simon[18] reported Ib to be a slightly stronger acid, pK_{MCS}* 8.86, than our results indicate. The correspondence of our values for benzoic acid (6.71) and Ia (8.60) with those of Simon [6.63 and 8.58, *cf.* W. Simon, A. Morikofer, and E. Heilbronner, *Helv. Chim. Acta*, 40, 1918 (1957), and ref 18] indicates that this discrepancy is not the result of differences in technique. It may result from contamination of their sample of Ib with the cis isomer, *cf.* ref 9.
(18) P. F. Sommer, C. Pascual, V. P. Arya, and W. Simon, *ibid.*, 46, 1734 (1963); P. F. Sommer, V. P. Arya, and W. Simon, *Tetrahedron Lett.*, No. 20, 18 (1960).

Table II. Ultraviolet Spectra of Keto Acids and Esters[a]

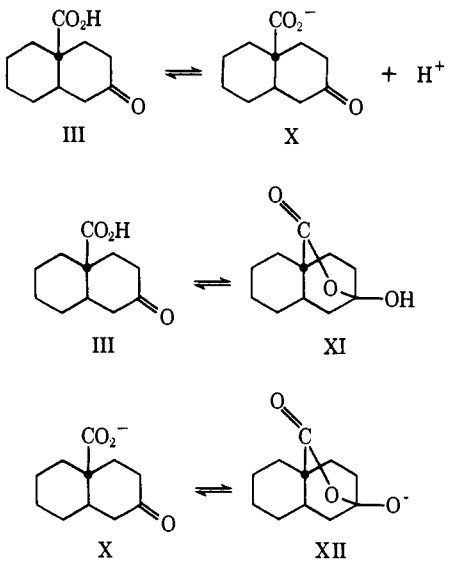
Compd (solvent[b])	Acid λ_{max}	Acid ϵ_{max}	Ester λ_{max}	Ester ϵ_{max}	% keto acid[c]	K_t	Log $(1 + K_t)$	pK^* corr	ΔpK^* corr
IIIa (EtOH)	285	20.5	282	22.5	95	0.053	0.02		
(MCS)	280	24			100	0	0	7.60	1.00
(Chf)	285	20			93	0.075	0.03		
(base)	282	24							
IIIb (EtOH)	286[d]	11[d]	284[e,f]	25[e,f]	55	0.96	0.29		
(MCS)	285	13			60	0.67	0.22	8.16	0.83
(Chf)	290	7.5			35	1.86	0.46		
(base)	287	26.5							
IIIc (EtOH)	280	8.2	282	20	38	1.63	0.42		
(MCS)	280	19.3	282	19	90	0.11	0.05	8.32	0.67
(Chf)	278	11	285	21	51	0.96	0.29		
(base)	280	27.5							

[a] Average of two or more determinations on independently prepared samples; $\lambda_{max} \pm 1$ nm, $\epsilon_{max} \pm 1.5$ or less. [b] EtOH = 95% ethanol, MCS = 80% methyl Cellosolve, Chf = chloroform, base = 0.14 *N* ethanolic potassium hydroxide. [c] Observed $\epsilon \times 100/21.5$; 21.5 being the average ϵ for the keto esters of this series. [d] Reported λ_{max} 287 (ϵ 12) in ref 3. [e] The reported λ_{max} 280 (ϵ 55) of ref 3 is in error. [f] Single determination.

three hydroxy acids. It further indicates that the effect of a substituent does not vary significantly due to its proximity to a highly substituted site (compare IIb and IIc).

Before the acid-strengthening effect of a keto group in the dimethyl acid series could be interpreted in terms of the conformations of this system, another aspect of the structure of the keto acids required investigation. If nonchair conformations are involved, the carboxyl and keto groups may be in suitable proximity for pseudoacid formation to be important (*e.g.*, III $\rightleftharpoons$ XI). In fact, we have already noted evidence for partial existence of keto acid IIIb as a pseudoacid in chloroform and in 95% ethanol.[3] Such keto acid–pseudoacid equilibria should be rapid in the presence of base,[19] *i.e.* under the titration conditions, and consequently the dissociation equilibrium (K_a^*, eq 1) and the tautomeric equilibrium (K_t, eq 2) must be simultaneously satisfied. Determination of the apparent dissociation constant as the hydrogen ion activity at half-neutralization, however, depends on the assumption that at that point the concentrations of un-ionized acid and its anion are equal, and this will definitely not be the case if the keto acid is in equilibrium with the pseudoacid. Essentially none of the anion should exist as the pseudoacid anion XII,[19] for in such a structure there is no delocalization of the negative charge (experimental support for this contention is described later). Hence, all of the acid which has been neutralized (one-half of the initial amount when the half-equivalence point is reached) is present as keto anion X, whereas only a fraction $(1/(1 + K_t))$ of the remaining un-ionized acid is present as the keto acid III. The ratio [HA]/[A$^-$] in eq 3 thus is less than unity at half-neutralization, and the pH is greater than the pK_a^* of the keto acid. Nonetheless, if K_t can be independently evaluated, the pK_a^* of interest can still be deduced, for at half-neutralization the expression (4) can readily be derived from eq 1–3.[20]

In order to estimate the keto acid–pseudoacid equilibrium constants (K_t), we examined the ultraviolet spectra of the three keto acids.[21] It was assumed that the



$$K_a^* = [H^+][X]/[III] \quad (1)$$

$$K_t = [XI]/[III] \quad (2)$$

$$pK_a^* = pH + \log [HA]/[A^-] \quad (3)$$

$$pK_a^* = pH - \log (1 + K_t) \quad (4)$$

pseudoacid would be transparent in the 280-nm region and that the ketonic n $\rightarrow$ π^* extinction coefficients would not be greatly altered by the difference between an angular carboxy and an angular carbethoxy group,[22] so that the fraction of keto acid at equilibrium would be given directly by the ratio of the extinction coefficient of the acid to that of a model keto ester for which such tautomerism is impossible. As the model keto ester extinction coefficient, we chose to use 21.5, which is the average of the observed ϵ's of the three keto esters corresponding to IIIa, IIIb, and IIIc.[23]

(19) R. E. Lutz, P. S. Bailey, C. Dien, and J. W. Rinker, *J. Amer. Chem. Soc.*, 75, 5039 (1953).

(20) C. Pascual, D. Wegmann, W. Graf, R. Scheffold, P. F. Sommer, and W. Simon (*Helv. Chim. Acta*, 47, 213 (1964)) have used an equivalent expression for estimating K_t's of a series of γ-keto acids for which pK_a^* was estimated from model compounds.

(21) M. S. Newman and C. W. Muth, *J. Amer. Chem. Soc.*, 73, 4627 (1951); see also ref 19.

(22) R. Cookson, *J. Chem. Soc.*, 282 (1954); R. Cookson and S. Dandegonker, *ibid.*, 352 (1955).

(23) We prefer to use this average value rather than compare each acid with its own ester because only a small quantity of the ester of IIIb, a liquid, was on hand, and only a single determination of its spectrum on a suitably purified sample was made, in contrast to the multiple determinations which were carried out for other substances. While glc showed this sample of IIIb ester to be at least 99% pure, in view of the very low ϵ's involved here, trace contamination might have contributed slightly but significantly to the observed absorption. If, however, the slightly higher ϵ recorded for this ester (25) is used as the basis for cal-

Results are presented in Table II. The desmethyl keto acid IIIa, which is not expected to exist in a nonchair conformation or as a pseudoacid, indeed has an extinction coefficient in 80% methyl Cellosolve which is essentially the same as that of the ester model. The ultraviolet data likewise indicate that in 80% methyl Cellosolve there is no significant pseudoacid formation from the 1,1-dimethyl-7-keto acid (IIIc). The 1,1-dimethyl-2-keto acid (IIIb), however, has an extinction coefficient which is somewhat more than half that of its ester, and thus the true keto acid form makes up but 60% of the equilibrium mixture. Correction of the observed pK_{MCS}* by a K_t of 0.67 leads to a true pK_{MCS}* of 8.16 for this compound, and a ΔpK_{MCS}* of 0.83 for introduction of the 2-keto group into Ib.

The salts of all three of the keto acids showed extinction coefficients slightly greater than those of their ethyl esters. This seems to be a clear justification of the assumption that there is no lactonic contribution to the structure of the keto anions (X $\rightleftharpoons$ XII), as is necessary for derivation of eq 4.

It should be noted that these tautomeric equilibrium constants, K_t, for 80% methyl Cellosolve need not apply to other solvents or to the solid state. In fact, infrared spectra of both methylated keto acids in potassium bromide suspension show a sharp hydroxyl absorption near 3.0 μ rather than the 3.2–3.8 μ absorption expected for the dimeric carboxyl; the unmethylated keto acid, on the other hand, has the typical carboxylic OH absorption rather than the alcoholic band. In chloroform solution the unmethylated keto acid IIIa absorbs at 3.2–3.5 and at 5.87 μ, as is expected for the keto acid form, but the two methylated acids have absorption in the 2.8- and 3.0-μ region and at 5.76 μ as well as between 3.3 and 4.2 and at 5.9 μ. These infrared data indicate that both dimethylated acids are almost exclusively in the lactol form in the solid state and extensively so in chloroform, whereas the unmethylated acid exists as the keto acid form in both these states. Ultraviolet spectra (Table II) also indicate a substantial lactol contribution to the equilibrium of both dimethylated keto acids in chloroform and in 95% ethanol.[24]

Using values of pK_{MCS}* which have been corrected for the presence of pseudoacid, one finds that the effect of introducing a keto group into the parent acids Ia and Ib is 1.00, 0.83, and 0.67 pK_{MCS}* units for the desmethyl acid (IIIa), the dimethyl-2-keto acid (IIIb), and the dimethyl-7-keto acid (IIIc), respectively. Since the desmethyl keto acid is a model for the chair conformation and the data from hydroxy acids indicate that the acidity enhancement due to a polar substituent should not change if the conformation does not change, it seems clear that the ketonic rings of the dimethyl keto acids IIIb and IIIc are not in chair conformations.

While it is clear that a change in the acid-strengthening effect should indicate a change in conformation, it is not *a priori* necessary that the converse is true, *i.e.*, that no difference in acid-strengthening effect means that the conformations of a substituted acid and the model acid are identical. The effect of a remote dipolar substituent on the ionization of an acidic proton is a function not only of the distance between the ionizing proton and the dipole, but on the angular orientation of the dipole with respect to the proton, and in principle it might have been possible for the distance and angle effects to cancel following a conformation change. In order to learn (a) whether the relative pK* increments for hydroxy and keto group introduction into the desmethyl acid IIIa were of the magnitude which should be expected for a chair form of this system, (b) whether the change in the keto group's effect in the dimethyl keto acids (a *decrease* in acid-strengthening influence compared to that in IIIa) was in a reasonable direction for transformation into a nonchair conformation, and (c) whether transformation into all reasonable nonchair conformations should produce a change in ΔpK_{MCS}* from that observed in the chair desmethyl system, we have attempted to calculate the approximate effects to be expected for various conformations of the 2-keto-*trans*-decalin-10-carboxylic acid system. These calculations were carried out using the Kirkwood–Westheimer modifications[25] of Bjerrum's equation[26] for determining the electrostatic influence (field effect) of an electric dipole on the ionization of a protonic acid (eq 5).

$$\Delta pK = \frac{Ne\mu \cos\theta}{2.30RTD_E r^2} \qquad (5)$$

Application of the Kirkwood–Westheimer eq 5 for calculation of the influence of a point dipole on the ionization of an acid requires knowledge of the distance (r) and angle (θ) between the departing proton and the dipole (μ) and on the nature (shape and dielectric constant) of the cavity in which the proton and dipole are located. The greatest difficulty in utilizing the relationship derives from incomplete understanding of the dielectric cavity;[25,27–29] this is usually not only solvent, but includes parts of the molecule itself, and its shape and dielectric properties are difficult to assign on an *a priori* basis. For the present problem we made no attempt to arrive at these properties from theory. Rather, we assumed that the shape of the cavity and its dielectric constant were the same in the keto acids and the hydroxy acids. Then by assuming that the hydroxy acids were all in chair forms, which seems justified both on conformational analysis grounds and by the identical pK_{MCS}* increment found for all three of them, we used the observed pK* increment together with angles and distances computed from the geometry of a chair cyclohexane[30] to compute the effective dielectric constant (D_E) appropriate to this system. The value so derived, 4.8, is quite reasonable when compared with those which have given acceptable results with other systems.[27–29,31,32] Using this value of the dielectric constant to compute the pK* increment expected for a 2-keto group in a chair system,[30] one obtains a factor of

culating K_t in this series, one finds that 52% rather than 60% of IIIb exists in the keto acid form in 80% MCS, which leads to an additional 0.06-unit correction in pK_{MCS}* and a corrected ΔpK_{MCS}* for the 2-keto group of 0.89. The conformational conclusions would be unaltered.

(24) Dependence of the position of the keto acid–pseudoacid equilibrium upon solvent is, of course, not unexpected; *cf.* ref 20.

(25) (a) F. H. Westheimer, *J. Amer. Chem. Soc.*, **61**, 1977 (1939); (b) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506 (1938); (c) F. H. Westheimer and J. G. Kirkwood, *ibid.*, **6**, 513 (1938).

(26) N. Bjerrum, *Z. Phys. Chem.*, **106**, 219 (1923).

(27) F. H. Westheimer, W. A. Jones, and R. A. Lad, *J. Chem. Phys.*, 10, 478 (1942).

(28) T. L. Hill, *J. Phys. Chem.*, 60, 253 (1956).

(29) C. Tanford, *J. Amer. Chem. Soc.*, 79, 5348 (1957).

(30) See the Experimental Section for details.

(31) J. D. Roberts and W. T. Moreland, *J. Amer. Chem. Soc.*, **75**, 2167 (1953).

(32) H. D. Holtz and L. M. Stock, *ibid.*, **86**, 5188 (1964); F. W. Baker, R. C. Parish, and L. M. Stock, *ibid.*, **89**, 5677 (1967).

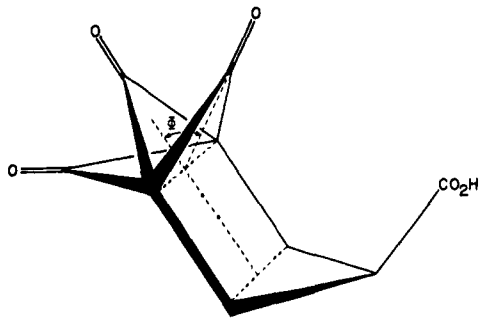


Figure 1. Conformations of cyclohexanone-4-carboxylic acid as a function of the angle Φ as used in application of eq 5.

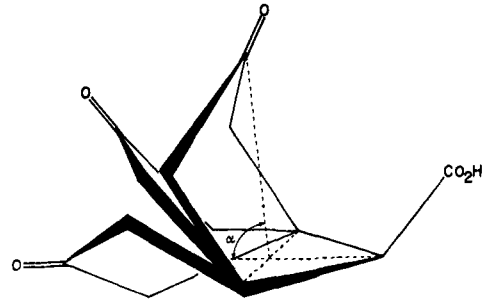


Figure 2. Conformations of cyclohexanone-4-carboxylic acid as a function of the angle α as used in application of eq 5.

1.1 pK* units. This is in very comfortable agreement with the 1.0 unit observed for the unmethylated keto acid IIIa, which is expected to exist in the chair conformation.

The acid-strengthening effect of a keto group was also calculated for a variety of nonchair conformations of the ketonic ring. Ring geometries were calculated from bond length and bond angle data[30] for the conformations which occur (a) as the cyclohexanone-4-carboxylic acid ring passes from chair to boat by movement of the carbonyl carbon (C-1) through the plane of the α and β carbons, and (b) as the ring undergoes the boat–twist pseudorotation.[15] The former set of conformations is conveniently defined in terms of the angle (Φ) which is the supplement of that formed by the projections of the 1,2 bond and the 2,3 bond on the plane formed by C-1, C-4, and the carboxyl carbon (Figure 1). We have found it convenient to define the geometry of the latter set in terms of the angle (α) which is the supplement of that formed by the projections of the 3,4 bond and a line joining C-1 to C-3 on the C-1–C-4–carboxyl carbon plane (Figure 2).[33] The results are shown in Figure 3 as a function of the computed ΔpK_{MCS}* *vs.* Φ and α. As can be seen, any of these nonchair forms is calculated to

(33) If cyclohexanone in a pure boat conformation with the keto group at the prow is placed in a coordinate system such that C-3, C-4, and C-5 are in the xy plane with the x axis bisecting the C-4 valence angle, one-half of the pseudorotational cycle (ref 15) may be examined by holding C-3, C-4, and C-5 in fixed locations while C-1 moves from its original position (x^0, y^0, z^0) through the x axis to a location (x^0, y^0, $-z^0$), with appropriate accompanying movements of C-2 and C-6. We have found this representation of the motion quite easy to program in terms of the angle (α), which is the reason for selection of α as the conformationally descriptive parameter rather than the conceptually simpler pseudorotational parameter θ used by Allinger and others, *cf.* ref 15. Unfortunately, a simple and precise relation between α and θ is unavailable. It is clear that the θ = 0° boat corresponds to the maximum value α can assume (α_{max}), and the θ = 90° twist corresponds to α = 0°. The θ = 30° twist and the θ = 60° boat turn out to correspond approximately, but not exactly, to $\alpha = 0.833\alpha_{max}$ and $0.5\alpha_{max}$ respectively.

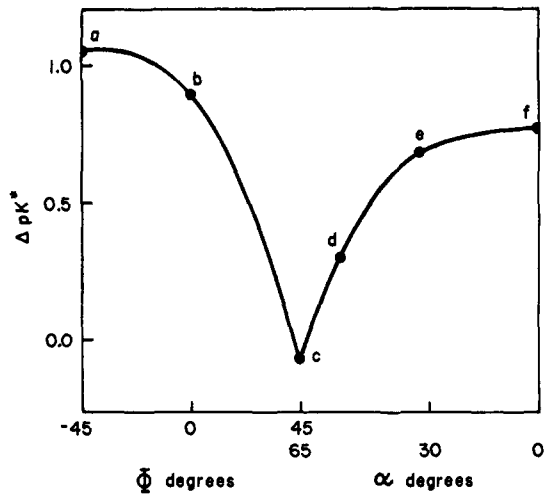


Figure 3. Dependence of ΔpK* of a cyclohexanone-4-carboxylic acid on its conformation, as predicted by eq 5. Conformations are defined in terms of the angles Φ and α (Figures 1 and 2). Labeled points correspond to: (a) chair, (b) flat chair, (c) boat with C=O at prow, (d) twist with C=O not on C_2 axis, (e) boat with C=O on gunwale, and (f) twist with C=O on C_2 axis.

have a smaller ΔpK_{MCS}* than that of the chair. Thus, the observed ΔpK_{MCS}* for the 1,1-dimethyl-2- and 7-keto acids IIIb and IIIc are indeed in the correct direction and of an appropriate magnitude to correspond to nonchair conformations of the ketonic ring, as concluded above.[34]

Although the ΔpK_{MCS}* of 0.67 for the 1,1-dimethyl-7-keto acid (IIIc) seems to be a clear indication that its ketonic ring is not in a chair form, that of the 1,1-dimethyl-2-keto acid (IIIb) (ΔpK_{MCS}* 0.83) may deserve further comment. One might well ask why the increment should be less for a nonchair form of the methylated ring than it is for a nonchair form of the unmethylated ring. Of course, one answer would be simply that different nonchair forms are involved, and another would observe that part of the difference might result from uncertainties in determining the correction of the value for IIIb due to the pseudoacid equilibrium. However, it is significant to note that these are not necessarily the only possible reasons. Unlike the situation in

(34) Although it might be tempting to use the results of the Kirkwood–Westheimer calculations and the observed ΔpK_{MCS}* to deduce the exact nonchair conformation which is involved, this would be unwarranted. The approximations and assumptions which are involved in the calculations are sufficiently imprecise that the calculated ΔpK_{MCS}* for any fixed conformation might well differ by 20–30% or more from the actual ΔpK_{MCS}*. The general difficulties in quantitative application of this theory have been well discussed elsewhere, *cf.* ref 29, 31, 32, and S. Siegel and J. M. Komarmy, *J. Amer. Chem. Soc.*, **82**, 2547 (1960). In addition, for example, in our system it is not completely clear how best to treat the hydroxyl dipole [*cf.* M. Kilpatrick and J. G. Morse, *ibid.*, 75, 1846 (1953) for a reasonable alternative], the shape of the dielectric cavity (and thus D_E) probably does change somewhat as the conformation of the ketonic ring changes, and we cannot be sure that the conformations of the acid and its anion are identical. Furthermore, the imprecision of the ultraviolet technique for determining K_t leads to an uncertainty of the probable magnitude of ±0.06–0.08 in the corrected pK_{MCS}* values of IIIb. We thus consider the results of the calculations only as support for interpretation in terms of conformation of the magnitudes of the ΔpK*'s and the direction in which they change on passing from compound to compound. Consequently, although calculations of the Allinger type (ref 15) suggest that both 1,1,10-trimethyl-*trans*-7-decalone and 1,1,10-trimethyl-*trans*-2-decalone should probably prefer flat chair conformations to chairs or flexible forms (R. W. Howard, M.S. Thesis, University of Arkansas, 1971), we do not suggest that something close to the flat chair (Figure 1, Φ = 0°) is given more compelling experimental support by the pK* data than are various other nonchair possibilities. It should also be noted that our data are equally consistent with the existence of IIIc as a single nonchair conformation or as an equilibrium mixture of several conformers at least one of which is nonchair.

IIIc, when the ketonic ring of IIIb is in a nonchair form the methyl groups are moved away from the carboxyl and the steric hindrance to solvation is appreciably diminished. This will have an acid-strengthening influence which will partially or completely offset the acid-weakening electrostatic effect due to reorientation of the carbonyl dipole. Such a change in steric hindrance to solvation could affect the acidity by as much as 0.3–0.4 pK_{MCS}* unit if the difference between the parent acids Ia and Ib is taken as an example, and superimposed on a ΔpK_{MCS}* of 0.6–0.7 for a nonchair form (as in IIIc), this would lead to an observed ΔpK_{MCS}* near 1.0. Thus, when the conformational distortion concerns the *methylated* ring, the ΔpK* for a nonchair may not differ greatly from that for a chair. Nonetheless, the fact that there is such a large proportion of pseudoacid in equilibrium with keto acid IIIb indicates that the conformation of the keto acid is much closer in energy to a nonchair system than is the case when the methyls are absent, a result which is completely consistent with the earlier conclusion that this system, too, is in a nonchair form. Thus, we feel that the pK* of IIIc and both the pK* and the pseudoacid equilibrium of IIIb indicate that these methylated acids are not in chair–chair conformations in 80% MCS. In view of the positions of the pseudoacid equilibria in ethanol and chloroform, these conformational conclusions can probably be extended to other solvents as well.

These results reinforce the conclusion that 1,1-dimethyl substitution and a trigonal carbon in the same ring of a *trans*-decalin-10-carboxylic acid give rise to a nonchair conformation of that ring.[3] They also indicate that dimethyl substitution and trigonal carbon in opposite rings lead to a nonchair form. The 1,1-dimethyl-2-keto acid (IIIb) is analogous to the A/B ring system of the 4,4-dimethyl-3-keto steroids and terpenoids, which a number of investigations have shown occur in A-ring nonchair conformations. This type of conformational distortion, which among other things relieves the syn-axial interactions of the methyl group with the angular substituent and two hydrogens, has been extensively discussed.[16] In the case of the 1,1-dimethyl-7-keto acid (IIIc) distortion of the ketonic ring to a nonchair relieves neither the syn-axial methyl–angular group interaction nor the syn-axial methyl–hydrogen interaction in the methylated ring, and yet the relief of other interactions (most notably those between the two methyls and the two peri hydrogens of the adjacent ring) is sufficient to render the nonchair more stable than or comparable in stability to the chair.

Experimental Section[35]

1,1-Dimethyl-*trans*-7-decalone-10-carboxylic Acid (IIIc). A. Saponification of Keto Ester IV. A solution of 0.758 g (0.00286 mol) of 1,1-dimethyl-10-carbethoxy-*trans*-7-decalone (IV),[7] mp 45–46.5°, and 2.22 g (0.039 mol) of potassium hydroxide in 100 ml of water and 50 ml of methanol was heated under reflux for 216 hr. The mixture was cooled, washed with ether, acidified with hydrochloric acid, and extracted with ether. Evaporation left 0.41 g (60%) of the crude crystalline keto acid IIIc, which was recrystallized from cyclohexane–methylene chloride to afford the keto acid as fine white needles: mp 124.2–125.7°; $\lambda_{max}^{CHCl_3}$ 2.77, 3.0 (broad), 3.2–4.2, 5.76, 5.88 μ; λ_{max}^{Kllr} 2.94, 5.80 μ (no CO*OH*); nmr (deuterioacetone) τ 9.17 (s) and 9.22 (s); $\lambda_{max}^{95\%\ EtOH}$ 280 nm (ϵ 8.2).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.29; H, 8.89.

B. *Via* Hydroxy Ketal V.[36] A mixture of 3.1 g (0.012 mol) of keto ester IV, 10 ml of ethylene glycol, 4 mg of *p*-toluenesulfonic acid, and 15 ml of benzene was refluxed for 21 hr under a Dean–Stark trap, cooled, and partitioned between ether and 5% sodium bicarbonate which was subsequently washed with ether. The ether solution was washed with brine, dried over magnesium sulfate, and evaporated to afford 3.4 g (96%) of the ketal as a colorless oil: bp 110° (0.5 mm); λ_{max}^{film} 5.85 μ; nmr ($CDCl_3$) τ 5.88 (q), 6.12 (s), 8.75 (t), 9.13 (s), 9.27 (s).

A solution of 14 g (0.047 mol) of this ketal in 150 ml of ether was added slowly to a cold (ice–salt) stirred solution of 4 g (0.11 mol) of lithium aluminum hydride in 400 ml of ether. The mixture was brought to room temperature. After 12 hr it was cooled in ice, sequentially 4 ml of water, 4 ml of 15% sodium hydroxide, and 12 ml of water were added with stirring, and after 20 min the mixture was filtered, washed with water which was extracted with ether, dried over magnesium sulfate, and distilled to afford 10.4 g (87%) of the hydroxy ketal V as a colorless glass: bp 120° (0.5 mm); $\lambda_{max}^{CHCl_3}$ 2.92 μ; nmr ($CDCl_3$) τ 6.10 (s), 6.25 (m), 9.15 (s), 9.27 (s); mass spectrum (70 eV) 254 (9), 163 (69), 99 (100).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.85; H, 10.31. Found: C, 70.74; H, 10.05.

To a cold solution of 555 mg (2.18 mmol) of the hydroxy ketal V in 80 ml of acetone was added 1.62 ml of Jones reagent.[37] After 5 min the mixture was poured into 500 ml of water, extracted with ether and chloroform, dried over sodium sulfate, and evaporated to leave 252 mg (52%) of keto acid IIIc. After one recrystallization from *n*-hexane–methylene chloride this had mp 122–123° and infrared and nmr spectra which were identical with those of the material prepared by route A.

1,1-Dimethyl-7β-hydroxy-*trans*-decalin-10-carboxylic Acid (IIc). A. From Keto Acid IIIc. To a solution of 0.360 g (0.00161 mol) of keto acid IIIc, mp 124–125°, in 60 ml of 95% ethanol was added 0.669 g (0.0175 mol) of sodium borohydride. The mixture was stirred at room temperature for 2.5 hr, acidified with concentrated hydrochloric acid, diluted with water, and extracted with methylene chloride. Evaporation of the methylene chloride left 0.373 g (100%) of the crude acid as white plates, which upon recrystallization from methylene chloride–cyclohexane afforded the hydroxy acid IIc as colorless needles: mp 188.5–189°; λ_{max}^{KBr} 2.93, 3.3–3.9 (br), and 5.92 μ.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.03; H, 9.73. Found: C, 68.80; H, 9.63.

B. From Keto Ester IV. A solution of 846 mg (0.00336 mol) of 10-carbethoxy-1,1-dimethyl-*trans*-7-decalone, mp 45–46.5°, in 125 ml of 95% ethanol to which had been added 1.286 g (0.0338 mol) of sodium borohydride was stirred under a nitrogen atmosphere for 3.5 hr at room temperature, diluted with 350 ml of water, and extracted with five 25-ml portions of methylene chloride. The organic phase was washed with water, dried over magnesium sulfate, and evaporated *in vacuo* to afford 869 mg (100%) of the hydroxy ester VI as a pale yellow oil which was 95% pure as estimated by glc and had $\lambda_{max}^{CHCl_3}$ 2.70, 2.83 (br), 5.83 μ; λ_{max}^{film} 2.93 (br), 5.82 μ; nmr (CCl_4) τ 9.25 (s), 9.10 (s), 8.72 (t, J = 7 Hz), 5.87 (q, J = 7 Hz).

An 860-mg (3.4 mmol) sample of this ester was saponified with 1.6 g of potassium hydroxide in 50 ml of water and 50 ml of ethanol during 70 hr at reflux. The mixture was diluted with 250 ml of water, washed with methylene chloride, acidified with 20 ml of 20% hydrochloric acid, and extracted with methylene chloride and ether–methylene chloride mixtures. Evaporation of the organic solvent at temperatures below 30° and recrystallization from ether–methylene chloride afforded 0.315 g (40%) of the hydroxy acid as colorless granular crystals: mp 187.5–187.7°; λ_{max}^{Nujol} 2.94, 3.2–4.0, 5.93 μ, fingerprint identical with that of the previously described sample.

(35) Infrared spectra were obtained on Perkin-Elmer Models 137, 137G, and 337 spectrophotometers, ultraviolet spectra were taken using Cary Models 14 or 16 or a Beckman DK-1 or a Zeiss PMQ-II spectrophotometer, and nmr spectra were obtained from dilute solutions with tetramethylsilane as internal standard using a Varian A-60 spectrometer. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU-6E spectrometer; the *m/e* of the parent peak and several prominent fragments are reported followed by their intensities as per cent of base peak intensity. Melting points were taken in open capillary tubes, and are corrected for stem exposure. Microanalyses are by Alfred Bernhardt, Mulheim, Germany.

(36) This preparation of hydroxy ketal V was provided by Dr. R. A. Manning of these laboratories.

(37) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

The methylene chloride solution from washing the original alkaline mixture was washed with water, dried, and evaporated to afford 0.1498 g of an oil whose infrared spectrum could be synthesized by addition of spectra of the hydroxy ester VI and lactone VII, the latter predominant.

1,1-Dimethyl-7β-hydroxy-*trans*-decalin-10-carboxylic Acid Lactone (VII). A solution of 1.026 g (0.00404 mol) of crude hydroxy ester VI (95% pure according to glc) and 1.523 g of potassium hydroxide in 200 ml of 95% ethanol was heated under reflux for 24 hr, diluted with water, basified to pH 11, and extracted with methylene chloride. Evaporation of the dried methylene chloride solution afforded 552 mg (66%) of the lactone VII which was purified by vacuum sublimation to produce colorless prisms, mp 57°; $\lambda_{max}^{CHCl_3}$ 5.75 μ.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.07; H, 9.01.

***trans*-Decalin-10-carboxylic Acid (Ia).** The preparative procedure of Bartlett, *et al.*,[6] was followed, with a modified isolation technique. The crude acid mixture (17.2 g, 81%) from the reaction of 18 g of β-decalol with 36 g of 88% formic acid and 200 g of 98% sulfuric acid according to "method I"[6] was dissolved in 150 ml of water containing 3.80 g of sodium hydroxide. To this solution was added 1.51 g of concentrated hydrochloric acid, sufficient to neutralize 37% of the base. The precipitated acidic material, which consisted almost entirely of the weaker trans acid, was extracted with ether and recrystallized thrice from 50% aqueous ethanol to afford the pure trans acid Ia as colorless plates, mp 133.5–134° (reported mp 134.6–135.4°,[4] 133–134°,[5] 134.5–135.5°[6]).

1,1-Dimethyl-*trans*-decalin-10-carboxylic acid (Ib) was recrystallized from 50% methanol to mp 90.5° (reported[7] mp 88.5–91 and 96–98°, polymorphic).

1,1-Dimethyl-2β-hydroxy-*trans*-decalin-10-carboxylic acid (IIb) was recrystallized repeatedly to mp 164–164.5°.[38]

1,1-Dimethyl-*trans*-2-decalone-10-carboxylic acid (IIc)[3] was recrystallized to mp 88.5° (reported mp 88.5°).

2β-Hydroxy-*trans*-decalin-10-carboxylic Acid (IIa). Our procedure was a modification of those of Hussey, Liao, and Baker[4] and Dauben, Tweit, and MacLean.[5] A solution of 12.64 g (0.0570 mol) of 10-carbethoxy-$\Delta^{1,9}$-2-octalone[39] (98% purity estimated by glc) in 120 ml of absolute ethanol was hydrogenated at 3 atm for 5.5 hr over 1.63 g of platinum oxide.[4] Filtration of the catalyst and evaporation of solvent left 12.32 g (97%) of the saturated keto ester as a viscous oil with $\lambda_{max}^{CHCl_3}$ 5.84 μ. This crude sample was treated with 10.76 g (0.055 mol) of sodium borohydride in 250 ml of 95% ethanol. After the mixture had been stirred 4 hr at room temperature, it was diluted with 500 ml of water, neutralized with hydrochloric acid, and extracted with methylene chloride. Evaporation of the solvent and distillation afforded 7.95 g (64%) of the hydroxy ester as a colorless liquid, bp 144–148° (4.5 mm); $\lambda_{max}^{CCl_4}$ 2.73, 2.86 (br), 5.77 μ. In our hands this product did not lactonize during distillation, as is reported.[4,5] It was saponified by treatment with 10.0 g (0.177 mol) of potassium hydroxide in 225 ml of methanol for 148 hr at reflux. The mixture was diluted with 700 ml of water, washed with ether, acidified to pH 2 with hydrochloric acid, and extracted with ether. The solvent was evaporated and the residual oil was chilled to induce crystallization. The crude solid was recrystallized twice from cyclohexane–methylene chloride to afford 2.54 g (23%) of the hydroxy acid IIa as colorless needles: mp 152.3–152.5° (reported mp 149.2–150.6°,[4] 152.4–152.9°[5]); λ_{max}^{KBr} 2.93, 3.1–4.1 (br), 5.90 μ.

***trans*-2-Decalone-10-carboxylic Acid (IIIa).** The procedure was adapted from the analogous preparation of IIIb.[3] A 0.884-g (4.5 mmol) sample of the hydroxy acid IIa, mp 152°, was dissolved in 260 ml of acetone and Jones reagent[37] was added dropwise under a nitrogen atmosphere until the orange color persisted. The mixture was diluted with 400 ml of water and filtered, and the filtrate was extracted with ether. Evaporation of the ether followed by recrystallization of the crude solid acid from cyclohexane–methylene chloride afforded 0.586 g (67%) of the keto acid IIIa as a white powder: mp 90.8–91° (reported[8] mp 91.5–93°); $\lambda_{max}^{CHCl_3}$ 3.0–4.0 (br), 5.88 μ; λ_{max}^{KBr} 2.9–4.2 (br), 5.88 μ; $\lambda_{max}^{95\%\ EtOH}$ 282 nm (ε 20.5).

Apparent Dissociation Constant Determinations. Titrations were run on a Radiometer-Denmark Automatic Titrator, using 1.00 mg of sample in 11 ml of 20% (by weight) water and 80% methyl Cellosolve (previously redistilled from calcium oxide). The titrant was 2.50×10^{-5} *N* sodium hydroxide in the same solvent. Duplicate determinations were made, and pK_{MCS}* agreed within 0.01 unit for the two titrations. The pK_{MCS}* was taken as the pH at half-neutralization (see discussion).

Kirkwood–Westheimer Calculations. Coordinates of cyclohexane and cyclohexanone systems were calculated using the set of carbon–carbon bond lengths and angles recommended by Eliel, Allinger, Angyal, and Morrison.[40] The ionizing proton was located on the extension of the bond joining the carboxyl carbon to the ring, 1.45 Å beyond the carboxyl carbon.[41] Carbon–oxygen single and double bond lengths of 1.43 and 1.20 Å, respectively, were used.[42] Group moments of 1.1 D for OH[32] and 2.7 D for C=O were used,[43] directed along the C–O bond axis. The point dipole was located at the center of the C–O bond. From the resulting coordinates of the proton and the point dipole, the parameters r and θ of eq 5 were readily calculated.

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(38) Our earlier report of mp 173° for this substance (ref 3) was a typographical error.

(39) M. Idelson and E. I. Becker, *J. Amer. Chem. Soc.*, 80, 908 (1958); M. Idelson, Ph.D. Thesis, Brooklyn Polytechnic Institute, 1955.

(40) See ref 16, p 455.

(41) F. H. Westheimer and W. Shookhoff, *J. Amer. Chem. Soc.*, 61, 555 (1939).

(42) L. Pauling, "The Nature of the Chemical Bond," 2nd ed, Cornell University Press, Ithaca, N. Y., 1940.

(43) C. P. Smyth, "Dielectric Behavior and Structure," McGraw-Hill, New York, N. Y., 1955, p 290.