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THE DISSOCIATION CONSTANTS OF METHYL ALKYL KETONE CYANOHYDRINS[1]

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Abstract—The dissociation constants of a series of methyl alkyl ketone cyanohydrins have been measured by NMR spectroscopy. The heats of solutions of the ketones and the cyanohydrins have been determined. The effect of alkyl groups on the heats of solution have been shown to be unimportant in determining the observed dissociation constants of the cyanohydrins of these ketones.

THE structural dependence of the rates of solvolysis of alkyl and cycloalkyl halides and aryl sulphonates has been of major theoretical interest for many years.[2] Of particular importance have been the attempts to evaluate substituent effects for classical carbonium ion formation so that, when a solvolysis rate is measured, an estimate can be provided of the degree (if any) of participation of neighbouring groups and shed light on the structure of the intermediate. As has been pointed out many times, the problem is a difficult one and not likely to be solved by any very simple means. Nonetheless, optimism persists, particularly along the line of correlating classical cation stabilities with various molecular properties. As one example, Brown has suggested that ketones might provide reasonably satisfactory models for carbonium ions of related structure.[3] On this basis structural changes which *facilitate* carbonium ion formation in a reaction where the coordination number of carbon changes from four to three are supposed to *hinder* addition reactions with ketones where the coordination number changes from three to four.

A number of reactions have been utilized in the studies of the effects of structure on the reactivity of ketones. These include the reactions of ketones with hydroxylamine,[4] phenylhydrazine,[5] and semicarbazide.[6] However, the available evidence indicates that the mechanisms of these reactions involve a number of stages and it is clear that the same type of step is not always rate-determining. The reduction of ketones in isopropyl alcohol with sodium borohydride appears to be a simpler reaction which exhibits simple second-order kinetics and seems to involve a common rate-determining step irrespective of the ketone substituents.[7] The dissociations of ketone cyanohydrins are also expected to be useful model reactions for studying structural

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[2] See A. Streitwieser, Jr., *Chem. Revs.* **56**, 571 (1956).

[3] H. C. Brown and K. Ichikawa, *Tetrahedron* **1**, 221 (1957).

[4] E. Barrett and A. Lapworth, *J. Chem. Soc.* **93**, 85 (1908).

[5] G. H. Stempel, Jr., and G. S. Schaffel, *J. Amer. Chem. Soc.* **66**, 1158 (1944).

[6] J. B. Conant and P. D. Bartlett, *J. Amer. Chem. Soc.* **54**, 2881 (1932).

[7] H. C. Brown, O. H. Wheeler and K. Ichikawa, *Tetrahedron* **1**, 214 (1957).

effects and here, of course, no problems arise with regard to the nature of the rate-controlling steps.

The proof of the pudding with regard to the relationship between the reactivity of ketones and the ease of formation of carbonium ions of related structure has been the correlation between the rates of sodium borohydride reduction of a number of cycloalkanones[3] and the dissociation constants of the cyanohydrins of these cycloalkanones[8] with the rates of solvolysis of the corresponding tosylates.[9] These comparisons for the C_5 to C_{10} compounds yield remarkably good linear free-energy relationships which have been attributed to changes in "internal strain" accompanying the change in the coordination number of the ring atom undergoing reaction.

Similar studies for acyclic ketones have been less satisfying. The rates of sodium borohydride addition to the acyclic ketones[10] show non-additive substituent effects from which it was concluded that substituent inductive effects were probably not a major factor. The pattern of observed rates was ascribed to special steric requirements of aliphatic substituents. The substituent factors which account for the rates of observed sodium borohydride reductions of acyclic ketones are noticeably absent in the rates of solvolysis of the corresponding secondary alkyl *p*-bromobenzene-sulphonates[11] and the tertiary aliphatic chlorides.[12] It was of interest to see if the postulated similarity of the structural features of the reactions of ketones with hydrogen cyanide and with sodium borohydride would lead to any relationship between the dissociation constants of ketone cyanohydrins and rates of sodium borohydride reduction of methyl alkyl ketones. The expectation is not borne out by the available data in the literature.[13] However, since reported cyanohydrin equilibrium constants were measured[13] only by titrating the residual cyanide after quenching the equilibrium with nitric acid, and the possibility of side equilibria such as hydrate or hemiketal formation was not taken into account, the lack of a correlation is perhaps not definitive. To avoid these difficulties, we have redetermined the dissociation constants of some methyl alkyl ketone cyanohydrins more directly by nuclear magnetic resonance spectroscopy.

RESULTS AND DISCUSSION

The relative dissociation constants were determined on solutions of acetone, the methyl alkyl ketone, and hydrogen cyanide in methanol at 33°. The proton magnetic resonance spectra of the reaction mixtures were taken and integrated areas of the methyl resonances of the ketone and the cyanohydrin were measured for both acetone and the methyl alkyl ketone. The relative dissociation constants were determined from:

$$K^{\text{rel.}}_{\text{Diss.}} = \frac{[\text{Area RCO}\underline{\text{CH}_3}]}{[\text{Area RC(CN)OH}\underline{\text{CH}_3}]} \times \frac{[\text{Area (}\underline{\text{CH}_3}\text{)}_2\text{C(CN)OH}]}{[\text{Area (}\underline{\text{CH}_3}\text{)}_2\text{CO}]} \qquad (1)$$

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[8] V. Prelog and M. Kobelt, *Helv. Chim. Acta* **32**, 1187 (1949).

[9] R. Heck and V. Prelog, *Helv. Chim. Acta* **38**, 1541 (1955).

[10] H. C. Brown and K. Ichikawa, *J. Amer. Chem. Soc.* **84**, 373 (1962).

[11a] S. Winstein, *Bull. Soc. Chim. Fr.* **18**, C55 (1951).

[11b] S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber and J. Corse, *J. Amer. Chem. Soc.* **74**, 1113 (1952).

[11c] S. Winstein and H. Marshall, *J. Amer. Chem. Soc.* **74**, 1120 (1952).

[11d] S. Winstein and J. Takahashi, *Tetrahedron* **2**, 316 (1958).

[12] H. C. Brown and R. S. Fletcher, *J. Amer. Chem. Soc.* **71**, 1845 (1949).

[13] A. Lapworth and R. H. F. Manske, *J. Chem. Soc.* 2533 (1928); 1976 (1930).

The results are given in Table 1 and are seen to be in substantial agreement with those reported earlier.

The NMR spectra provided no evidence for formation of hemiketals. Nonetheless, the possibility was not wholly eliminated of a very rapid, reversible hemiketal formation which would produce a small discrepancy between the real and apparent concentration of the ketone.[14] A more definitive demonstration that hemiketal formation does not invalidate the results was obtained by measuring the relative dissociation constants of the cyanohydrins in carbon tetrachloride solution (Table 1). The similarity of the relative dissociation constants in methanol, ethanol and carbon tetrachloride solution indicate that the order of the dissociation constants is not a result of a side equilibrium between the ketones and the solvent.

TABLE 1. RELATIVE DISSOCIATION CONSTANTS OF METHYL ALKYL KETONE CYANOHYDRINS

Ketone	$K^{\text{rel.}}_{\text{Diss.}}$			
	CH_3OH(33°)	CCl_4(33°)	CH_3CH_2OH[a]	CH_3CH_2OH[b]
Acetone	(1·0)	(1·0)	(1·0)	(1·0)
Methyl ethyl	0·82	0·8	0·87	0·76
Methyl *n*-propyl	1·17	~1·0[c]	1·16	1·30
Methyl *i*-propyl	0·34	—	0·51	0·78
Methyl cyclopropyl	>2	—	—	
Methyl *n*-butyl	~1·1[c]	—	1·05	1·18
Methyl *i*-butyl	>2	—	—	
Methyl *t*-butyl	0·95	1·1	1·02	0.93

[a] From Lapworth and Manske[15] at 20°

[b] From Evans and Young[16] at 35°

[c] The uncertainty was large (±0·2) because of overlap of the methyl resonance of the cyanohydrin with that of the alkyl group of the ketone.

The effect of substituents on the position of cyanohydrin equilibria in solution may of course not be the same as in the vapor phase because of effects on the free energy of solution of the ketone and effects on the free energy of solution of the cyanohydrin. As may be seen from the following energy cycle:

$$\begin{tikzcd}
R_2CO(g) + HCN(g) \arrow[r, shift left, "\Delta F_g"] \arrow[d, shift right] & R_2C(CN)OH(g) \arrow[l, shift left] \arrow[d, shift left, "\Delta F_{s2}"] \\
R_2CO(s) + HCN(s) \arrow[u, shift right, "\Delta F_{s1}"] \arrow[r, shift left, "\Delta F_0"] & R_2C(CN)OH(s) \arrow[l, shift left] \arrow[u, shift left]
\end{tikzcd}$$

the free energy of dissociation of the cyanohydrin (ΔF_0) is then the sum of the free energy of vaporization of the reactants ($-\Delta F_{s2}$), the free energy of dissociation in the vapor phase (ΔF_g) and the free energy of solution of the products (ΔF_{s1}). For interpretation of the effect of structure on the

$$\Delta F_g = \Delta F_0 - \Delta F_{s1} + \Delta F_{s2} \tag{2}$$

"intrinsic" reaction rates or equilibria, it is most desirable to use data for vapor-phase

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[14] It is however not very likely that the rate of hemiketal formation would be sufficiently fast on the NMR time scale to average the resonance peaks for the ketone and the hemiketal.

reactions where the complications of solvation effects can be ignored since intermolecular interactions are at a minimum. In practice, such data are often difficult to obtain for many reactions of interest—vapour-phase ionic reactions being slow and equilibrium conditions difficult to obtain.

One way of testing for solvent-solute interactions is by comparison of heats of solution to see if trends in heats of solutions could account for the trends in the cyanohydrin dissociations; the heats of solution of the methyl alkyl ketones and two of the corresponding cyanohydrins in methanol were measured in a non-isothermal calorimeter.[15] The results are summarized in Table 2. Since the cyanohydrins have half-lives of several hours at room temperature,[16] no anomalous heats of solution due to cyanohydrin dissociation are expected.

TABLE 2. HEATS OF SOLUTION OF ALKYL METHYL KETONES AND CYANOHYDRINS

Compound	ΔH_s, kcal/mole (of compound)[a]
Acetone	0·50[b]
Methyl ethyl ketone	0·56
Methyl *i*-propyl ketone	0·62
Methyl *n*-propyl ketone	0·68
Methyl *t*-butyl ketone	0·67
Methyl *i*-butyl ketone	0·64
Acetone cyanohydrin	−0·69
Methyl *i*-propyl ketone cyanohydrin	−0·67

[a] Heat absorbed.
[b] M. Timofejev, *Chem. Zentr.* **76**, 429 (1905).

We had originally considered that the relative cyanohydrin dissociation constants might be determined by the heats of solution of the corresponding ketones. Bulky substituents α to the carbonyl group could perturb the solvent shell and thus decrease the relative stability of the ketone in solution.[17] One might expect the heats of solution of the cyanohydrins to be less sensitive to α-substituents than the heats of solution of the corresponding ketones since interaction of the cyanohydrin with the solvent will occur predominantly through the cyano and the hydroxy groups which are somewhat further removed from the α-substituent than the ketone carbonyl groups. The expected α-substituent effects on the heats of solution of the ketone were observed. However, the differences in the heats of solution of the ketones are smaller than the differences in the free energies of dissociation of the cyanohydrins. Furthermore, for the two cyanohydrins (acetone and methyl isopropyl ketone) that have been measured, the differences in heats of solution of the ketone and corresponding cyanohydrin for the two compounds is only 0·10 kcal/mole—a value too small to account for differences in dissociation.

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[15] J. M. Sturtevant, in Weissberger, *Techniques of Organic Chemistry*, Vol. I, p. 523. Interscience, New York, N.Y. (1959).

[16] W. J. Svirbely and J. F. Roth, *J. Amer. Chem. Soc.* **75**, 3106 (1953).

[17] A similar explanation has been offered for the decrease in pK_a with increasing size of the alkyl group for a series of aliphatic acids: G. S. Hammond and D. H. Hogle, *J. Amer. Chem. Soc.* **77**, 338 (1955).

The observed order of dissociation constants of the cyanohydrins of the ketones: CH_3COR, R = $CH_3 > C_2H_5 > i\text{-}C_3H_7 < t\text{-Bu}$, can be most readily explained in terms of a combination of steric and hyperconjugative effects. As the number of hydrogens α- to the ketone decreases the relative stability of the ketone decreases. The trend is reversed for R = *t*-butyl presumably because of steric destabilization of the tetrahedral cyanohydrin with respect to the trigonal ketone. This explanation is generally consistent with the dissociation constants of $RR^1C{=}O$ cyanohydrins.[18] As the size of the second alkyl group increases, steric destabilization would be expected to occur sooner in the series Me, Et, *i*-Pr, *t*-Bu.

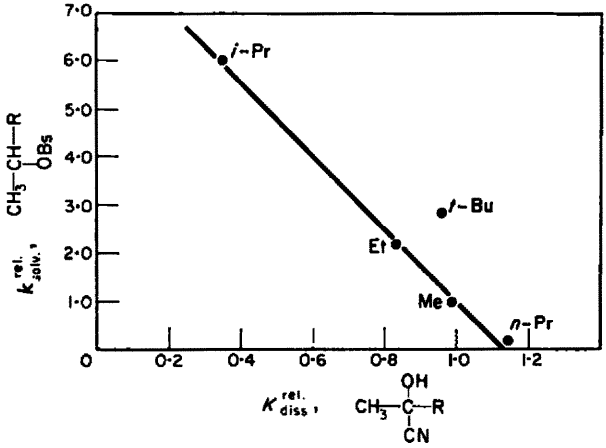

FIG. 1. Relationship between the dissociation constants of methyl alkyl cyanohydrins and the rate constants for the solvolysis of the corresponding *p*-bromobenzenesulphonates.[19]

Fig. 1 shows a plot of the relative rates of solvolysis of the secondary alkyl benzenesulphonates against the relative dissociation constants of the corresponding methyl alkyl ketone cyanohydrins. There appears to be a reasonably close correlation which, however, is *opposite* in slope to that found for cycloalkyl derivatives. The hypothesis that ketone reactivities can be correlated with carbonium ion reactivities does not seem very fruitful for these substances.

EXPERIMENTAL

Cyanohydrin Equilibria. The ketones (all commercially available) were first distilled and then purified by preparative vapour phase chromatography on a Beckman Megachrom using Apiezon L columns. MeOH was dried by distillation from magnesium methoxide. HCN was prepared from NaCN and H_2SO_4 and was dried by passing it through an anhydrous $CaSO_4$ drying tower and stored in heavy-wall glass cylinder with a Teflon needle valve.

To a Varian precision NMR tube was added MeOH (containing 1 drop of triethylamine per 50 ml), acetone, and the ketone. The tube was attached to the vacuum line, cooled, and evacuated; HCN was then distilled into the tube and the tube sealed. The mixtures were allowed to equilibrate several weeks at room temp before the dissociation constants were measured.

The PMR spectra were taken on the Varian A-60 (probe temp = ~33°) using a Hewlett Packard 405 CR D.C. Digital Voltmeter for integral measurements. The integrated areas of the methyl

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[18] D. P. Evans and J. R. Young, *J. Chem. Soc.* 1310 (1954).

[19] In acetic acid at 25°, Ref. 11. The value for *n*-propyl was calculated from the reported rate of acetolysis of 2-pentyl tosylate, cf. E. S. Lewis and C. E. Boozer, *J. Amer. Chem. Soc.* **76**, 791 (1954).

resonances of the ketones and the cyanohydrin were measured for both acetone and the respective ketone. Numerous integrations were averaged for each sample. The relative dissociation constants were determined from Eq. (1).

For *t*-butyl methyl ketone, the methyl resonance was found to be nearly coincident with that of acetone; the areas of the *t*-butyl resonances in the ketone and the cyanohydrin were measured and used to determine the relative dissociation constant.

The relative dissociation constant of the cyanohydrin of *n*-butyl methyl ketone could not be accurately determined since the methyl resonance peak of the cyanohydrin overlapped with the resonance of the alkyl portion of the ketone.

The dissociation constants of the cyanohydrins in CCl_4 were determined in a similar fashion.

Heats of solution. A non-isothermal calorimeter was constructed from a 500-ml silvered dewar flask encased in a large polystyrene foam block. A Teflon-coated magnetic bar was used for stirring. Temp were measured to $\pm 0{\cdot}002$ with a Beckman thermometer. The ketone (10·0 ml) was contained in a glass tube closed at one end with a disc of Al foil sealed on with paraffin wax. The calorimeter containing 200·0 ml MeOH was assembled and allowed to reach thermal equilibrium. The Al foil disc was punctured with a thin glass rod and the temp change recorded. The heat capacity of the calorimeter and solution was then determined from the temp change resulting from the input of a known amount of electrical energy. The heater and timing circuits were similar to those described by Sturtevant.[15]

The heat capacities were essentially constant from run to run. The average of several determinations for each ketone was used.

Since the dewar flask contained a moderately large air volume, difficulty was encountered in the determination of heats of solution of very volatile ketones. For acetone, the temp continued to fall for several min after mixing due to cooling resulting from vaporization of the ketone.