

The Acidities of Ketones and the Mechanism of Prototropic Change

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The observation of acidity in the brominated acetones is attributed to coordination of carbonyl carbon and hydroxyl ion, the process being preceded by electromeric change to the semipolar form. Acid- and base-catalyzed prototropy is regarded as involving a similar electromeric change, brought about by interaction with the catalyst, and followed by transformation of the semipolar form either to ketone or to enolic ion. The measured velocity

will thus be dependent upon (a) the rate of reaction of ketone and catalyst, and (b) the proportion of the semipolar form which changes to enol. The application of this view, in conjunction with the conception of quantum-mechanical resonance as developed by Pauling, renders possible the satisfactory interpretation of a number of observations relating to the prototropic changes of carbonyl compounds.

IT was observed some three years ago¹ that the substitution of halogen atoms in the acetone molecule confers upon the ketone acidic characters which become progressively stronger as the number of substituent atoms is increased. Thus the *pH* values of *M*/400 aqueous solutions of various brominated acetones were found to be as follows:

monobromoacetone	5.4
<i>as</i> -dibromoacetone	4.7
<i>s</i> -dibromoacetone	4.3
<i>aaa</i> -tribromoacetone	3.8
<i>as</i> -tetrabromoacetone	2.8.

None of the ketones gave an instantaneous reaction with bromine, the absence of any detectable quantity of enolide thus being indicated. It was evident, therefore, that the acidity is associated with the ketonic form, and ionization of α -hydrogen was postulated, notwithstanding the fact that the acidity developed slowly, some hours being required for the attainment of the final maximum values recorded above. We wish now to suggest an alternative interpretation which, we feel, is more in harmony with the general reactions of carbonyl compounds, and particularly with our recent observation that benzophenone (in which there is no α -hydrogen) also has a definite though small acidity.

Numerous investigations have demonstrated the capacity of the carbonyl group to coordinate both with protons and with anions, and it is evident that processes such as cyanohydrin formation (where the anion adds first²) and the

alkaline hydrolysis of esters (involving addition of hydroxyl³) must be accompanied by the transfer of a pair of electrons from the double bond to the sole control of the oxygen atom.⁴ Indeed, both the reactivity of the carbonyl group and the ketonic ultraviolet absorption band have been ascribed by Lowry⁵ to "polar activation" in which electrons are "displaced from carbon towards oxygen, a process which (if continued far enough) would culminate in the ionization of one link of the bond, and the conversion of the nonpolar into a semipolar double bond, as indicated by the scheme $\text{>C=O} \rightleftharpoons \text{>C}^{\ominus}\text{-O}^{\oplus}$,"

while Pauling and Sherman⁶ have recently suggested that the unusually high energy of formation of the carbonyl group is due to quantum-mechanical resonance between the normal and semipolar structures. The "decreased rigidity" of the carbon-nitrogen double bond in oximes, brought about by interaction with an ion-pair,⁷ may be due to an electromeric change of a similar type, while the same process may be supposed to occur in the production of aldols, hydrazones, oximes, pinacols and metal ketyls, and to be responsible for the colors of solutions of aldehydes and ketones in concentrated sulphuric acid.⁸

¹ Lowry, *J. Chem. Soc.* **127**, 1379 (1925). Ingold and Ingold, *ibid.* (1932), 756.

² Compare Robinson, *Outline of an Electrochemical (Electronic) Theory of the Course of Organic Reactions*, Institute of Chemistry, London, 1932, p. 16.

³ Lowry, *J. Chem. Soc.* **123**, 822 (1923); (1926), 620.

⁴ Pauling and Sherman, *J. Chem. Phys.* **1**, 606 (1933).

⁵ Taylor and Roberts, *J. Chem. Soc.* (1933), 1439.

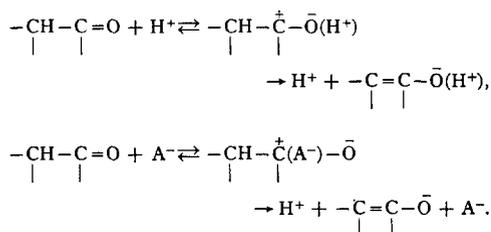
⁶ Baker, *J. Chem. Soc.* (1931), 307. Compare Pfeiffer's conception of "one-sided saturation," *Ann.* **404**, 1 (1914); **412**, 253 (1916).

¹ Watson and Yates, *J. Chem. Soc.* (1932), 1207.

² Lapworth, *J. Chem. Soc.* **83**, 995 (1903); **85**, 1206 (1904).

internal facilitating process occurs. It is unnecessary, moreover, to postulate the formation of the enol itself in all bromination processes, for the enolic ion doubtless reacts instantaneously with halogen.

An advantage that may be claimed for the view here presented is the similarity between the acid and basic mechanisms, which is obvious when they are represented as follows:



Assuming these mechanisms, the measured velocity of prototropic change (rate of bromination) will depend upon two factors, *viz.*, (A) the rate of reaction of the ketone with the catalyst, and (B) the proportion of the semipolar form which is transformed to the enolic ion. The application of these views, in conjunction with the conception of quantum-mechanical resonance as developed by Pauling, provides a very satisfactory interpretation of numerous observations relating to the prototropy of carbonyl compounds.

THE PROTOTROPY OF NUCLEAR-SUBSTITUTED ACETOPHENONES

In a series of *very similar compounds* undergoing change with *identical conditions* of temperature, medium, and catalyst concentration, it may probably be assumed that the second factor, *viz.*, the proportion of semipolar form becoming enol ion, will not vary appreciably. Further, Bradfield and his collaborators¹³ have observed that the differences in the velocities of chlorination of a series of phenolic ethers of the general formula X.C₆H₄.OR are due solely

to different energies of activation,* and it is reasonable to suppose that the same will apply to the prototropy of a series of compounds such as the *p*-substituted acetophenones.¹⁴ In the acid-catalyzed reaction, the presence of an electron-attracting substituent will render less facile the approach of the positive ion, additional work being performed by the approaching ion against the superimposed field due to the substituent, and the reverse will, of course, hold for an electron-repelling group. The result will be an increase or decrease in the energy of activation, and, in fact, when the kinetic equation is applied in its simplest form (velocity = collision number $\times e^{-E/RT}$), an accurate relationship is found¹⁴ between the differences in the energies of activation for the prototropy of X.C₆H₄.CO.CH₃ and C₆H₅.CO.CH₃ (calculated from the relative velocities of bromination) and the dipole moments of C₆H₅X, the relevant expression being $E - E_0 = -C(\mu - a\mu^2)$. An attempt is now being made to obtain direct experimental proof of the postulate that, in the system here considered, substituents affect only (or at any rate principally) the energy of activation. It may also be noted that Hammett and Pfluger¹⁵ have recently found a quantitative relationship between the velocities of reaction of substituted benzoic esters with trimethylamine and the dissociation constants of the corresponding benzoic acids.

THE PROTOTROPY OF HALOGENATED ACETONES

Parallel with the increasing acidity which accompanies the introduction of halogen atoms into the acetone molecule (referred to in the opening paragraph of this paper), there is a decrease in the effectiveness of acids as catalysts of the prototropic changes of these compounds, and a similar increase in the effectiveness of basic catalysts.¹ Thus, employing 0.1M ketone solutions in 50 percent acetic acid, the point at which the velocity of prototropy of acetone has

* Since the preparation of this paper, Williams and Hinshelwood (J. Chem. Soc. (1934), 1079) have observed that the influence of substituents upon the velocity of benzylation of aromatic amines depends principally upon changes in activation energy.

¹³ Nathan and Watson, J. Chem. Soc. (1933), 890.

¹³ Bradfield and Jones, J. Chem. Soc. (1928), 1106, 3073; (1929), 2810; (1931), 2903. Bradfield, Jones and Spencer, *ibid.* (1931), 2907. Bradfield, Chemistry and Industry 51, 254 (1932).

¹⁵ Hammett and Pfluger, J. Am. Chem. Soc. 55, 4079 (1933).

its minimum value¹⁶ is not detectable, while, in order to reach this point for monobromo-, *as*-dibromo-, and *s*-dibromoacetones, the addition of hydrochloric acid at concentrations of 0.002, 0.2 and 0.45M, respectively, is necessary, and the prototropic changes of $\alpha\alpha$ -tribromo- and *as*-tetrabromo-acetones occur via the basic mechanism even in presence of 2M hydrochloric acid. The influence of the powerfully electron-attractive halogen atoms upon the reaction of ketone with catalyst is sufficient to explain these observations, for it will oppose the approach of hydrogen ion and facilitate the approach of an anion. Probably then, this is again the main factor involved.

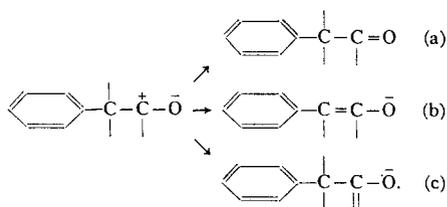
THE PROTOTROPY OF THE PHENYLACETONES

A very different position is here revealed. The velocities of prototropic change of mono- and *s*-diphenylacetones* for 0.1M solutions in 75 percent acetic acid at 25°, we find, are as follows, the figures referring to fall of *N*/50 titre per minute for 20 cc of reaction mixture;

Ketone	Velocity		
	HCl=0	HCl=0.0095M	HCl=0.476M
acetone	0.013	0.109	0.675
monophenylacetone	0.016	0.227	1.390
<i>s</i> -diphenylacetone (acetophenone)	0.007	0.076	0.625 0.243

The relative strengths of phenylacetic and acetic acids ($K=4.88 \times 10^{-5}$ and 1.76×10^{-5} , respectively¹⁷) indicate that, relatively to hydrogen, phenyl is a weakly electron-attracting group, as

pointed out by G. N. Lewis¹⁸ and by Ashworth and Burkhardt.¹⁹ Its presence will therefore be unfavorable to coordination with an acid catalyst, and the rates of reaction of the ketones referred to in the table will no doubt be in the descending order acetone > monophenylacetone > diphenylacetone > acetophenone (in the last-named, phenyl is attached directly to carbonyl, and hence will exert a relatively large effect). This is not, however, the order of the measured velocities, and, if the views outlined above be correct, there must be considerable variation in the proportion of semipolar form which is transformed to enol. In the case of monophenylacetone, the rearrangement of this form may give rise to three distinct entities, the ketonic and two enolic forms;



The product isolated after bromination of this ketone is $C_6H_5 \cdot CHBr \cdot CO \cdot CH_3$,²⁰ and it is thus shown experimentally that, of the two enols, the favored form is (b). It is evident, too, that the stability of (b), which contains a long system of alternate single and double bonds, will be considerably enhanced by resonance.* Pauling and Sherman⁶ calculate the value 1.71 v.e. for the resonance energy of phenyl between the five possible structures, and find that the additional double bond in phenylethylene contributes a further 0.29 v.e. There is good reason to suppose, therefore, that, in the case of monophenyl-

¹⁶ Compare Dawson and Dean, *J. Chem. Soc.* (1926), 2872.

* Dawson and Ark (*J. Chem. Soc.* 99, 1742 (1911)), by measurement of velocities of iodination, found that phenylacetone undergoes prototropic change much more rapidly than does acetone, but they failed to obtain satisfactory results for *s*-diphenylacetone. We experienced great difficulty in preparing pure specimens of these ketones from the appropriate calcium salts. An instantaneous bromine absorption was ultimately removed from monophenylacetone by two treatments with 5 percent of bromine in carbon tetrachloride, followed by vacuum distillation. The pure ketone has b.p. 87°/4 mm. *s*-diphenylacetone was obtained pure (b.p. 154°/5 mm, m.p. 33.9°, compare Young, *J. Chem. Soc.* 59, 623 (1891)), by very carefully regulated heating of calcium phenylacetate followed by crystallization from carbon tetrachloride or petroleum ether. We found later that the impurities can be removed by steam, the residue giving a pure product on crystallization. Samples of both ketones deteriorate on keeping, particularly if light and air are admitted.

¹⁷ Jeffery and Vogel, *J. Chem. Soc.* (1933), 1637; (1934), 166. Dippy and Williams, *ibid.* (1934), 161.

¹⁸ Lewis, *Valence and the Structure of Atoms and Molecules* (1923), p. 150.

¹⁹ Ashworth and Burkhardt, *J. Chem. Soc.* (1928), 1793. Compare Nathan and Watson, *ibid.* (1933), 217.

²⁰ Kolb, *Ann.* 291, 267 (1896).

* "The tendency of two or more double bonds to arrange themselves alternately with single bonds" is referred to by Lapworth and Manske (*J. Chem. Soc.* (1928), 2535), who note that "such an arrangement is ordinarily associated with an element of stability." In this "Thiele factor" they find (*ibid.* (1930), 1976) an interpretation of the low stability of the cyanohydrins of ketones where phenyl is in direct attachment to carbonyl. Compare Linstead, *ibid.* (1929), 2501; Watson and Yates, reference 23.

acetone, a relatively high proportion of the semipolar form will be transformed to the enol (b), and this suffices to explain the high value of the measured velocity of prototropic change. The velocity is thus influenced by two opposing factors (depression of the speed of reaction with the catalyst, and increase in the proportion of semipolar form changing to enol), and in *s*-diphenylacetone, where the electron-attractive characters of *two* phenyl groups oppose reaction with the acid catalyst, these factors approximately balance each other, the resulting speed being not very different from that observed in the case of acetone itself. Preliminary experiments upon the prototropy of monobenzylacetone have indicated that this compound also changes at about the same rate as acetone, both effects being practically eliminated by the intervening methylene group.

A discussion, on similar lines, of the prototropy of the carbethoxyacetones (acetoacetic and acetone-dicarbocyclic esters) is contemplated, but is at present undesirable, owing to the conflicting evidence regarding the effect of acid catalysts.²¹

SATURATED ALIPHATIC ACIDS

Pauling and Sherman⁶ find that the carboxyl group has a resonance energy of 1.2 v.e. because of the complete degeneracy between two equivalent forms (as expressed by the Hantzsch for-

mula). The absence of carbonyl properties is thus readily accounted for, and it also becomes evident that the enolic form, in which this group is destroyed, will be relatively unstable, and hence produced in negligible quantity from the semipolar form (if, indeed, the last-named ever exists). One of us has shown, indeed,²² that the halogenation of acetic acid and its homologs is not preceded by prototropic change. In an acyl halide (e.g., acetyl bromide) the dipolar character of the bond linking halogen with carbonyl carbon will doubtless prevent any appreciable reaction with an acid catalyst, while the properties of the compound preclude prototropy by the basic mechanism. Neither the saturated monocarboxylic acids nor their halides, therefore, undergo prototropic change, so far as can be detected, and the fact that acyl halides can be directly halogenated at the α -carbon atom must be ascribed to some additional property of the halogen, not necessarily connected with the dipolar nature of the carbon-halogen bond.²³ Malonic acid, however, is known to undergo prototropic change with relative ease, while succinic acid may perhaps react with halogens in its enolic form.²⁴ In both cases the enol retains the stability due to *one* carboxyl group, and in the former, additional stability is gained²⁵ by resonance between the structures $O=C-C=C-O$ and $O-C=C-C=O$.

²² Watson, J. Chem. Soc. 127, 2067 (1925). Compare Chem. Rev., reference 9.

²³ Compare Watson and Yates, reference 21.

²⁴ Hughes and Watson, J. Chem. Soc. (1930), 1733.

²⁵ Compare Wheland, J. Chem. Phys. 1, 731 (1933).

²¹ K. H. Meyer, Ann. 380, 212 (1911). Watson and Yates, J. Chem. Soc. (1933), 220. Pedersen, J. Phys. Chem. 37, 751 (1933).