60. *Constitutional Factors controlling Prototropic Changes in Carbonyl Compounds. Part III. The Prototropy of Nuclear-substituted Acetophenones.*

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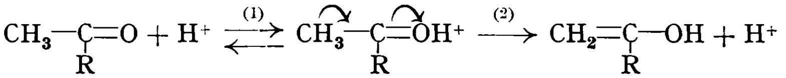
CO-ORDINATION with the catalyst is the first step in the scheme put forward by Lapworth and Hann (J., 1902, **81**, 1513) to represent an acid-catalysed prototropic change, and in all " acid mechanisms " suggested subsequently (*e.g.*, Hughes and Watson, J., 1929, 1949). Numerous experimental facts indicate that such co-ordination occurs, and in the present series of investigations it has been made evident by the considerable rise of temperature produced when hydrochloric acid is mixed with acetone or acetophenone, the increased solubility of the brominated acetones and of acetophenone due to the presence of mineral acid, and the fact that, in the preparation of suitable buffer solutions for the determination of free bromine in presence of brominated ketone (Part I; J., 1931, 3323), the presence of acetophenone reduces the quantity of sodium acetate necessary. These observations lead to the further conclusion that co-ordination is a relatively rapid process; it is not, therefore, the measurable stage in a prototropic change proceeding *via* the " acid mechanism."

Emphasis has already been laid on the influence of neighbouring atoms and groups upon the capacity of carbonyl oxygen for co-ordination, as shown by the effects of acid catalysts upon the prototropic changes of various ketones; *e.g.*, substitution of halogen atoms in the acetone molecule leads to a progressive decrease in the efficiency of acid catalysts (Part II; J., 1932, 1207). The acid-catalysed prototropic change of the compound $CH_3\cdot COR$ may be represented thus,



$$\underset{R}{CH_3-C=O} + H^+ \xrightleftharpoons{(1)} \underset{R}{CH_3-C=OH^+} \xrightarrow{(2)} \underset{R}{CH_2=C-OH} + H^+$$

where (2) is the measurable stage. The velocity of the change, under any given conditions, is

$$V = k\,[\text{complex}] = kK\,[\text{ketone}][H^+] = k\,.\,k_{ass.}/k_{diss.}\,.\,[\text{ketone}][H^+],$$

where $k_{ass.}$ and $k_{diss.}$ are the velocity coefficients of the association and the dissociation respectively of the complex. Consideration of the experimental data as a whole leads us to introduce, at least provisionally, a simple and not unreasonable assumption that alteration of the nature of R will produce a change in the dissociation of proton from oxygen (stage 1 reversed) of the same character as and proportional to the change in the dissociation of proton from α-carbon (stage 2). Then, for a series of ketones $CH_3\cdot COR$, $k = ck_{diss.}$, where c is a constant for the series, whence

$$V = ck_{ass.}[\text{ketone}][H^+].$$

$k_{ass.}$ (and therefore V) will obviously be increased by accession of electrons to, and decreased by recession of electrons from, carbonyl oxygen.

A simple example is found when acetaldehyde and acetone (R = H and CH_3 respectively) are compared. Both compounds react with halogen after preliminary prototropic change (Lapworth, J., 1904, **85**, 30; Dawson and Leslie, J., 1909, **95**, 1860; Dawson, Burton, and Ark, J., 1914, **105**, 1275), which occurs at an almost negligible rate in aqueous solution but is accelerated powerfully by acids. The results of Dawson and his collaborators, though not strictly comparable, indicate qualitatively that, in presence of an equal concentration of acid, acetone changes more rapidly than does acetaldehyde. Observation is thus in harmony with anticipation, since, relatively to hydrogen, methyl causes accession of electrons to the carbonyl group. A group causing electron-recession from carbonyl, on the other hand, will oppose co-ordination, and hence the prototropic change of pyruvic acid (R = CO_2H) is accelerated but little by acids (Hughes and Watson, *loc. cit.*), and the " basic mechanism " predominates in neutral or slightly acid solution (Part II; p. 1211). The halogenated acetones provide a similar example.

The present communication describes an investigation of the kinetics of bromination of acetophenone and certain of its nuclear-substituted derivatives (R in $CH_3{\cdot}COR = C_6H_5$ and C_6H_4X). The measurements were conducted at 25° in 50% or 75% acetic acid medium, since the solubility of the majority of the ketones in water is but small, and excess of the ketone (at least 20 mols. per mol. of bromine) was employed throughout. As in the case of acetone, the velocity is independent of the concentration of the halogen; Dawson, Wheatley, and Ark (J., 1910, **97**, 2048; 1911, **99**, 1740) observed a similar phenomenon in the iodination of certain of these compounds. Under the conditions of our experiments the reactions are exceedingly slow in absence of added catalyst, but greatly accelerated by mineral acids. The measured velocity is therefore that of a prototropic change proceeding *via* the " acid mechanism."

Dawson and Wheatley (*loc. cit.*) found that, in presence of an equal concentration of acid, acetophenone undergoes prototropic change less readily than acetone, the ratio of the velocities being 0·37 to 1. Our bromination experiments have confirmed this result, and it appears, therefore, that acetophenone co-ordinates with the catalyst less readily than does acetone; the inference is that phenyl, relatively to methyl, causes electron-recession from carbonyl.

For a series of *p*-substituted derivatives of acetophenone, in presence of a constant concentration of hydrochloric acid, the order of velocities is *p*-Me>H>*p*-I>*p*-Br>*p*-Cl>*p*-NO_2. Thus, methyl, which is consistently electron-repelling, induces the most rapid reaction, while nitroxyl, which is invariably electron-attracting, causes the greatest retardation, and, in general, the order of velocities of prototropic change of compounds $CH_3{\cdot}CO{\cdot}C_6H_4X$ is the same as that of the dipole moments of C_6H_5X.

The results are summarised in the table, which records the fall in *N*/50-thiosulphate titre per minute for 20 c.c. of 0·1*M*-solutions of the ketones in 75% or 50% acetic acid. The values of dipole moments are those found by Tiganik (*Z. physikal. Chem.*, 1931, **13**. 452). The corresponding velocities for acetone are added for comparison.

Bromination of $CH_3{\cdot}CO{\cdot}C_6H_4X$.

		75% Acetic acid.		50% Acetic acid.		
X.	10^{18} μ.	HCl = 0·5*M*.	HCl = *M*.	HCl = *M*.	HCl = 2*M*.	HCl = 0.
CH_3	0·39	0·273	0·964	0·335	1·068	0·00709
H	—	0·243	0·793	0·297	0·954	0·00592
I	−1·38	0·208	0·696	—	—	—
Br	−1·53	0·197	0·656	0·217	0·737	0·00404
Cl	−1·56	—	—	0·216	0·727	0·00397
NO_2	−3·97	0·125	0·446	—	—	—
(Acetone)	—	0·675	—	0·796	—	0·019

The order is the converse of that observed by Shoppee (J., 1930, 968; 1931, 1225; 1932, 696) for the influence of substituents upon the mobility of the $\alpha\gamma$-diphenylpropene and diphenylmethyleneazomethine systems, and it confirms very definitely the conclusion that an acid-catalysed prototropic change in a carbonyl compound is facilitated by electron-accession to the system, whereas the changes investigated by Shoppee require electron-recession from the point of reaction. As Shoppee points out, the facilitation of prototropy in the systems studied by him runs parallel with the facilitation of anionic aromatic replacements and of side-chain reactions classified by Ingold and Rothstein (J., 1928, 1217) as " type B " ; in the present instance, on the other hand, the analogy is with the facilitation of kationic aromatic replacements and side-chain reactions of Ingold and Rothstein's " type A." Our results show, therefore, that the governing factor in the acid-catalysed prototropic change of a carbonyl compound is the co-ordination of the carbonyl oxygen with the catalyst.

DISCUSSION.

The application of electrochemical and electronic ideas to the study of the reactions of organic chemistry has led unavoidably to the conclusion that the polar influences exerted by atoms and groups are of at least two types. In its present form, this view appears first to have been expressed in 1922 (Kermack and Robinson, J., 1922, **121**, 430; Lapworth and Shoesmith, *ibid.*, p. 1391), but it was foreshadowed in Vorländer's suggestion (*Annalen*, 1902, **320**, 110) that the influence of a group is dependent both on its polar character and on its state of unsaturation, and also in Flürscheim's distinction (J., 1909, **95**, 718) between the " quantitative factor " and the " polar factor," for such terms as " unsaturation " and " affinity demand " admit readily of translation into electronic language. Flürscheim's " polar factor " or its equivalent has reappeared under the titles of " general polar effect " (Allan, Oxford, Robinson, and Smith, J., 1926, 401), " inductive " and " direct " effects (Ingold, *Ann. Reports*, 1926, 140; Ingold and Vass, J., 1928, 417), and " electropolar effect " (Cocker, Lapworth, and Walton, J., 1930, 443). Molecular polarisation of this type, measurable by the dipole moment, and, though diminishing with distance, yet capable of transmission to a point separated from its source by a chain of saturated atoms (as visualised at a relatively early date by G. N. Lewis, *J. Amer. Chem. Soc.*, 1916, **38**, 762), is spoken of in this series of communications as the " inductive effect " ($\pm I$), the term being used, as is frequently the case elsewhere, without reference to the mode of transmission of the effect. The electronic analogue of Flürscheim's " quantitative factor," and of Lapworth's " alternate polarity " induced by a key-atom (*Mem. Manchester Phil. Soc.*, 1920, **64**, No. 3; J., 1922, **121**, 416; cf. Kermack and Robinson, *loc. cit.*), may be found in the " conjugative effect " (Allan, Oxford, Robinson, and Smith, *loc. cit.*), the " tautomeric effect " (Ingold, *loc. cit.*), and the " primary interior effect " (Lapworth and Manske, J., 1928, 2536), although the significance attached to these terms by the authors named is by no means identical. Ingold's term " tautomeric effect " ($\pm T$) is here used to denote " molecular polarisability," operative only on demand (but see Ingold, Lapworth, Rothstein, and Ward, J., 1931, 1960, footnote), and propagated only through a " loose " electronic system. The classification of polar effects adopted in this series of papers is thus that given by Ingold and Ingold (J., 1931, 2359); we are fully aware, however, that similar conclusions would in all probability be reached if the problems were approached from the standpoint of Lapworth or of Robinson.

The fact that the velocities of acid-catalysed prototropic change of $CH_3{\cdot}CO{\cdot}C_6H_4X$ follow the order of the dipole moments of C_6H_5X indicates that the co-ordination of a *p*-substituted acetophenone is governed, mainly at least, by the inductive effect of the substituent X, and that, if X is capable of initiating tautomeric displacements, these do not affect the results to any great extent. Thus, substitution of halogen ($-I+T$) for hydrogen leads to a decrease in velocity, in spite of the demand for accession of electrons to carbonyl oxygen and of the existence of a suitable path for the transmission of the tautomeric effect. It seems probable, then, that in the more general case of a carbonyl compound $CH_3{\cdot}COR$ co-ordination is governed almost entirely by the inductive effect of R. Shoppee (J., 1931, 1226) suggests that the operation of the tautomeric effect may be responsible for the divergence from the dipole moment sequence of the velocity coefficients for the alkaline hydrolysis of ethyl benzoates with a halogen or hydroxyl substituent (Kindler, *Annalen*, 1926, **450**, 1), but in the present case, if tautomeric displacements do occur, they are insufficient to cause a similar divergence. The circumstances under which the tautomeric effect is operative have been discussed by Shoppee (J., 1930, 969) and by Ingold and Ingold (*loc. cit.*), but it would appear that some further limit is to be placed upon the operation of this effect, and the definition of this limit is one of the most difficult problems presented by the modern electronic theory of organic reactions.

The case of acetophenone itself calls for comment. Consideration of a wide range of phenomena has led Ingold (*Ann. Reports*, 1928, 121) to suggest that the principal effect of phenyl is a tautomeric one of either sign ($\pm T$). This does not exclude the existence of a somewhat weak inductive effect ($-I$), which is indicated by the dissociation constants of phenyl-substituted carboxylic acids (*e.g.*, phenylacetic stronger than acetic, α- and β-phenylpropionic acids both stronger than propionic), and by the different dipole moments of HX and PhX. It should here be noted that Ashworth and Burkhardt (J., 1928, 1793) ascribe to phenyl a general (inductive) effect in addition to a conjugative effect, and the relative velocities of prototropic change of acetone and acetophenone are in harmony with this conception. Phenomena attributed by Shoppee (J., 1932, 697) to the " permanent component " of the tautomeric effect of phenyl would appear, indeed, to be capable of an equally good interpretation on the basis of a — *I* effect.

EXPERIMENTAL.

Preparation of Materials.—Acetophenone was twice distilled and further purified by freezing. *p*-Chloro-, *p*-bromo-, *p*-iodo-, and *p*-methyl-acetophenones were prepared by the Friedel–Crafts method, Ac_2O and the appropriate substituted benzene being used (for details, see " Organic Syntheses," V, 17). The halogenated acetophenones were purified by distillation in vac., followed by two crystns. from light petroleum. M. p.'s 19·8°, 51·6°, and 84·8 respectively. In the prepn. of *p*-iodo-acetophenone it was necessary to carry out the operations as rapidly as possible, owing to liberation of I and subsequent loss of yield as ω-iodo-compound. *p*-Methyl-acetophenone was distilled several times under low press.; b. p. 83—83·5°/6 mm. *p*-Nitroacetophenone was prepared from ethyl *p*-nitrocinnamate by Drewsen's method (*Annalen*, 1882, **212**, 160), and finally purified by steam distillation, followed by crystn. from aq. AcOH and then light petroleum. The product was very pale yellow; m. p. 78·4°. In this case, steam distillation was the only process which removed a trace of impurity which reacted rapidly with Br.

Velocity Measurements.—Solutions of the desired concn. ([Ketone] = 0·1*M*; [Ketone]/[Br] not less than 20) were made up in 75% or 50% AcOH, purified by the method of Orton and Bradfield (J., 1927, 983), and the reaction at 25° followed by withdrawing 20 c.c. at intervals and adding them to a solution (80 c.c.) containing 1 g. NaAc and sufficient KI to give a 50% excess over the anticipated titre. The results are summarised in the text.

The authors are indebted to Imperial Chemical Industries, Ltd., for a grant.

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[*Received, January* 23*rd*, 1933.]