THE REACTIONS OF HALOGENS WITH COMPOUNDS CONTAINING THE CARBONYL GROUP

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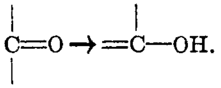
I. KETONES AND KETONIC ACIDS

It was first suggested by Lapworth (53) in 1904 that the characteristic replacement by halogens of the α-hydrogen atom in carbonyl compounds might involve a preliminary change of the compound to its enolic form,



$$\text{C}{=}\text{O} \rightarrow {=}\text{C}{-}\text{OH}.$$

The suggestion was based on his discovery that bromine reacts with acetone in dilute aqueous solution (to give monobromoacetone) at a rate which is proportional to the concentration of the ketone, but independent of that of the halogen; the reaction, moreover, is accelerated to a very marked extent by mineral acids (well-known catalysts of keto-enol changes (52) (54) (62)). These observations led Lapworth to suggest that a slow change to the enolic form (catalyzed by acids) is followed by a very rapid reaction of the latter with bromine,

$$CH_3 \cdot CO \cdot CH_3 \xrightarrow{\text{(slow)}} CH_2{:}C(OH) \cdot CH_3 \xrightarrow{Br_2 \text{ (rapid)}} CH_2Br \cdot CO \cdot CH_3 + HBr.$$

The results of Dawson and his co-workers (14, 15, 16, 17, 18), who examined the iodination of acetone and other ketones and of acetaldehyde, confirmed the conclusion that the reactions of the halogens with ketones and aldehydes are preceded by enolization of the carbonyl compound.

An extensive investigation of the keto-enol tautomerism of the β-diketones and β-ketonic esters (e.g. acetylacetone, ethyl acetoacetate) by K. H. Meyer, Knorr, and others, showed that

CHEMICAL REVIEWS, VOL. VII, NO. 2

these substances exhibit this type of isomerism with great clearness. In the case of acetone, the actual existence of an enolide has never been demonstrated, although Freer (24, 25, 26, 27, 28, 29) has attributed an enolic structure to certain metallic derivatives, and the presence of enolide in alkaline solutions has been inferred (20) (23) (100) from the nature of its oxidation products. The β-diketones and β-ketonic esters, on the other hand, are normally equilibrium mixtures of the ketonic and enolic forms, and the relative amounts of each present have been determined by both physical and chemical methods. Moreover, in a number of instances, the individual tautomerides have been isolated in the pure state (50) (51) (65), e.g., the two forms $CH_3{\cdot}CO{\cdot}CH_2{\cdot}COOEt$ and $CH_3{\cdot}C(OH){:}CH{\cdot}COOEt$ of ethyl acetoacetate. Bromine reacts instantaneously with the enolides, but not with the ketonic isomers.

It has recently been demonstrated, particularly by Dufraisse and H. Moureu (21) (22) (67) (68), that the α-diketones also are tautomeric substances, and these workers have isolated the individual isomerides of phenylbenzyl, phenylanisyl, and benzylmethyl diketones. The existence of the same phenomenon in the α-ketonic acids was indicated by the work of Schiff (84), Bougault and Hemmerlé (6), and Gault and Weick (31), the last-named of whom isolated three forms of ethyl phenylpyruvate (the ketonic and two stereoisomeric monoenolic forms). Further evidence of the enolization of α-ketonic acids has recently been obtained (42) by an investigation of the kinetics of bromination of pyruvic acid. In aqueous solution, the acid reacts with bromine at a rate which is independent of the concentration of the halogen, and this result is interpreted in a simple manner (compare acetone) by supposing that a comparatively slow change to enolide is followed by a rapid reaction of the latter with bromine,

$$CH_3{\cdot}CO{\cdot}COOH \xrightarrow{\text{(slow)}} CH_2{:}C(OH){\cdot}COOH \xrightarrow{Br_2\ \text{(rapid)}} CH_2Br{\cdot}CO{\cdot}COOH + HBr.$$

The pure acid, however, under ordinary conditions, contains no appreciable amount of enolide, since the measurable reaction is never preceded by an instantaneous disappearance of a portion of the bromine. This is in harmony with the results of the physical measurements of Perkin (76) and Brühl (9).

Although keto-enol tautomerism is clearly possible also in γ-diketones and γ-ketonic acids, its existence has not been demonstrated until recently. Investigation of the bromination of levulic acid in aqueous solution (42) has now indicated, however, that this acid reacts with bromine in its enolic form to give the β-brominated derivative,

$$\mathrm{CH_3\cdot CO\cdot CH_2\cdot CH_2\cdot COOH} \xrightarrow{\text{(slow)}} \mathrm{CH_3\cdot C(OH){:}CH\cdot CH_2\cdot COOH}$$

$$\xrightarrow{\mathrm{Br_2}\ \text{(rapid)}} \mathrm{CH_3\cdot CO\cdot CHBr\cdot CH_2\cdot COOH + HBr},$$

while the latter reacts more slowly, also after enolization, to form $\beta\delta$-dibromolevulic acid,

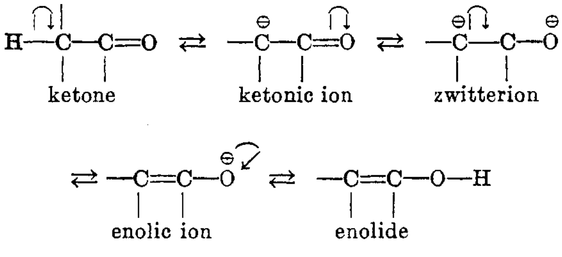
$$\mathrm{CH_3\cdot CO\cdot CHBr\cdot CH_2\cdot COOH} \xrightarrow{\text{(slow)}} \mathrm{CH_2{:}C(OH)\cdot CHBr\cdot CH_2\cdot COOH}$$

$$\xrightarrow{\mathrm{Br_2}\ \text{(rapid)}} \mathrm{CH_2Br\cdot CO\cdot CHBr\cdot CH_2\cdot COOH + HBr}.$$

The facts outlined above point to the conclusion that, in general, the reactions of halogens with ketones, aldehydes, diketones, and ketonic acids are preceded by a change of the carbonyl compound to its enolic form. It is significant, however, that the enolide $\mathrm{CH_3\cdot CO\cdot CH{:}C(OH)_2}$ of ethyl acetoacetate has never been observed, while levulic acid brominates in the β- and δ-positions and not in the α-position. Such evidence appears to indicate that, in the carboxyl group, the properties are modified in such a way that enolization does not occur. This is discussed fully in section II of this paper.

The mechanism of enolization and other prototropic changes has recently been discussed in terms of the electronic theory of valency, by Lowry (57) (58), Ingold, Shoppee and Thorpe (46), and Baker (3). Lowry believes (and the suggestion dates back as far as 1899) that prototropic changes are not spontaneous, but depend upon the presence in the system of other molecules; this idea is based upon the observation of arrests of irregular duration in the mutarotation of nitrocamphor (56) and of tetramethylglucose (61) in anhydrous media. He defines such arrests as the "period of time during which a pure substance is taking up the impurities which are needed to promote the change." Experiments on the bromination of acetone, pyruvic acid and levulic acid (42) in chloroform or carbon tetrachloride medium confirm Lowry's view. In aqueous solution these substances react with bromine at a slow rate, i.e., slow enolization takes place, but in the anhydrous solvents there is a relatively rapid reaction after an initial latent period, the duration of which varies for different portions of the same specimens of the reagents. Ward (92) observed a similar phenomenon in the bromination of pure pyruvic acid. The experimental facts point, therefore, to the conclusion that enolization takes place only when some outside agent is introduced or developed in the system.

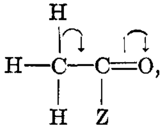
According to Lowry, prototropic changes are possible only in presence of both a proton donator and a proton acceptor, the change consisting not merely in the transference of a proton from one point in the molecule to another, but in the release of the proton to the acceptor and the gain of another proton from the donator. This theory, as applied to mutarotation, has been verified in a striking manner by the observation (60) that, although pyridine (proton acceptor) and cresol (proton donator) do not individually catalyze the mutarotation of tetramethylglucose, the two acting in conjunction form a powerful catalyst. Lowry's view, therefore, is that two catalytic agents are necessary for the promotion of prototropic changes; he describes water, however, as a "complete catalyst," since it fulfils both functions. As an extension of these ideas, Lowry has elaborated (58) a mechanism to represent the change of enolide to ketone, which, when applied to the reverse change, may be formulated as follows:



According to this scheme, the catalyst has no function other than that of proton acceptor and donator. A somewhat different view of the effects of catalysts on prototropic changes has been put forward by Baker (3); on the basis of a mechanism suggested by Ingold, Shoppee and Thorpe (46) to represent the interconversion of three-carbon tautomerides, he suggests that catalysts are of two types,—(*a*) those whch attack the ionizing proton directly, and (*b*) those which facilitate indirectly its liberation.

It was pointed out by Meyer (62) that acids catalyze enolization far more powerfully in non-ionizing than in ionizing media—i.e., the acid exerts a far greater influence when in the covalent state (vide Sidgwick, Electronic Theory of Valency, p. 93) than when ionized. This fact has been further demonstrated by the author's measurements of the speeds of halogenation of carbonyl compounds in different media, and particularly by the observation that, in moist chloroform, the bromination of acetone, pyruvic acid and levulic acid (autocatalyzed by hydrogen bromide), although not showing an arrest, is very much slower than in dry chloroform. It is difficult to understand how this could be the case if the function of the catalyst is only that of proton donator and acceptor, but the observed effects of water and acids upon enolization may perhaps be interpreted by the following scheme, which includes the ideas of both Lowry and Baker. Water is regarded as merely giving and accepting a proton, while acids combine these functions with that of facilitating the removal of the proton (Baker's second type).

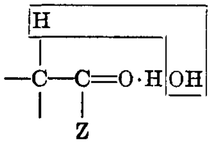
In carbonyl compounds there is doubtless a partial appropriation of electrons by the oxygen atom of the carbonyl group (81) (5), and in the general case of a compound $CH_3 \cdot CO \cdot Z$ (where $Z = CH_3$, COOH, etc.) this will result in one of the hydrogen atoms of the methyl group being in a state of "incipient ionization" (41) (46),



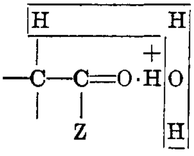
$$\begin{array}{ccccc} & & H & & \\ & & | & & \\ H & — & C & — & C{=}O, \\ & & | & & | \\ & & H & & Z \end{array}$$

i.e., the electrons forming the covalent link are not shared equally, but come more under the influence of the carbon than of the hydrogen nucleus. Considering now the case of enolization, (*a*) in pure water, (*b*) in water in presence of halogen or other acid, and (*c*) in non-ionizing media in presence of acids, the agents by which the change is induced are respectively, (*a*) H_2O, (*b*) the H_3O^+ ion, (*c*) the covalent acid. These may be regarded as coördinating with the carbonyl oxygen, to give respectively,

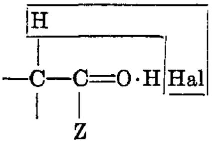
(a)



(b)



(c)



The coördinated group thus provides a proton. In cases (*b*) and (*c*), however, an additional influence comes into play, for the "inductive effect" (44) of the positive pole in (*b*) and of the halogen atom in (*c*) will augment the electron shifts which lead to the ionizing of the proton, and will thus facilitate enolization.[1] The remainder of the coördinated group (OH′, H_2O, Hal′) will then withdraw the incipiently ionized hydrogen atom, and these processes, together with the consequent movement of electrons through the molecule (perhaps as indicated by Lowry), will result in the production of the enolide.

On this scheme, water acts only (as in Lowry's mechanism) as a proton acceptor and donator, but acids, both ionized and covalent, also accelerate the change by rendering more easy the ionizing of the proton. The catalytic effect of acids is thus interpreted. Moreover, the superiority of covalent to ionized acids as catalysts is explained, for the proton will clearly unite with a bromine (or other negative) ion to give covalent acid more readily than with a neutral water molecule to give the H_3O^+ ion.

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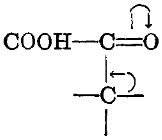
[1] The powerful electron affinity of the halogens is exemplified in the increasing proportion of meta-derivative formed in the nitration of the series toluene, benzyl chloride, benzal chloride, benzotrichloride; $PhCH_3$, 4.4%; $PhCH_2Cl$, 16%; $PhCHCl_2$, 33.8%; $PhCCl_3$, 64.5%. Holleman; Rec. trav. chim. **33**, 1 (1914). Baker and Ingold: J. Chem. Soc. **1926**, 2466. Ingold and Rothstein: ibid. **1928**, 1278.

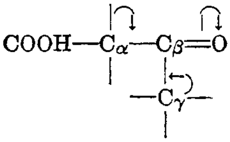
Considering now the special case of ketonic acids, and taking pyruvic, acetoacetic and levulic acids as typical examples of the α-, β-, and γ-types, the effect of the partial appropriation of electrons by the carbonyl oxygen may be represented as follows (oxygen in the *carboxyl* group does not have this effect, see following section);

pyruvic



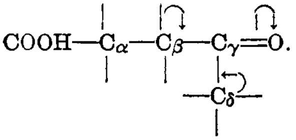
$\mathrm{COOH{-}C{=}O}$

acetoacetic



$\mathrm{COOH{-}C_{\alpha}{-}C_{\beta}{=}O}$

levulic.



$\mathrm{COOH{-}C_{\alpha}{-}C_{\beta}{-}C_{\gamma}{=}O.}$

In acetoacetic and levulic acids, therefore, the effect is shared by an α- and a γ-hydrogen atom and by a β- and a δ-hydrogen atom respectively. Superimposed on this, however, is the inductive effect of the carboxyl group,[2] and as early as 1904 the different enolizing tendencies of acetone and ethyl acetoacetate were ascribed by Lowry to the presence of the carbethoxyl group in the latter. This effect of the carboxyl group causes pyruvic acid to enolize more rapidly than acetone; moreover, it tends powerfully towards the ionization of the α-hydrogen of acetoacetic acid, and the β-hydrogen of levulic acid. This is in harmony with the facts that (*a*) in ethyl acetoacetate only the *one* enolide $\mathrm{CH_3{\cdot}C(OH){:}CH{\cdot}COOH}$ is known, and (*b*) the β-hydrogen atom of levulic acid enolizes more readily than the δ-hydrogen atom. The tendency to enolization is undoubtedly stronger in acetoacetic than in levulic acid (ethyl acetoacetate normally contains 7 per cent of enol), and this may be attributed to a screening of the effect of the carboxyl group in the latter by the α-carbon atom.[3]

There is, therefore, a large amount of experimental evidence for the assertion that, in general, compounds containing a car-

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[2] Attraction of electrons, as indicated, for example, by the fact that nitration of benzoic acid yields 80.2 per cent of the meta-derivative. Holleman: Rec. trav. chim. **18,** 267 (1899). Ingold: Annual Report **1926,** 138.

[3] Compare the decrease in percentage of meta-derivative in the nitration of the series nitrobenzene, phenylnitromethane, β-phenyl-nitroethane: $\mathrm{PhNO_2}$, 93%; $\mathrm{PhCH_2NO_2}$, 48%; $\mathrm{PhCH_2CH_2NO_2}$, 13%. Ingold: Annual Report **1926,** 132.

bonyl group (excluding the *carboxyl* group), with at least one hydrogen atom situated in the α-position with respect to that group, react with halogens in their enolic forms. Moreover, the phenomena observed are such as would be anticipated, on theoretical grounds, from the electronic theory of valency.

II. CARBOXYLIC ACIDS

The case of the carboxyl group calls for special discussion, and is best illustrated by reference to acetic acid and its homologues. At the ordinary temperature these acids are not attacked by chlorine or bromine at an appreciable rate, but at a more elevated temperature (e.g., 100°) replacement of one α-hydrogen occurs,

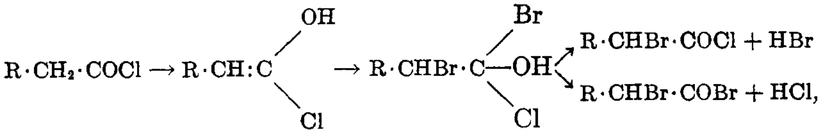
$$\mathrm{R\cdot CH_2\cdot COOH + X_2 = R\cdot CHX\cdot COOH + HX}$$

The replacement of a second α-hydrogen atom is a matter of very considerable difficulty, and if there is no α-hydrogen atom, substitution does not take place, as is exemplified by the fact that trimethylacetic acid gives no brominated acid when treated with bromine at 100–135° (82).

The facts that substitution always takes place at the α-position, and that the reaction is accelerated by halogen acids (first observed by Hell and Mühlhäuser (36)) appear to indicate an analogy with the bromination of acetone, and Lapworth (53) in 1904 suggested tentatively that the acid might perhaps react in its enolic form, according to the scheme

$$\mathrm{R\cdot CH_2\cdot COOH} \xrightarrow{\text{(slow)}} \mathrm{R\cdot CH{:}C(OH)_2} \xrightarrow{\mathrm{Br_2}\text{ (rapid)}} \mathrm{R\cdot CHBr\cdot COOH + HBr.}$$

The catalytic influence of halogen acids would then consist in an acceleration of the enolization. Aschan (1) adopted Lapworth's suggestion to explain the production of brominated acid bromide, as well as brominated acid chloride, when bromine reacts with an acid chloride, which he represented

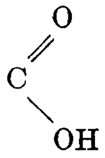
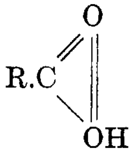
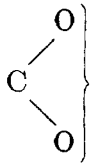


$$\mathrm{R\cdot CH_2\cdot COCl} \rightarrow \mathrm{R\cdot CH{:}C}\begin{matrix}\diagup\mathrm{OH}\\ \diagdown\mathrm{Cl}\end{matrix} \rightarrow \mathrm{R\cdot CHBr\cdot}\overset{\mathrm{Br}}{\underset{\mathrm{Cl}}{\mathrm{C}}}\mathrm{{-}OH}\begin{matrix}\nearrow\mathrm{R\cdot CHBr\cdot COCl + HBr}\\ \searrow\mathrm{R\cdot CHBr\cdot COBr + HCl,}\end{matrix}$$

but Meyer pointed out (64) that such an interpretation is unnecessary, since the observation is explained equally well by postulating bromination of the ketonic form, followed by a reaction of hydrogen bromide with the brominated acid chloride,

$$\mathrm{R{\cdot}CHBr{\cdot}COCl + HBr \rightleftarrows R{\cdot}CHBr{\cdot}COBr + HCl},$$

a type of reaction which is known to occur under suitable conditions (87) (66).

It is curious that the supporters of the "enolic form theory" apparently overlooked the results of Hell and Urech (37), who observed that the rate of bromination of acetic acid and its homologues is dependent upon the concentration of bromine; this could not be the case if slow enolization were followed by a practically instantaneous reaction of the enolide with halogen. The theory, moreover, demands the existence of the carboxylic acid in a form which is neither observed nor indicated elsewhere. It may also be urged that, since the reactions of the carbonyl group of a carboxylic acid differ in many respects from those of the same group in a ketone, it is unsafe to force an analogy between the two types of compounds, and the distinction is borne out by the fact that many physical properties of carboxylic acids (e.g., refractive index, Brühl (10); diamagnetism, Pascal (75); rotatory dispersion, Pickard and Kenyon (78); optical absorption, Hantzsch (35); parachor, Sugden (88)) do not give the values which would be anticipated if a carbonyl group of the usual type were present. In the light of these facts, a number of investigators have supposed that the ordinarily accepted formula  $\mathrm{R.\,C}\begin{array}{l}/\!\!/\,\mathrm{O}\\ \diagdown\,\mathrm{OH}\end{array}$ is not a correct representation, and alternative formulas such as  $\mathrm{R.C}\begin{array}{l}/\!\!/\,\mathrm{O}\\ \quad\|\\ \diagdown\,\mathrm{OH}\end{array}$ (Smedley (86)) and  $\mathrm{R.\,C}\left.\begin{array}{l}/\,\mathrm{O}\\ \diagdown\,\mathrm{O}\end{array}\right\}\mathrm{H}$ (Hantzsch (35)) have been suggested. On modern views, the failure of the carboxyl group to exhibit the typical carbonyl reactions is ascribed to the competition $\overset{\curvearrowright}{HO} - \underset{|}{C} = \overset{\curvearrowright}{O}$ (81) (46); the effect of the partial appropriation of electrons by the carbonyl oxygen is thus neutralized, and the tendency of the α-hydrogen atom to ionize is removed. It is not to be expected, therefore, that the halogenation of acetic acid and its homologues will be preceded by a change of the acid to its enolic form, and this has been demonstrated by an investigation of the kinetics of these reactions at 100° (93) (95) (97) (96).

The investigation has provided definite confirmation of the facts (first stated by Hell and Urech (37)) that the speed of bromination of these acids is (*a*) dependent upon the concentration of bromine, and (*b*) increased by the presence of halogen acids.

TABLE 1

Bromination of acetic acid at 100°C.

Catalyst added	nil	HBr = 0.053M	HCl = 0.064M	AcBr = 0.047M
Initial titre	9.48	9.58	10.02	9.55
Fall in 30 minutes	0.20	1.05	0.52	8.00

Thus, when no catalyst is present initally, the course of the reaction indicates autocatalysis by the hydrogen bromide produced, for the rate of disappearance of bromine gradually rises to a maximum and finally decreases; variation in the initial concentration of bromine has a marked effect, while the presence of a moderate initial concentration of hydrogen bromide induces a much faster reaction, the period of increasing speed disappearing. The effect of hydrogen chloride resembles that of hydrogen bromide, but is somewhat less powerful. The influence of halogen acids, however, is specific, and not common to acids in general, for sulfuric and trichloroacetic acids do not have a similar effect; the acceleration produced by halogen acids is not likely, therefore, to consist merely in a speeding up of the enolization of the carboxylic acid, and this fact, together with the dependence of the velocity upon the concentration of bromine, provides evidence against the validity of the simple "enolic form theory."

The outstanding feature of the reaction, as revealed in this investigation, is the enormous acceleration produced by a small quantity of an acid bromide, different acid bromides having identical effects. The magnitude of this acceleration is obvious from table 1. Further, in presence of acetyl bromide (or other acid bromide), the velocity is proportional to the concentration of both acid bromide and bromine. The autocatalytic effect of the hydrogen bromide formed during the reaction will clearly be inappreciable in the presence of the more powerful accelerator.

A similar rapid reaction results from the introduction of an acid anhydride (compare Hentschel (38); Shaw (85)) or acid chloride, but there is now an initial period of relatively low but increasing speed; this period is easily interpreted as the time needed for the conversion of anhydride or acid chloride into acid bromide,

$$\begin{aligned} &(R{\cdot}CH_2{\cdot}CO)_2O + Br_2 = R{\cdot}CHBr{\cdot}COOH + R{\cdot}CH_2{\cdot}COBr \\ &(R{\cdot}CH_2{\cdot}CO)_2O + HBr \rightleftarrows R{\cdot}CH_2{\cdot}COOH + R{\cdot}CH_2{\cdot}COBr \\ &R{\cdot}CH_2{\cdot}COCl + HBr \rightleftarrows R{\cdot}CH_2{\cdot}COBr + HCl, \end{aligned}$$

and such an explanation is confirmed by two observations: (*a*) the initial period disappears if excess of hydrogen bromide is introduced with the anhydride; the latter is doubtless, under these conditions, converted very rapidly to acid bromide (this reaction proceeds readily even at room temperature), and the bromide is thus present from the commencement at its maximum concentration; (*b*) excess of hydrogen chloride introduced in conjunction with the anhydride has a retarding influence; the anhydride now forms acid chloride,

$$(R{\cdot}CH_2{\cdot}CO)_2O + HCl \rightleftarrows R{\cdot}CH_2{\cdot}COOH + R{\cdot}CH_2{\cdot}COCl$$

(Gal (30)), and anything approaching complete conversion to acid bromide during the reaction is prevented by the excess of hydrogen chloride.

Investigation of the chlorination of acetic acid has yielded a similar series of observations (the acid chloride here being the powerful accelerator), except that (*a*) the reaction is somewhat slower than bromination, and (*b*) in presence of an acid chloride the velocity decreases less rapidly than the concentration of chlorine. These peculiarities are discussed later (p. 185).

An interpretation of the facts outlined above may be found in the following considerations. It has long been known that halogens react with the halides of carboxylic acids more rapidly than with the acids themselves, and the Hell-Volhard method of bromination is based upon this fact. The peculiarly powerful effect of acyl halides as accelerators of the halogenation of carboxylic acids may be interpreted, accordingly, by supposing that the halide first reacts with halogen,

$$R\cdot CH_2\cdot COX + X_2 = R\cdot CHX\cdot COX + HX, \qquad (1)$$

the halogenated acid then being formed as the result of a reaction between the unsubstituted acid and the halogenated halide,

$$R\cdot CHX\cdot COX + R\cdot CH_2\cdot COOH \rightleftarrows R\cdot CH_2\cdot COX + R\cdot CHX\cdot COOH. \qquad (2)$$

The acyl halide is thus free to go through the same series of changes again. If the halide of a different carboxylic acid be present initially, reactions (1) and (2) will be preceded by

$$R'\cdot COX + R\cdot CH_2\cdot COOH \rightleftarrows R\cdot CH_2\cdot COX + R'\cdot COOH, \qquad (2a)$$

which is exactly similar in character to reaction (2).

It has been suggested by Hentschel (38), Shaw (85) and Brückner (8) that the halogenation of carboxylic acids proceeds through the anhydride (which also reacts with halogens far more readily than does the acid itself), by the following pair of alternating reactions,

$$(R\cdot CH_2\cdot CO)_2O + X_2 = R\cdot CH_2\cdot COX + R\cdot CHX\cdot COOH$$
$$R\cdot CH_2\cdot COX + R\cdot CH_2\cdot COOH \rightleftarrows (R\cdot CH_2\cdot CO)_2O + HX.$$

It has been pointed out above, however, that in both chlorination and bromination the introduction of a small amount of the acid anhydride leads to a rapid reaction *after* an initial period of relatively low speed, while there is no such period when the appropriate acid halide is introduced; this observation indicates clearly that the halogenation proceeds through the halide, the initial period being easily accounted for as described above.

It will be seen from the following discussion of other relevant facts that the author's scheme is supported by a considerable amount of experimental evidence.

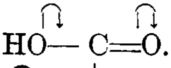
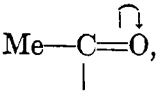
Reaction (*1*) (p. 184). The results of Urech (90) indicate that the bromination of acetyl bromide proceeds at a rate which is proportional to the concentrations of bromine and of acid bromide, and the author has confirmed this observation by an investigation of the reaction at 25° (95), using an apparatus specially designed to avoid contact of the acid bromide with atmospheric moisture. If now, in the scheme outlined above, reaction (2) proceeds at very great speed, and practically to completion in presence of the excess of the carboxylic acid (as is indicated in the case of the analogous reaction (2a) by the identical effects of different acid bromides), the concentration of acyl halide will remain constant during any given reaction, and the velocity will vary, therefore, only as the concentration of bromine, but will be proportional to the initial concentration of the acyl bromide. This is in complete agreement with the observed facts for the bromination of carboxylic acids, and it is clear, therefore, that the halogen does not react with the enolic form of the acid to a measurable degree, a conclusion which is confirmed by the observation that such powerful accelerators of enolization as sulfuric acid and ferric chloride do not affect the halogenation appreciably.

In the case of chlorination (97), complications arise from the fact that side reactions take place during the chlorination of acetyl chloride. The velocity of chlorination of the pure chloride, in fact, actually increases as the reaction proceeds, owing to these side reactions (which however are imperceptible in presence of a powerful catalyst such as iodine, when the velocity is proportional to the concentration of chlorine), and it is thus easy to explain the absence, in the chlorination of acetic acid, of a simple relation between the fall in concentration of chlorine and the velocity.

It appears at first sight remarkable that chlorination is slower than bromination. This is due, however, to the fact that halogens react with acid chlorides far less rapidly than with acid bromides; for example, the reactions (*a*) acetyl bromide + bromine, (*b*) acetyl chloride + bromine, (*c*) acetyl chloride + chlorine, stand in decreasing order of speed. In view of this fact, the chlorination of acetic acid, which involves the reaction of chlorine with acetyl chloride, must be less rapid than its bromination, which depends upon the reaction of bromine with acetyl bromide. Moreover, in presence of an acid chloride, the bromination of acetic acid doubtless proceeds through the series of reactions:

$$CH_3\cdot COCl + Br_2 = CH_2Br\cdot COCl + HBr$$
$$CH_2Br\cdot COCl + CH_3\cdot COOH \rightleftharpoons CH_2Br\cdot COOH + CH_3\cdot COCl.$$

The reaction is not rapid, however, owing to the relatively slow rate of bromination of acetyl chloride. Hence, the reaction of bromine with a carboxylic acid in presence of an acid chloride does not reach its maximum speed until sufficient hydrogen bromide has been formed to bring about conversion of acid chloride to acid bromide; the above reactions are then replaced by those in which the acid bromide takes part.

Finally, the relative rates of halogenation of the compounds considered above are such as would be predicted on theoretical grounds. It has already been pointed out (p. 182) that the failure of acetic acid to enolize is ascribed, on modern theory, to the competition  $\mathrm{HO}\overset{\curvearrowright}{—}\,\overset{\curvearrowright}{\mathrm{C}{=}}\mathrm{O}$. There is no such competition in acetone,  $\mathrm{Me}—\overset{\curvearrowright}{\mathrm{C}{=}}\mathrm{O}$, and the latter reacts with halogens in its enolic form, slow enolization being followed by a relatively instantaneous reaction of the enolide with halogen. Similarly, enolization of the acyl halides should also be possible, and enolization will here be facilitated by the inductive effect of the halogen atoms.[4]

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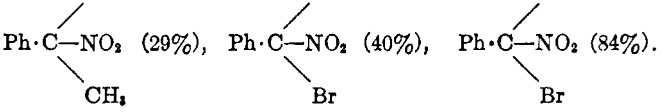
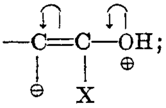
[4] The relative inductive effects of methyl and halogen are exemplified by a comparison of the strengths of *o*-bromobenzoic ($K = 1.215 \times 10^{-3}$) and monobromoacetic ($K = 1.5 \times 10^{-3}$) acids with those of *o*-toluic ($K = 1.2 \times 10^{-4}$) and propionic ($K = 1.34 \times 10^{-5}$) acids; also in the increasing proportion of meta-derivative formed (see Baker and Ingold: J. Chem. Soc. **1926**, 2466) in the nitration of the series.



$\mathrm{Ph\cdot C(CH_3)_2{-}NO_2}$ (29%), $\mathrm{Ph\cdot C(CH_3)(Br){-}NO_2}$ (40%), $\mathrm{Ph\cdot CBr_2{-}NO_2}$ (84%).

It is to be anticipated, therefore, that acetyl chloride and bromide will enolize at a much greater rate than does acetone. After enolization, the enolide will become activated as follows,



$$-\underset{\ominus}{\overset{\curvearrowleft}{\text{C}}}=\underset{\text{X}}{\text{C}}-\underset{\oplus}{\overset{\curvearrowleft}{\text{OH}}};$$

and this activation will now be opposed by the effect of the halogen. It may be predicted, therefore, that in the acyl halides rapid enolization will be followed by a relatively slow reaction of the enolide with halogen[5]; if this be the case, the velocity of halogenation will be proportional to the concentration of the halogen, as is found by experiment. The fact that substitution in aliphatic acids invariably occurs at the α-position finds a simple explanation in this suggestion. The relatively slow rate of halogenation of acetyl chloride (as compared with the acid bromide, see p. 185) is probably to be attributed to the greater inductive effect of chlorine than of bromine (4) (43).

Reactions (2) and (2a) (p. 184). The reaction of a carboxylic acid with the halide of another acid was observed by Polzenius (80), who isolated benzoic acid and acetyl chloride by distilling acetic acid with benzoyl chloride, and a similar reaction was suggested by Orton (70) as providing a possible explanation of the formation of acid amides, sometimes in 75 per cent yield, by the reaction of benzoyl chloride with carboxylic acids in presence of ammonia.

An investigation of the products of the reaction of acetic acid with its halogenated halides has indicated that these reactions

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[5] An analogy is found in the suggestion (West: J. Chem. Soc. **125**, 1277 (1924)) that, in the bromination of monobromomalonic acid, rapid enolization is followed by a slow reaction with halogen,

$$\text{HOOC}\cdot\text{CHBr}\cdot\text{COOH} \xrightarrow{\text{rapid}} \text{HOOC}\cdot\text{CBr}:\text{C(OH)}_2 \xrightarrow{\text{Br}_2\text{ (slow)}} \text{HOOC}\cdot\text{CBr}_2\cdot\text{COOH} + \text{HBr}.$$

In order to account for the fact that the enolic forms of these compounds have never been observed, it is necessary to suppose that the change of enol to keto is extremely rapid.

occur in two stages, a mixed anhydride being formed as intermediate product, thus;

$$\begin{gathered}CH_2X{\cdot}COX + CH_3{\cdot}COOH \rightleftharpoons CH_2X{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3 + HX\\ CH_2X{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3 + HX \rightleftharpoons CH_2X{\cdot}COOH + CH_3{\cdot}COX.\end{gathered}$$

Thus, on distillation of acetic acid with chloroacetyl chloride, the first product is acetyl chloride, and if the remainder be fractionated under reduced pressure, acetic chloroacetic anhydride may be obtained. The mixed anhydrides undergo various changes according to the experimental conditions; they react with halogen acids (as above equation) with great readiness even at room temperature, and in the halogenation of acetic acid at 100° (when halogen acid is formed continuously) this change will doubtless be practically instantaneous.

The halogenation of carboxylic acids in presence of a trace of acyl halide has thus been shown to proceed through the series of reactions:

$$\begin{gathered}R{\cdot}CH_2{\cdot}COX + X_2 = R{\cdot}CHX{\cdot}COX + HX\\ R{\cdot}CHX{\cdot}COX + R{\cdot}CH_2{\cdot}COOH \rightleftharpoons R{\cdot}CHX{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_2{\cdot}R + HX\\ R{\cdot}CHX{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_2{\cdot}R + HX \rightleftharpoons R{\cdot}CHX{\cdot}COOH + R{\cdot}CH_2{\cdot}COX.\end{gathered}$$

This scheme appears to be in harmony with all the experimental results.

Catalytic effect of phosphorus. The original Hell-Volhard reaction obviously consisted in the bromination of the acid bromide. The acid was treated with sufficient phosphorus and bromine for complete conversion to bromide and bromination of the latter, and the product was treated with water in order to obtain the halogenated acid. It was found, however, that a vast increase in speed of bromination was produced by a very small quantity of phosphorus, and the effect of the catalyst was here difficult to explain. Lapworth (53) suggested that it might be attributed to the production of hydrogen bromide which accelerated the enolization of the acid, but this idea has been shown to be untenable. Moreover, Ward's results (91) showed clearly that the catalytic effect of phosphorus is far more powerful than that of halogen acids; it is, in fact, of the same order of magnitude as that of acid bromides observed by the author. In bromination in presence of phosphorus a small amount, at least, of the acid bromide is always formed, and may be detected in the product; it is quite obvious, therefore, that the acceleration is due to this small quantity of acid bromide, the reaction proceeding according to the scheme outlined above. The similar effect of phosphorus or phosphorus pentachloride on the chlorination of carboxylic acids (see Brückner (7)) may be interpreted in the same manner.

Catalytic effect of halogen acids. It may be further suggested that the effect of halogen acids is due to traces of the acyl halide present in equilibrium with the acid,

$$R\cdot COOH + HX \rightleftharpoons R\cdot COX + H_2O.$$

The very different effects of halogen acids and acyl halides indicate that the quantity of acyl halide necessary to produce the observed velocity would be too small for detection, and the existence of such an equilibrium has never been demonstrated. It is not impossible, however, in view of the reversible nature of the hydrolysis of many inorganic chlorides, while it is suggested by reactions of the type:

$$R\cdot CN + R'COOH + 2\,HCl = R\cdot CO\cdot NH_2\cdot HCl + R'\cdot COCl$$

(Colson (13)). Such an interpretation is supported by the following facts:

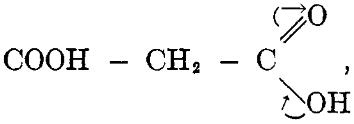
(*a*) the influence of halogen acids is specific, and not common to acids in general;

(*b*) Lapworth observed that a small quantity of water (which would displace the above equilibrium towards the left-hand side, thus reducing the concentration of acyl halide) reduces very considerably the speed of bromination, and this result has been confirmed by the author;

(*c*) when varying amounts of the acid bromide are added to acetic acid containing a small amount (e.g., 0.1 per cent) of water, there is a continuous increase in velocity as the amount of acid bromide becomes greater, and not a sudden increase at the point where the bromide is just in excess of the water; addition of anhydride, on the other hand, causes a sudden increase at this point.

In the former case, therefore, a gradual increase in the amount rather than a sudden change in the nature of the catalyst is indicated.

The above suggestion brings into harmony all previous observations of the catalyzed halogenation of carboxylic acids, by postulating in every case a similar mechanism, viz., the series of reactions involving the halogenation of the acyl halide.

Dicarboxylic acids. The results outlined above indicate clearly that acetic acid and its homologues show little or no tendency to enolization. It is obviously necessary to explain the fact that malonic acid is known to react with bromine in its enolic form (64) (99). As in the case of acetic acid, there is here the competition  $\mathrm{COOH - CH_2 - C}\genfrac{}{}{0pt}{}{\nearrow\!\!\nearrow \mathrm{O}}{\searrow \mathrm{OH}}$, which, as already pointed out, neutralizes the effect of the partial appropriation of electrons by the carbonyl oxygen, and removes (in the case of acetic and homologous acids) the tendency of the α-hydrogen atom to ionize. In malonic acid, however, there is also the powerful inductive effect of the second carboxyl group (compare p. 179), and it is doubtless this influence which causes enolization to take place readily even at temperatures as low as 0°. In the case of monobromomalonic acid, the combined effects of the carboxyl group and the bromine atom tend in this direction, and it appears (99) that here the rate of enolization is very rapid in comparison with the speed of reaction of the enolide with bromine.

Succinic acid is known to react with bromine in aqueous solution at temperatures above 100°; the conditions are obviously unfavorable to the production of the acyl halide, and it may be suggested that here also the acid reacts in its enolic form. If this be the case, enolization occurs less readily than in the case of malonic acid, since a much higher temperature is needed for bromination, and this may be ascribed to the screening effect of the second carbon atom (compare p. 179). Succinic acid is brominated far more rapidly by the Hell-Volhard method, however, and it may be inferred that, as in the case of the monocarboxylic acids, the acid bromide enolizes with greater ease than the acid itself.

If these suggestions be correct, further increase in the length of the chain between the carboxyl groups should result in a progressive decrease in the speed of bromination, and it is significant that there is no reference in the literature to the bromination of glutaric and the higher acids in aqueous solution, although these acids may be brominated by the Hell-Volhard method. The bromination of dicarboxylic acids is now being further investigated.

III. ACID ANHYDRIDES

The results of certain experiments carried out in this laboratory during the period 1911–14 (71) (33) (73) led to the conclusion that pure acetic anhydride is unattacked by halogens at the ordinary temperature when light is completely excluded, but that the presence of very small quantities of various foreign substances induces a fairly rapid reaction. The observations were not in harmony with the work of earlier investigators (Gal (30); Urech (90); Lapworth (53)), who state that the anhydride reacts, in absence of a catalyst, to give acyl halide and monohalogenated acid,

$$(CH_3\cdot CO)_2O + X_2 = CH_3\cdot COX + CH_2X\cdot COOH.$$

It was significant that all the experiments in which the anhydride was found to be stable to halogens were carried out with the same batch of Kahlbaum's acetic anhydride "free from homologues," purified by fractional distillation, and in order to test the truth of the conclusion reached, an examination was made of the stability to bromine of specimens of acetic anhydride of varied origin and purified by different methods (74). In every case reaction occurred, and it appears probable that the material employed by the pre-war workers contained a trace of some inhibitor which was not removed by fractionation. A search for possible inhibitors has revealed the fact that the introduction of quinoline in minute quantity prevents the reaction from proceeding to a perceptible extent during a long interval of time (in an experiment using $Br_2 = 0.25M$ and $C_9H_7N = 0.006M$ the latent period was of ninety-three hours' duration), after which a fall in bromine concentration commences. Moreover, acetic anhydride containing a trace of quinoline is still stable to bromine after fractionation. Sodium acetate exerts an influence which is similar to, but not as powerful as that of quinoline, whilst (in descending order) pyridine, dimethylaniline, triethylamine, isoquinoline, ammonium acetate, methylamine and ethylamine are less effective. Addition of a trace of nitric acid or of acetyl nitrate is accompanied by an extremely powerful inhibition; the effect of the former is probably due to acetyl nitrate formed (79) by reaction of the acid with acetic anhydride, for the bromination of propionic anhydride (which is similar to that of acetic anhydride, but considerably slower) is inhibited by acetic anhydride and nitric acid in conjunction but not by nitric acid alone. It is remarkable, however, that these substances which inhibit the bromination of acetic anhydride have no similar effect on the chlorination of the same substance. This peculiarity is discussed later.

The mechanism of the reaction. The idea that the reaction of chlorine or bromine with acetic anhydride (to give acyl halide and monohalogenated acid) might occur in more than one stage is due originally to Lapworth (53), who discovered that the introduction of mineral acid led to an increase in speed, and suggested (by analogy with the bromination of acetone) that halogenation might be preceded by enolization of the anhydride. The results of Orton and Jones (71) appeared to indicate that the speed of halogenation in presence of a catalyst was independent of the concentration of halogen, and thus to confirm Lapworth's suggestion. Fuller investigation (74) (97) of the reaction of chlorine and of bromine with acetic anhydride at 25°, however, has shown that the velocity is very greatly influenced by changes in the concentration of halogen, and, moreover, is increased by the presence of an acyl halide. The effect of halogen acids is identical with that of acyl halides, owing to the conversion (all but complete)

$$(CH_3\cdot CO)_2O + HX \rightleftharpoons CH_3\cdot COX + CH_3\cdot COOH.$$

Chlorination is a much slower process than bromination.

These observations recall the halogenation of carboxylic acids (preceding section), and suggest a series of changes of the following type;

$$CH_3\cdot COX + X_2 = CH_2X\cdot COX + HX \quad (1)$$
$$(CH_3\cdot CO)_2O + CH_2X\cdot COX \rightleftharpoons CH_2X\cdot CO\cdot O\cdot CO\cdot CH_3 + CH_3\cdot COX \quad (2)$$
$$(CH_3\cdot CO)_2O + HX \rightleftharpoons CH_3\cdot COX + CH_3\cdot COOH \quad (5)$$
$$CH_3\cdot COOH + CH_2X\cdot CO\cdot O\cdot CO\cdot CH_3 \rightleftharpoons CH_2X\cdot COOH + (CH_3\cdot CO)_2O \quad (6)$$

preceded, if the halide of another acid is added initially, by

$$(CH_3\cdot CO)_2O + R\cdot COX \leftrightarrows CH_3\cdot CO\cdot O\cdot CO\cdot R + CH_3\cdot COX,$$

or

$$(CH_3\cdot CO)_2O + 2\ R\cdot COX \leftrightarrows (R\cdot CO)_2O + 2\ CH_3\cdot COX.$$

Reactions similar to (6) have been observed by Kaufmann and Luterbacher (49), and the reactions of acetic anhydride with certain acyl halides have been carried out by the author, who finds, for example, that when the anhydride is distilled with chloroacetyl chloride, the products are acetyl chloride and either acetic chloroacetic anhydride or chloroacetic anhydride, depending upon the relative proportions of the reagents.

In the above series of reactions, the rate of disappearance of halogen will be

$$dx/dt = k\ (a - x)\ [\text{acyl halide}]$$

where a is the initial concentration of halogen. If the acyl halide be present in excess, the reaction will be of the first order; the calculated values of

$$k_1 = 1/t\cdot \log_e a/a - x,$$

however, are not constant. If the halogen also reacts with the enolic form of the anhydride (this form being produced slowly and reacting with halogens rapidly), the rate of disappearance of chlorine or bromine will be

$$dx/dt = k(a-x)\ [\text{acyl halide}] + k'[\text{anhydride}],$$

where x is the total amount of the halogen which reacts in time t. In the case where both acyl halide and anhydride are in excess, this reduces to

$$dx/dt = C(a-x) + C' = C(a-x+P),\ \text{where}\ C' = CP,$$

which on integration becomes

$$C = 1/t \cdot \log_e (a+P)/(a+P-x).$$

Constant values of C are obtained by the use of this expression, and the calculated values of k' are the same for both chlorination and bromination. The side reactions which have been observed to take place during the chlorination of acetyl chloride (p. 185) are here not perceptible, owing to the relatively great speed of reaction of chlorine with the acid chloride in acetic anhydride medium (see p. 195).

The results indicate, therefore, that the halogenation of acetic anhydride proceeds by two routes, A and B, as follows;

(A)

$$CH_3 \cdot COX + X_2 = CH_2X \cdot COX + HX \qquad (1)$$

$$(CH_3 \cdot CO)_2O + CH_2X \cdot COX \rightleftharpoons CH_2X \cdot CO \cdot O \cdot CO \cdot CH_3 + CH_3 \cdot COX \qquad (2)$$

(B)

$$(CH_3 \cdot CO)_2O \rightleftharpoons CH_2{:}C(OH) \cdot O \cdot CO \cdot CH_3 \qquad (3)$$

$$CH_2{:}C(OH) \cdot O \cdot CO \cdot CH_3 + X_2 = CH_2X \cdot CO \cdot O \cdot CO \cdot CH_3 + HX \qquad (4)$$

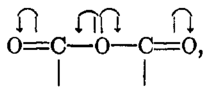
the ultimate products then being formed by the further reactions

$$(CH_3 \cdot CO)_2O + HX \rightleftharpoons CH_3 \cdot COX + CH_3 \cdot COOH \qquad (5)$$

$$CH_3 \cdot COOH + CH_2X \cdot CO \cdot O \cdot CO \cdot CH_3 \rightleftharpoons CH_2X \cdot COOH + (CH_3 \cdot CO)_2O \qquad (6)$$

Route A is the more rapid. The difference in speed between chlorination and bromination is due entirely to the difference in the velocities of halogenation of the acyl halides (compare p. 185).

The fact that acetic anhydride enolizes more readily than acetic acid may be attributed to the sharing of the influence of the singly linked oxygen by the two carbonyl groups,



an effect which is described by Robinson (83) (55) as a "side tracking by a neighboring system of high capacity," and the result is a less complete neutralization of the effect of the carbonyl oxygen. The halogenation of the anhydride, unlike that of acetic acid, is accelerated powerfully by small quantities of sulfuric acid or ferric chloride; the effect of these substances consists in a speeding up of the enolization of the anhydride, for they have no effect on the halogenation of the acyl halide.

It has thus been demonstrated that the reactions of the halogens with carboxylic acids and with acid anhydrides involve similar series of changes, viz., the halogenation of the acyl halide, followed by an interaction of the substituted halide with the acid or anhydride. In the case of the anhydrides, however, the reaction proceeds readily at 25°, while a much higher temperature (e.g., 100°) is required for the halogenation of the acids. This difference appears to be due to the effect of the medium on the velocity of halogenation of the acyl halide, acetic anhydride being a much more favorable medium than acetic acid. Such an explanation is confirmed by the author's observation that addition of a small quantity of acetic anhydride to acetyl bromide results in a great increase in the speed of bromination, whereas the acid bromide reacts with bromine but slowly in acetic acid medium at 25°, and not perceptibly in media such as carbon tetrachloride. The halogenation of the anhydrides of carboxylic acids is thus, in general, analogous to that of the acids themselves, although there are various differences in detail.

The inhibition of bromination. The peculiar effect of quinoline and other substances, which has been referred to above, may be interpreted on the basis of the mechanism which has now been established for the reactions of the halogens with acetic anhydride. In order to throw further light upon the action of quinoline, its effect on the bromination of acetone has been studied (94). When bromine is added to acetone in carbon tetrachloride medium at 25°, no measurable reaction occurs for a short time (which is of variable duration, see p. 176); the disappearance of bromine then becomes perceptible, and almost immediately attains great speed, owing to the very powerful catalytic effect of hydrogen bromide upon enolization in non-ionizing media. Addition of a trace of quinoline arrests the reaction during a long period (several days; the arrests are immensely greater than those referred to on p. 175), and it seems simplest to suggest that the arrest is due to the removal of hydrogen bromide as the hydrobromide (or hydrobromide perbromide (34) (89)) of the base. The well-known inhibition, by certain nitrogen-containing compounds, of gaseous photochemical reactions, has been interpreted in terms of the energetics of the system (11) (12), and of surface phenomena (69), and K. C. Bailey (2) has suggested that the inhibition of esterification by pyridine is due to the preoccupation of active points of the glass surface of the vessel by pyridine molecules, which remove the molecules of acid from postulated acid-alcohol complexes. The author's view of the case under discussion appears, however, to account for the observed facts, and it is immaterial whether the reaction occurs at the surface of the vessel or in the body of the liquid.

A similar interpretation may be applied to the case of acetic anhydride. The reaction of the base with the halogen acid produced in the bromination of the enolized anhydride will prevent the formation of any appreciable quantity of acetyl bromide (or perhaps any acid bromide formed may be converted into an additive compound with quinoline (19)); the main series of reactions, which involves the bromination of the acid bromide, is thus eliminated, until sufficient hydrogen bromide has been formed (in the slow change through the enolized anhydride) to react with the whole of the base. If, however, in presence of quinoline, the enolization of the anhydride took place at the rate indicated by the values of k' referred to on page 193, the small quantities of the inhibitor employed would be removed in a few minutes, whereas the arrests observed are of many hours' duration. In the absence of an inhibitor, however, a small quantity of hydrogen bromide is always present in the equilibrium

$$(CH_3\cdot CO)_2O + HBr \rightleftharpoons CH_3\cdot COBr + CH_3\cdot COOH,$$

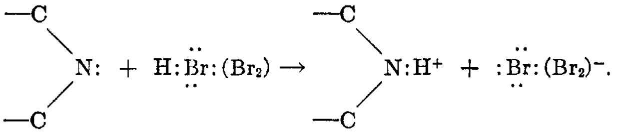
and since acetic anhydride behaves in all respects as a "normal" liquid (compare D. C. Jones and Betts (48); D. C. Jones (47)), this halogen acid will be present in the covalent form; a very minute quantity will therefore produce a marked acceleration of the enolization (compare p. 177). Removal by quinoline of the greater part of this hydrogen bromide will render the enolization of the anhydride so slow as to be imperceptible, and the prolonged period of inertness is thus explained. The shorter duration of this period in presence of pyridine, isoquinoline, triethylamine and dimethylaniline may be attributed to a larger amount of hydrogen bromide present in equilibrium with the base and its hydrobromide, $B \cdot HBr \rightleftarrows B + HBr$. The relatively feeble effect of aliphatic primary and secondary amines is to be expected, since they can be acetylated by the anhydride, as is also the complete inactivity (and even slight accelerating influence) of aniline and monomethylaniline, which are not only acetylated but also substituted in the benzene nucleus, with production of hydrogen bromide.

The negative catalytic effects of organic bases on the bromination of acetic anhydride may be ascribed, therefore, to the removal of hydrogen bromide (or perhaps sometimes of acetyl bromide) by combination with the base. The series of reactions involving the acid bromide is thus eliminated, and, in addition, the speed of enolization of the anhydride very considerably decreased. Sodium and ammonium acetates produce a similar effect owing to the reaction

$$CH_3 \cdot COOM + HBr = CH_3 \cdot COOH + MBr,$$

which proceeds further in the case of the former, as is indicated by its superior inhibiting action.

Even more remarkable than the inhibition of the bromination of acetic anhydride by these basic substances is the fact that they have no similar effect upon chlorination; an explanation of this unexpected difference may be found, however, in the following considerations. Since in acetic anhydride medium the halogen acids are doubtless covalent compounds, their reaction with a base must consist in the giving up of a proton covalently linked to the halogen, and if such release of the proton is not possible no reaction with the base will occur, and halogenation will not be inhibited. It is well-known that in presence of an excess of bromine, hydrogen bromide exists almost entirely as the perbromide HBr_3; the powerful electron affinity of the two coördinated bromine atoms (compare p. 178) will bring about a loosening of the proton, thus enabling its appropriation by the base to take place readily. The reaction of quinoline with the acid is therefore represented



An analogy, consisting in the withdrawl of a proton covalently attached to oxygen, is found in the production of hydroxo-ammines of cobalt and chromium by the action of pyridine or ammonia on the corresponding aquo-ammines (98) (77), as exemplified in the reaction

$$[Cr(NH_3)_2(H_2O)_4]\,Cl_3 + 2\,C_5H_5N = [Cr(NH_3)_2(H_2O)_2(OH)_2]\,Cl + 2\,C_5H_5N\cdot HCl.$$

In the case of hydrogen chloride, there is but little perhalide formation (compare the relative effects of hydrogen chloride and bromide on the chlorination and bromination respectively of acetanilide (72)); weakening of the covalent bond does not therefore occur, and the base has no opportunity of combining with the proton. The hydrogen chloride is thus free to react with a molar quantity of anhydride

$$(CH_3\cdot CO)_2O + HCl \rightleftharpoons CH_3\cdot COCl + CH_3\cdot COOH;$$

the chlorination of the acid chloride then proceeds, and, moreover, the enolization of the anhydride is catalyzed not only by the small quantity of halogen acid present in the above equilibrium, but also by the base (the latter being, however, comparatively insignificant). Chlorination is therefore not inhibited, but to some extent accelerated.

The effect of acetyl nitrate on the bromination of acetic anhydride may also be ascribed to the removal of hydrogen bromide (or perhaps of acetyl bromide), in this case by oxidation, for there is considerable liberation of bromine when acetyl bromide is added to acetic anhydride containing nitric acid. As in the case of the basic substances, the main series of reactions will thus be eliminated, and the enolization of the anhydride rendered imperceptibly slow. As might be expected, however, from the relative indifference of hydrogen chloride to oxidizing agents, acetyl nitrate does not inhibit chlorination.

CONCLUSION

The investigation, described in the preceding pages, of the reactions of chlorine and bromine with compounds containing the carbonyl group, has led to a confirmation of the idea, suggested originally by Lapworth, that these changes are preceded, in all cases, by the conversion of the carbonyl compound to its enolic isomeride. In the case of ketones and ketonic acids, slow enolization is followed by a relatively instantaneous reaction with the halogen. Acetic acid and its homologues, on the other hand, do not enolize to a perceptible extent. Their substitution products result from the reaction of the acid with its monohalogenated halide, the latter being formed, however, by a process which appears to consist in rapid enolization of the unsubstituted chloride or bromide, followed by a slow reaction of the enolide with halogen. Acid anhydrides react with halogens in their enolic forms, but here also the change proceeds mainly through the acyl halide.

All the experimental results are such as would be anticipated from theoretical considerations involving the application of the electronic theory of valency, while the well-known fact that substitution invariably occurs at the α-carbon atom receives a simple explanation.

In conclusion, the author wishes to place on record his indebtedness to the late Professor Kennedy Orton, M.A., Ph.D., F.R.S., whose helpful and inspiring advice and criticism have contributed in no small degree to the success of the series of investigations here described.

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