290. *The Reaction Kinetics of the Acid Hydrolysis of Phenolic Ethers.*

By Rustom P. Ghaswalla and Frederick G. Donnan.

The velocity of hydrolysis (or strictly, " acidolysis ") in acid solution of a number of phenolic ethers has been studied, with the object of throwing further light on aromatic side-chain reactivity and the effect of nuclear substituents thereon. Hydrochloric and hydrobromic acids have been used as the hydrolysing agents (with hydriodic acid the reaction velocity was too great to measure by the method employed). In order to secure homogeneous solutions, the solvent medium was a mixture of water and a saturated aliphatic acid (generally acetic acid). The experiments were carried out in sealed glass tubes immersed in an oil thermostat, the reaction temperature being generally 120°. The reaction was followed by suddenly chilling (in cold oil) at different intervals of time the various tubes of an initially identical series, and then opening the tubes and analysing their contents. The acid hydrolysis of some phenolic ethers in anhydrous or nearly anhydrous formic and acetic acids has been studied by Birosel (*J. Amer. Chem. Soc.*, 1930, **52**, 1944; 1931, **53**, 1408), using hydrobromic acid as the " hydrolysing " agent. With excess of acid the reaction was found to be one of the first order, a result which corresponds with that found in the present investigation.

Phenolic Ethers.—Some of the ethers were purchased and then purified; others were specially prepared in the laboratory. The following is a list of the ethers examined: (A) Anisoles, *o*-, *m*-, *p*-nitro-; *o*-, *m*-, *p*-chloro-; *o*-, *m*-, *p*-bromo-; *o*-, *m*-, *p*-methyl; *o*-, *m*-, *p*-amino-; *o*-, *m*-, *p*-hydroxy-; *o*-, *m*-, *p*-methoxy-; *o*-. *m*-, *p*-acetyl. (B) Phenetoles, *p*-nitro-; *p*-chloro-; *p*-methyl.

Methods of Analysis.—For the purpose of determining the amounts of the unchanged phenolic ether and the corresponding free phenol in the cooled reaction mixture, the following three methods were employed.

Method 1. The mixture was made alkaline, the unchanged phenol ether extracted with ethyl ether, the free phenol then brominated by means of a potassium bromide–bromate mixture in the presence of concentrated hydrochloric acid, and the unused bromine determined by thiosulphate. By means of tests with synthetic mixtures of known composition, this method was found to give excellent results with chloro-, bromo-, nitro-, methyl-, and acetyl-substituted ethers.

Method 2. The mixture was treated with a slight excess of alkali, the unchanged phenol ether extracted with ethyl ether, the extract transferred to a beaker, the ether evaporated off, and the residue of phenol ether dried and weighed. This method was tested and gave satisfactory results in the case of methoxy- and amino-substituted ethers.

Method 3. The acid reaction mixture was just neutralised with sodium bicarbonate, the phenol and the phenolic ether extracted together with ethyl ether, the extract evaporated to dryness, and the residue weighed. The methoxy-group was then estimated by Perkin's modification of Zeisel's method. This method was tested on synthetic mixtures and gave satisfactory results. It was used in the cases of *m*- and *p*-methoxyanisoles.

The Order of the Reaction.—Two experiments were carried out at 120°, the initial reaction mixture containing in each case equimolar concentrations of phenolic ether and hydrochloric acid. In the following data, k_1 and k_2 denote velocity coefficients calculated on the basis of a first-order and a second-order reaction, respectively, with respect to the phenolic ether.

Expt. 1. Volume of initial reaction fluid = 12 ml. Initial composition (mols.) : 0·175 HOAc, 0·0883 H_2O, 0·02 PhOMe, 0·02 HCl.

Time (mins.).	Ether unhydrolysed, mols.	$k_1 \times 10^4$.	$k_2 \times 10^4$.	$k_3 \times 10^3$.	Time (mins.).	Ether unhydrolysed, mols.	$k_1 \times 10^4$.	$k_2 \times 10^4$.	$k_3 \times 10^3$.
30	0·01914	14·6	745	38·8	150	0·01640	13·2	734	40·6
60	0·01833	14·4	759	42·0	180	0·01580	13·1	740	42·0
90	0·01758	14·2	757	40·8	240	0·01470	12·8	735	43·0
120	0·01702	14·0	730	39·9	300	0·01387	12·1	736	44·0

Expt. 2. Volume of initial reaction fluid = 12 ml. Initial composition (mols.) : 0·175 HOAc, 0·0883 H_2O, 0·01 *m*-$C_6H_4Me{\cdot}OMe$, 0·01 HCl.

30	0·00972	96·0	970	99	180	0·00852	89·0	965	107
60	0·00944	95·9	988	101	210	0·00834	86·0	947	107
90	0·00918	95·0	992	103	240	0·00814	84·0	952	104
120	0·00895	92·0	969	106	300	0·00786	80·2	962	107
150	0·00873	90·6	969	104					

It will be seen that in both cases the value of k_1 steadily falls, whilst that of k_2 remains fairly constant (the values given under the rubric k_3 will be discussed later). When the acid was in large excess of the phenolic ether (molar ratio acid/ether = 10), the value of the first-order velocity coefficient was always found to be satisfactorily constant in any given reaction (as also found by Birosel). The simplest and most direct formulation of these results would be the bimolecular reaction

$$\mathrm{Ph{\cdot}OR} + \mathrm{HX} \longrightarrow \mathrm{Ph{\cdot}OH} + \mathrm{RX} \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where Ph = aryl radical, R = alkyl radical, X = halogen atom.

The Products of the Reaction and the Probable Reaction Mechanism.—In the case of three different anisoles, the final liberated phenol was separated from the unchanged anisole (amount = x g.), and after estimation was calculated back to the equivalent amount of anisole (amount calculated = y g.). The value of $x + y$ may then be compared with the known initial amount of anisole (z g.). The following results were obtained.

	o-Methylanisole.	*p*-Bromoanisole.	*m*-Acetylanisole.
z	0·488	0·748	0·600
$x + y$	0·466	0·725	0·563
	0·960	0·965	0·940

These results appear to show that the final amount of phenol produced is somewhat less than that to be expected from the formulation (1). Furthermore, when the final amount of RX produced is analytically determined, it is found to be about 20% less than that corresponding to formulation (1). Now, it is probable that the mechanism of the reaction corresponds to the *initial* formation of an oxonium salt, *i.e.*,

$$\mathrm{Ph{\cdot}OR + HX} \longrightarrow \left[\mathrm{Ph{\cdot}\overset{H}{O}{\cdot}R}\right]^{+}\mathrm{X}^{-} \qquad (2)$$

The oxonium compound might then break up in two ways :

$$\left[\mathrm{Ph{\cdot}\overset{H}{O}{\cdot}R}\right]\mathrm{X} \begin{array}{ll} \nearrow \mathrm{Ph{\cdot}OH + RX} & \qquad (3) \\ \searrow \mathrm{Ph{\cdot}X + R{\cdot}OH} & \qquad (4) \end{array}$$

The existence of reaction (4) might account for the small observed deficit in the amount of Ph·OH calculated for reaction (3) alone, whilst the greater deficit in RX might be accounted for by the reversible hydrolysis, $\mathrm{RX + H_2O \rightleftarrows R{\cdot}OH + HX}$ and the formation of some acetic ester from the alcohol so formed. Against the assumption that the deficit in Ph·OH is to be attributed to reaction (4) occurring as well as reaction (3), it may be noted that no Ph·X was found in the products of the reaction. This fact is also in agreement with the assumption that the deficit in Ph·OH is not to be attributed to the reaction $\mathrm{Ph{\cdot}OH + HX \rightleftarrows PhX + H_2O}$.

It is assumed in the present paper that no serious error is produced in the study of the reaction kinetics by the assumption that the free phenol produced corresponds to formulation (1), or formulations (2) and (3).

On the assumption that the initial reaction is the formation of an oxonium compound, the observed reaction kinetics may be explained in the following manner. We can make the following reaction table, where S denotes the oxonium compound and S its concentration :

Time.	Ph·OR, mols.	HX, mols.	S, mols.	Ph·OH, mols.
0	a	b	0	0
t	$a - x$	$b - x$	S	y

Then always

$$S + y = x \qquad (5)$$

If we assume that there exists always the rapidly attained reversible equilibrium

$$\mathrm{Ph{\cdot}OR + HX \rightleftarrows S} \qquad (6)$$

then practically always

$$S = K(a - x)(b - x) \qquad (7)$$

Now

$$dy/dt = kS \qquad (8)$$

We now assume that, except at the beginning of the reaction, S is very small compared with y (small value of K). Then from (5) we have the generally good approximation $y = x$, and hence from (7) and (8)

$$dx/dt = kK(a - x)(b - x) \qquad (9)$$

If b is large compared with a, then approximately

$$dx/dt = kKb(a - x) = k'(a - x)$$

where kKb is equal to the pseudo-unimolecular velocity coefficient k'. It is true that when b is large compared with a the reaction is found to be one of the first order, but the surprising fact—to be discussed later—is that the pseudo-unimolecular coefficient k' is by no means proportional to b. Since by our assumptions K is relatively small, the reaction as formulated by equation (9), which in a certain sense is a pseudo-bimolecular reaction, will appear as a rather slow bimolecular reaction.

Velocity Coefficients with Hydrochloric Acid at 120°.—The phenolic ethers listed above were subjected to hydrolysis in sealed glass tubes at 120°. The initial composition corresponded in all cases to the following *molar* proportions (total volume = 12 ml.) : $\mathrm{H_2O}$, 0·221; HOAc, 0·1221; HCl, 0·05; phenolic ether, 0·005. The tabulated values of k' are those of the first-order reaction with respect to the phenolic ether. They are therefore the ***pseudo-unimolecular*** velocity coefficients referred to in the preceding section.

TABLE I.

Values of $10^4k'_{120^\circ}$ *for the anisoles.*

(Unsubstituted anisole, $10^4k'_{120^\circ} = 71·4$.)

	p.	*o.*	*m.*		*p.*	*o.*	*m.*
Methoxy	339	274	187	Chloro	37·2	29·3	16·4
Methyl	102	80·1	75·1	Bromo	23·9	12·4	8·9
Hydroxy	82·1	—	24·9	Acetyl	13·9	17·8	23·3
Amino	46·5	34·8	19·5	Nitro	6·89	7·28	11·9

TABLE II.

Values of $10^4k'_{120^\circ}$ *for the phenetoles.*

Phenetole	82·0	*p*-Nitrophenetole	7·31
p-Chlorophenetole	80·0	*p*-Methylphenetole	132

The bearing of these results on the theory of side-chain reactivity will be discussed in a later section.

Comparison of Hydrochloric and Hydrobromic Acids.—The temperature (120°) and the initial composition were the same as in the experiments the results of which are given in the foregoing section.

Phenolic ether.	k'_{HBr}.	k'_{HCl}.	k'_{HBr}/k'_{HCl}.
Anisole	0·0451	0·00710	6·35
o-Bromoanisole	0·00724	0·00124	5·85
o-Nitroanisole	0·00478	0·000728	6·50
p-Methylanisole	0·0611	0·0102	6·00
o-Methylanisole	0·0497	0·00801	6·30

It will be seen that with hydrobromic acid the velocity coefficient is approximately six times as great as with hydrochloric acid. With hydriodic acid the reaction is too fast to be measured by the method employed. The order is therefore $k'_{HI} > k'_{HBr} > k'_{HCl}$.

Effect of increasing the Proportion of Water in the Initial Reaction Fluid.—In these experiments the temperature was 120°. The initial composition was 0·004 mol. anisole, 0·05 mol. hydrogen chloride, and 0·621 mol. (acetic acid + water), the molar percentage of acetic acid being varied.

HOAc, mols. %	75	70	60	50	40
$10^5k'_{120^\circ}$	541	430	237	158	101

It will be seen that as the proportion of water increases the value of k' diminishes. This result agrees with the view that the primary reaction is not a direct hydrolysis of the phenolic ether by water. It has been assumed that this latter reaction, *i.e.*, Ph·OR + $H_2O \longrightarrow$ Ph·OH + R·OH, does not occur.

Variation of the Pseudo-unimolecular Velocity Coefficient k' *with the Initial Concentration of Hydrogen Chloride.*—Whether the reaction be viewed as a simple direct bimolecular reaction (equation 1) or as one involving the intermediate formation of an oxonium salt (equation 2), the pseudo-unimolecular velocity coefficient k' should be proportional to the initial concentration of HX, provided that the latter is much in excess of the initial concentration of the phenolic ether and that the variation of the medium can be neglected. In the following experiments (at 120°) the initial reaction fluid contained (in 12 ml.) 0·175 mol. acetic acid, 0·0883 mol. water, and 0·005 mol. phenolic ether. The initial quantities of hydrogen chloride were 0·05, 0·04, and 0·03 mol. in the different experiments. The following table of results shows how the pseudo-unimolecular velocity coefficient k' varies with the initial concentration of hydrogen chloride.

Ratio of [HCl].	Ratio of $[HCl]^2$.	Ratio of k'.	Ratio of [HCl].	Ratio of $[HCl]^2$.	Ratio of k'.	Ratio of [HCl].	Ratio of $[HCl]^2$.	Ratio of k'.
	o-Nitroanisole.			*p*-Methylanisole.			*p*-Bromoanisole.	
0·80	0·64	0·59	0·80	0·64	0·61	0·80	0·64	0·61
0·75	0·56	0·50	0·75	0·56	0·50	0·75	0·56	0·50
0·60	0·36	0·35	0·60	0·36	0·30	0·60	0·36	0·30

Although in these experiments the initial molar ratio [HCl]/[Ph·OR] was not always great enough (varying from 10 to 6), the results indicate that k' is certainly not proportional to [HCl], being much more nearly proportional to $[\text{HCl}]^2$. This would involve the formulation, rate of disappearance of phenolic ether = rate of formation of free phenol = constant × [phenolic ether] × $[\text{HCl}]^2$. With initially equivalent concentrations of phenolic ether and hydrogen chloride the reaction should then be formally one of the *third* order. The third-order velocity coefficients (multiplied by a power of 10) are given on p. **1342** under the rubric k_3. It will be seen that they show a very satisfactory degree of constancy. The occurrence of the squared term $[\text{HCl}]^2$ has been observed in certain reactions by Dawson and his collaborators (*e.g.*, Dawson and Millet, J., 1932, 1920), who explain it by the assumption that the effective reagent is the *un-ionised acid.* If this be present in small concentration compared with the total (analytically determined) acid, *i.e.*, un-ionised acid plus ions, and if the simple (ideal) law of equilibrium be assumed to hold good for the practically instantaneous ionic equilibrium, the existence of the squared term can be explained. The very marked order, $k'_{\text{HI}} > k'_{\text{HBr}} > k'_{\text{HCl}}$, observed in the present work, may be significant in this connection, and might be due to the varying small amounts of the un-ionised acids present in the reaction medium employed (compare also the results obtained by Birosel, *loc. cit.*). If Dawson's hypothesis be rejected, the following alternative one might apply to the present case. Consider the formulation given on p. **1343**. Assuming that the oxonium salt is completely ionised, we may put S = concentration of oxonium cation. Assume now that the reaction directly producing the free phenol is a *bimolecular* reaction between the oxonium cation and the halogen ion. If we also assume that the halogen acid is practically completely ionised, then

$$dx/dt = kS(b - x) = kK(a - x)(b - x)^2.$$

We have then for the pseudo-unimolecular velocity coefficient k' the equation $k' = kKb^2$, instead of the equation $k' = kKb$.

Effect of Temperature.—Experiments were made with *o*-nitroanisole at 110°, 120°, and 130°. The molar proportions in the initial solution were in each case : water 0·221; acetic acid 0·1221; hydrogen chloride 0·05; *o*-nitroanisole 0·005. The results are shown below.

Temp.	110°	120°	130°
Value of k'	0·000281	0·000728	0·00160

From these results $k'_{120°}/k'_{110°} = 2{\cdot}6$, $k'_{130°}/k'_{120°} = 2{\cdot}2$. These data are not in agreement with the Arrhenius equation and do not give a constant energy of activation. This may be due to experimental error or to other causes.

Effect of the Nuclear Substituents on the Velocity.—From Table I it will be seen that for the *op*-orienting substituents of the anisoles, the rate of hydrolysis of the phenolic ethers places the nuclear-substituting groups in the order

$$\text{OMe} > \text{Me} > \text{OH} > \text{H} > \text{NH}_2(\text{HX}) > \text{Cl} > \text{Br}.$$

In every case examined the order of the three isomers is $p > o > m$. For the *m*-orienting substituents the order found is acetyl > nitro, and in each case the order of the isomers is reversed, *i.e.*, $m > o > p$. These results are in agreement with those obtained by Olivier (*Rec. trav. chim.*, 1923, **42**, 755) on the hydrolysis of the nuclear-substituted benzoyl chlorides (compare also Bennett and Jones, J., 1935, 1815). In the case of the phenetoles (Table II), only some *p*-substituted ethers have been examined. The order found here is Me > H > Cl for the *op*-orienting substituents, in agreement with the order found in the case of the anisoles. The comparatively high value found for k' with the methoxyanisoles will be due in part to a probability factor, since there are in these cases two methoxy-groups which can be attacked by the halogen acid (or the hydrogen ion).

It will be seen from a comparison of Tables I and II that the substitution of ethoxyl for methoxyl increases the values of k'. This is to be expected, since, ethyl being a stronger electron-repelling group than methyl, the oxygen of ethoxyl will, under similar conditions, be more negative than that of methoxyl. This will lead to a greater formation of the intermediate oxonium compound (greater value of K), and thus to a higher reaction velocity, since the oxonium formation is due to attack by a negative centre-seeking reagent. In the present work the effect of nuclear halogens on the reactivity is in the order Cl > Br. This agrees with the order found by Olivier (*loc. cit.*), *i.e.*, Cl > Br > I (compare also Bennett, J., **1933**, 1112).

SUMMARY.

(1) The kinetics of the acid hydrolysis of a number of anisoles and phenetoles in an aqueous-aliphatic acid medium has been studied.

(2) Hydrogen chloride and bromide have been used as " hydrolysing " agents.

(3) The results are in agreement with the assumption that oxonium-salt formation occurs as an intermediary step.

(4) With excess of hydrogen chloride or bromide the reaction is pseudo-unimolecular, the velocity coefficient for the latter being about six times as great as that for the former.

(5) With equivalent concentrations of phenolic ether and halogen acid, the reaction appears to be formally one of the third order. This is due to the halogen acid concentration entering as a squared term in the reaction-rate equation. Two hypotheses to account for this are discussed.

(6) The rate-controlling reaction is probably the decomposition of the intermediate oxonium compound. The concentration of the latter is assumed to be subject to the oxonium salt equilibrium.

(7) The influence of a number of nuclear substituents on the rate of the reaction has been determined and discussed.

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THE SIR WILLIAM RAMSAY LABORATORIES OF INORGANIC AND PHYSICAL CHEMISTRY,
UNIVERSITY COLLEGE, LONDON, W.C. 1.

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