

CXXIX.—*The Mechanism of, and Constitutional Factors controlling, the Hydrolysis of Carboxylic Esters. Part I. The Constitutional Significance of Hydrolytic Stability Maxima.*

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ALTHOUGH the mass of data, accumulated by Victor Meyer, Kellas, Sudborough, Reid, and others, relating to the rates of hydrolysis of carboxylic esters and amides, forms one of the main pillars of the theory of steric inhibition, an examination of the results reveals the existence of a large number of anomalies of which no explanation has yet been given. The point may be exemplified by reference to the acid hydrolysis of two simple series, one of ethyl esters (Löwenherz, *Z. physikal. Chem.*, 1894, **15**, 388), and the other of acetates (Palomaa, *Ann. Acad. Sci. Fennicæ*, 1913, *A*, **4**, 2; **5**, 4; Skrabal and Hügetz, *Monatsh.*, 1926, **47**, 17; and others), for which the data * fail to show the continuous gradations which might have been expected.

	$k \times 10^3 (40^\circ).$		$k \times 10^3 (25^\circ).$
Ethyl acetate	26.2 min. ⁻¹	Methyl acetate	6.8 min. ⁻¹
„ chloroacetate ...	15.2 „	Ethyl acetate	6.6 „
„ dichloroacetate	24.4 „	isoPropyl acetate	3.6 „
		tert.-Butyl acetate	7.5 „

On the other hand, it has recently been proved that the hydrolysis of carboxylic esters is just as susceptible to polar influence as are

* It will be the uniform practice in these papers to employ minutes as time units and to use \log_e , not \log_{10} , in integration formulæ for velocity coefficients. Data from the literature are corrected, where necessary, to conform with these conventions.

most other reactions. Probably the clearest demonstration of this is to be found in the circumstance that Kindler's results (*Annalen*, 1926, 450, 1) for the speed of hydrolysis of benzoic esters containing various substituents in the *m*- and *p*-positions are in excellent agreement with the purely electropolar scheme which has been evolved (Ingold, *Ann. Reports*, 1927, 24, 155; 1928, 25, 146; Ingold and Rothstein, J., 1928, 1217; compare Williams, this vol., p. 37) for the interpretation of the influence of *m*- and *p*-nuclear substitution on aromatic side-chain reactions generally. In such a group of examples, complication is at a minimum: the electronic conductivity of the benzene ring guarantees the facile transmission of polar influences, whilst its configuration and spatial rigidity render steric inhibition practically inoperative. The clear implication, however, is that in the general case of ester hydrolysis, in which spatial effects are obviously of importance, internal polar factors will also play a part, and that this may explain the anomalies illustrated.

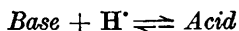
The theoretical object contemplated in this series of communications is the development of methods for the separation of the two factors presumed to be present in general on the basis of the arguments indicated. An analogy for the procedure adopted is provided by a contemporaneous investigation (Gane and Ingold, J., 1929, 1691; and earlier) in which a similar problem is envisaged, *viz.*, the separation of the spatial and internal polar factors which together control the strengths of polybasic acids. Here the analysis was greatly facilitated by the consideration, in the first instance, not of the dissociation constants themselves, but of a function of them, presumed, on the basis of an approximate theory, to be related mainly to one of the operating factors.

The development of an analogous procedure for the hydrolysis of esters necessitates some consideration of the theory of the dynamics of homogeneous catalysis as it has been elaborated by Brönsted and Dawson especially. It may be stated that our investigation is based on—indeed, was rendered possible by—Dawson's elegant methods for the analysis of superimposed catalytic effects; and, further, that due consideration has of necessity been given to certain highly important points raised by Brönsted in the course of his work.

The Arrhenius-Ostwald theory of catalysis by hydrogen and hydroxyl ions (symbolised, $v = v_{\text{H}} + v_{\text{OH}}$) has more recently been extended, in several well-defined stages, to include catalysis by a large variety of molecules and ions. The "dual" theory of catalysis ($v = v_{\text{H}} + v_{\text{OH}} + v_{\text{m}}$) envisaged catalysis by the undissociated molecules of acids (Acree and Johnson, *Amer. Chem. J.*, 1907, 37, 410; 38, 258; Senter, J., 1907, 91, 460; Lapworth, 1910,

97, 19; Goldschmidt and Thuesen, *Z. physikal. Chem.*, 1910, **70**, 627; 1912, **81**, 30; *Z. Elektrochem.*, 1911, **17**, 684; Bredig, Miller, and Braune, *ibid.*, 1912, **18**, 535; Sneathlge, *ibid.*, p. 539; Taylor, *ibid.*, 1914, **20**, 201; Dawson, Powis, and Reiman, J., 1913, **103**, 2135; 1915, **107**, 1426), and the most important step in its super-session by a still more general theory ($v = v_H + v_{OH} + v_m + v_a$) consisted in the recognition of catalysis by the anions of acids (Brönsted, Pedersen, and Duus, *Z. physikal. Chem.*, 1924, **108**, 185; 1925, **117**, 299; Dawson and Carter, J., 1926, 2282). Many claims have been made for the recognition of a small but distinct catalytic effect of the water molecule on reactions in aqueous solution, but few are substantial ($v = v_H + v_{OH} + v_m + v_a + v_{H_2O}$); the established cases include the mutarotation of glucose (Hudson, *J. Amer. Chem. Soc.*, 1907, **29**, 1571; Brönsted and Guggenheim, *ibid.*, 1927, **49**, 2554) and the iodination of acetone (Dawson and Key, J., 1928, 543).

Brönsted and Guggenheim discussed their results on the mutarotation of glucose in relation to the conception in accordance with which acids and bases are defined by the equation


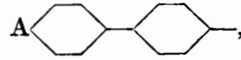
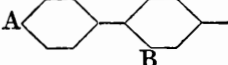


{e.g., $[\text{Co}(\text{NH}_3)_5\text{OH}]^{2+}, \text{NH}_3, \text{OH}^-$ } {e.g., $\text{NH}_4^+, \text{H}\cdot\text{CO}_2\text{H}, [\text{CO}_2\cdot\text{CO}_2\text{H}]^-$ }

independently of their state of electrification. (In this scheme OH^- appears as a special instance of a base, and the hydrion, H_3O^+ , as a special case of an acid; water is remarkable as belonging to both categories.) They showed that the catalytic efficiencies of a series of bases (including OH^-) increased with the strength of the base, and that the logarithmic plot of the catalytic coefficients against the equilibrium constants of the reaction formulated above approximated to a straight line having a certain slope. Similarly, the catalytic effects of a series of acids (including H_3O^+) increased with the strength of the acid, and an analogous plot of the data yielded another straight line of different slope. Evidently there are two catalytic mechanisms corresponding to the two lines: in acid catalysis the reactant receives from the catalyst a positive charge, and in basic catalysis it confers on the catalyst a positive charge. These conditions are fulfilled by both Lowry's (J., 1925, **127**, 1371) and Baker's (J., 1928, 1583) theories of catalytic effects on mutarotation in the sugar series, but the general conclusion must hold independently of the accuracy of the assumed mechanistic details; and it is clear, moreover, that the actual mechanism of catalysis by hydrions is also that of catalysis by acids, and that the mechanism of catalysis by hydroxyl ions applies equally to catalysis by bases, in the generalised interpretation of the terms acid and base. Again, since the coefficients representing the catalytic

activities of ten acids and five bases on the iodination of acetone (Dawson and others, J., 1926, 2282; 1928, 543, 2844; 1929, 1884, 2530) yield a closely similar bilinear plot, it can be claimed that there is experimental evidence for extending the same two mechanisms, with their distinctive electropolar characteristics, to prototropic change generally, for it is usually accepted that the prototropy of acetone is here involved. Furthermore, Dawson and Lawson's results (J., 1927, 2107; 1928, 2152; 1929, 393, 1229) for the effect of three acids and two bases on the hydrolysis of ethyl acetate adumbrate yet another diagram of the same type, so that the principle of a dualistic mechanism of polar catalysis in relation to the generalised conception of acids and bases may evidently be extended to the hydrolysis of carboxylic esters. It should be stated that Lowry (*loc. cit.*), on theoretical grounds, suggested a close relation between the catalysis of sugar mutarotation and that of ester hydrolysis. Probably a still wider generalisation would be justifiable.

The explicit discussion will now be confined to catalysis by hydrogen and hydroxyl ions in ester hydrolysis, the implication being that the statements made are applicable to acid and basic catalysis generally, except in so far as quantitative modification is necessitated by the specific nature of an acid or base.

Consider the n th ester of an isotypic series. (We cannot yet define the word "isotypic," which is inserted to retain the right to exclude certain cases: the theory here advanced is an approximate one, and whilst the comparison to be instituted *might* embrace all carboxylic esters, except, perhaps, a few special classes such as lactones or 1:1-alkylidene di-esters, it might, on the other hand, prove to be much more restricted.) First, the formula of the series may be taken as $R \cdot CO \cdot OR'$ in which R is variable and R' constant. Let k_H and k_{OH} be the catalytic coefficients expressing the rates of hydrolysis of the typical member at a given temperature by hydrogen and hydroxyl ions respectively. Now, it is possible to suppose that the *polar* effect of the variable group R on the constant residue $\cdot CO \cdot OR'$ is capable of being quantitatively *imitated* by a group G of such a form that, when R is varied, the variations of G necessary to preserve the imitation do not alter the *steric* value of G in relation to the residue $\cdot CO \cdot OR'$. (For example, G might be of such a form as A , A , or A , where A is variable, and B constant.) Let

k_H^p and k_{OH}^p be the corresponding catalytic coefficients for the hydrolysis of $G \cdot CO \cdot OR'$. These coefficients, k_H^p and k_{OH}^p , may now be regarded as the polar constituents of those, k_H and k_{OH} , of the

series $R \cdot CO_2R'$; they are the values which k_H and k_{OH} would assume in the presence of a constant steric effect arbitrarily fixed by the choice of the form of G . For the n th ester considered, let $k_H = k_H^p/S$, where S is a factor introduced to express the effect of steric inhibition in the hydrolytic reaction involving hydrogen ions; S will clearly depend on n , that is, on the nature of R . The value of k_{OH} will not, of course, be k_{OH}^p/S because the mechanism of the reaction with hydroxyl ions is different; a different connecting factor will, in general, be required, and may be expressed by CS in the relation $k_{OH} = k_{OH}^p/CS$. Now the basic assumption here made is that, because the difference between hydrogen- and hydroxyl-ion catalysis repeats itself throughout the series of esters of which the hydrolysis is being considered, C will be independent of n to a first approximation; in other words, that S , having been defined for each ester by reference to hydrion catalysis, takes sufficient account, for another kind of catalysis, of the varying nature of the esters, leaving the constant C to take charge, as it were, of the (constant) nature of the second catalyst. It is not expected that C will be exactly constant; but the larger C is—that is, the more diverse the mechanisms with regard to their susceptibility to steric effects—the more nearly true should be the suggested relation. The constancy of C being assumed, it follows that $C(k_{OH}/k_H) = k_{OH}/k_H^p$, that is, that k_{OH}^p/k_H^p is a function of polarity only. Similarly, if R is kept constant and R' is made to vary, $C'(k_{OH}/k_H) = k_{OH}^p/k_H^p$. Finally, both C and C' are arbitrary constants, since they depend on the forms chosen for G and G' ; therefore, the general relationship for all the isotypic esters, $R \cdot CO_2R'$, with variable R and R' , is that k_{OH}/k_H is directly proportional to its polar constituent.†

This view, namely, that k_{OH}/k_H is, probably within wide limits, a function of polarity only, and is untrammelled by the complications due to steric hindrance which affect k_{OH} and k_H separately, may be tested by reference to experimental data; and it is convenient to use two types of data for this purpose.

The first uses the theory of the v - p_H isotherm. That the velocity of an aqueous reaction catalysed by hydrogen and hydroxyl ions must pass through a minimum (at $p_H = p_H^*$) is obvious *a priori*, but was first observed by Wijs for the hydrolysis of methyl acetate

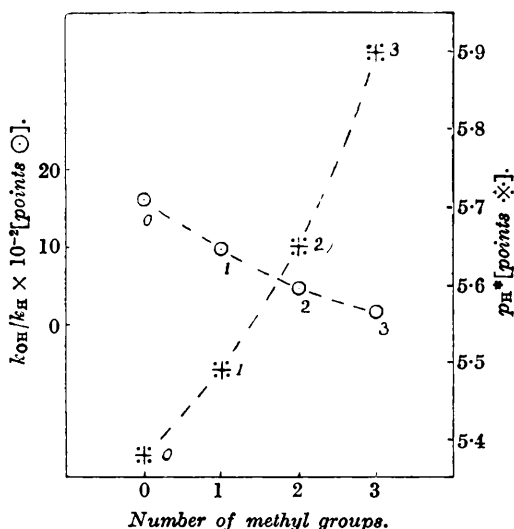
† It will be observed that this conclusion is reached without specific assumptions relating to mechanism. It is necessary only that the mechanisms obtaining should admit the validity of the basic hypothesis, namely, that the relative steric effects on velocity are expressible as the product of two coefficients singly dependent, respectively, on the ester and the catalyst. This granted, it follows that the conclusion drawn should apply to a pair of acid or of basic catalysts, *e.g.*, to $k_{weak\ acid}/k_H$ or to $k_{weak\ base}/k_{OH}$, as well as to a pair composed of one catalyst of each kind.

(*Z. physikal. Chem.*, 1893, **11**, 492; **12**, 514); and the symmetry of the v - p_{H} curve, which is important for the location of the stability maximum, *i.e.*, of p_{H}^* , seems to have been first shown by Euler and Hedelius (*Biochem. Z.*, 1920, **107**, 150; compare Euler and Svanberg, *Z. physikal. Chem.*, 1921, **115**, 139, and Euler and Laurin, *Arkiv Kemi, Min. Geol.*, 1920, **7**, No. 30, 1) for the mutarotation of glucose. Dawson, partly with Dean and Hoskins (J., 1926, 2872, 3166; 1927, 213, 1148, 1290), has directed attention to the consequences of applying the (concentration) mass law, amongst which are (a) that the v - p_{H} isotherm should be symmetrical because it should be a catenary, (b) that $-2p_{\text{H}}^* - \log K_w = \log(k_{\text{OH}}/k_{\text{H}})$, where K_w is the ionic product of water, and (c) that, when the p_{H} variation is produced by a series of buffers of which either the acidic or the saline component is kept constant in concentration, catalysis by the buffer constituents causes some displacement of p_{H}^* , but preserves the catenary form of the curve. We are not here concerned with the point (Brönsted and Guggenheim, *loc. cit.*) that relations cannot be absolute which neglect effects due to ionic environment in buffers, because, in applying (b) to calculate $k_{\text{OH}}/k_{\text{H}}$ from observed values of p_{H}^* , the fact has to be faced that the available data for p_{H}^* neglect the correction for buffer constituents altogether (this defect in method is remedied in Part II). However, despite the approximate character of the data (Karlsson, *Z. anorg. Chem.*, 1921, **119**, 69; 1925, **145**, 1; Bolin, *ibid.*, 1925, **142**, 201; 1928, **177**, 227; compare Dawson, J., 1927, 1148), the examples to which they apply are so diverse that the general character of the suggested relation between $k_{\text{OH}}/k_{\text{H}}$ and polarity can be observed over a greater range of structural variation than it is at present possible to traverse in any other way. From the first series in Table I, it will be seen that $k_{\text{OH}}/k_{\text{H}}$ increases regularly, as it should, with the efficacy of the electron-sink; it is also noteworthy that the polar group may act from either of the residues attached to $-\text{CO}\cdot\text{O}-$. Ester No. 2 was glycerol monoacetate, but is formulated, for convenience in tabulation, as though it were glycol monoacetate, for the polar effect of the terminal $\cdot\text{CH}_2\cdot\text{OH}$ group is expected to be negligible. Ester No. 5 was actually ethyl aminoacetate; but the velocity minimum occurs at p_{H} 3.5, *i.e.*, in *acid* solution, so that the entity to which $k_{\text{OH}}/k_{\text{H}}$ refers is the ammonium kation, and this agrees with the very high value of $k_{\text{OH}}/k_{\text{H}}$. The value of $k_{\text{OH}}/k_{\text{H}}$ for methyl formate, regarded as the parent of the second series in Table I, is not known; but it is known qualitatively to be considerably greater than for ethyl formate. In this series, the value of $k_{\text{OH}}/k_{\text{H}}$ diminishes, as it should, with the efficacy of the electron-source, which, as before, may act from either of the groups attached to $-\text{CO}\cdot\text{O}-$.

TABLE I.

No.	X.	Y.	pH*.	Temp.	$K_w \cdot 10^{14}$.	$(k_{OH}/k_H) \times 10^{-3}$.
<i>First Series: X-CH₂-CO-O-CH₂-CH₂-Y.—Effect of electron-sink.</i>						
1	H-	H-	5.36	25°	1.0	2
2	H-	HO←	5.0	25	1.0	10
3	Cl←	H-	4.8	20	0.8	32
4	MeCO←	H-	4.4	25	1.0	160
5	⊕NH ₃ ←	H-	3.5	20	0.8	12,000
<i>Second Series: X-CO-O-CH₂-Y.—Effect of electron-source.</i>						
1	H-	H-	—	—	—	Large
2	H-	CH ₃ →	4.65	20	0.8	63
3	CH ₃ →	H-	5.15	25	1.0	5
4	CH ₃ →	CH ₃ →	5.36	25	1.0	1.9
5	CH ₃ →	CH ₃ →CH ₂ →CH ₂ →	5.65	25	1.0	0.5

In the above examples there is a certain variety in the types of polar substituents, and, accordingly, a very great diversity in the



Rates of hydrolysis of methylacetic esters as function of structure.

values of k_{OH}/k_H ; and one of the advantages of this method of estimating k_{OH}/k_H is that the ease with which the ratio is determined is independent of its order of magnitude, at least between 10^2 and 10^7 . When the order of magnitude of the ratio becomes greater than 10^3 , difficulties enter the independent *direct* determination of k_{OH} and k_H at the same temperature,† and, therefore, the range

† The numerous alleged determinations of k_{OH} in buffers, but without correction, or data permitting the application of a correction, for the buffer constituents, are, of course, valueless, except as indications of order of magnitude.

of polar substituents which can be examined by reference to data of this kind is more restricted; on the other hand, the values of k_{OH}/k_H thus obtained should be more accurate than those derived from stability maxima in the absence of a correction for the buffer, and should therefore suffice to distinguish the effects of finer polar differences. In illustration, reference may again be made to the apparently anomalous series of simple alkyl acetates tabulated at the outset. The calculated values of k_{OH}/k_H are as shown in Table II, and it will be seen that in these values there is no perceptible anomaly; if plotted against the number of β -methyl groups, k_{OH}/k_H and p_H^* both give smooth uninflected curves of small curvature (see fig.).

TABLE II.

Acetate (25°).	$(k_{OH}/k_H) \times 10^{-2}$.	p_H^* .	Source of k_{OH} and k_H .
CH_3	16.1	5.39	Means from literature.
$CH_3 \rightarrow CH_2$	9.9	5.50	" " " "
$(CH_3)_2 \rightarrow CH$	4.7	5.66	Means from <i>b</i> , <i>c</i> (k_{OH}) and <i>a</i> , <i>c</i> (k_H).
$(CH_3)_3 \rightarrow C$	1.5	5.91	Means from <i>b</i> , <i>c</i> (k_{OH}) and <i>c</i> , <i>d</i> (k_H).

References: (a) Palomaa, *loc. cit.*; (b) Olsson, *Z. physikal. Chem.*, 1925, **118**, 107; (c) Skrabal and Hügetz, *loc. cit.*; (d) Olsson, *Z. physikal. Chem.*, 1927, **125**, 243; 1928, **133**, 233.

Having explained the *a priori* considerations on which this series of investigations will be based, and illustrated their reasonableness by reference to existing data, the object of this introductory communication is accomplished. Any estimate of the extent to which the method outlined can be pressed in the analytical separation of the two main constitutional influences which affect the stability of esters towards hydrolysis must await a wider range of data such as will be provided in ensuing papers.

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[Received, March 5th, 1930.]