which precipitated was collected and washed immediately with large amounts of ether, then with smaller amounts of 1-to-1 ether- alcohol and air-dried; 1.80 g., m.p. 195° dec. Recrystallization from 95% ethanol gave 1.45 g. (82 %), $\alpha^{27}D$ −184° (c 1.50, alcohol) m.p. 195° dec., undepressed by admixture of 1,7-dibromodihydrocodeinone hydrobromide prepared by dibromination of dihydrocodeinone. Its infrared absorption spectrum showed an absorption maximum at 5.74μ (1743 cm.$^{-1}$).

Anal. Calcd. for $C_{18}H_{20}NO_3Br_3\cdot 1.5H_2O$: C, 38.25; H, 4.10. Found: C, 38.09; H, 3.80.

***cis*-1,7-Dibromodihydrocodeinone Hydrobromide (XI) by Dibromination of *cis*-Dihydrocodeinone (XIII).**—*cis*-Dihydrocodeinone (1.43 g.) dissolved in 15 cc. of glacial acetic acid containing a five molar excess of dry hydrogen bromide was treated dropwise with 5 cc. of a bromine–glacial acetic acid solution containing 1.73 g. (0.0958 mole) of bromine. Decoloration of the bromine was rapid. The solution was allowed to stand at room temperature for 5 hours, concentrated under reduced pressure, and treated with 10 cc. of ether. The solid precipitate was collected and immediately washed with large volumes of ether. Recrystallization from water gave 2.5 g. (92%), m.p. 195° dec. The compound dissolves in potassium hydroxide solution but gives a negative ferric chloride test. It shows infrared absorption at 5.73μ (1748 cm.$^{-1}$).

Anal. Calcd. for $C_{18}H_{20}NO_3Br_3\cdot 1.5H_2O$: C, 38.25; H, 4.10. Found: C, 38.27; H, 3.79.

Repetition of the bromination without added hydrogen bromide gave essentially the same results (89%, m.p. 195–197° dec.).

1-Bromodesoxycodeine-C.—*cis*-1,7-Dibromodihydrocodeinone hydrobromide (XI) (300 mg.) in 15 cc. of methyl alcohol was treated with a solution of 0.06 g. of sodium borohydride in 10 cc. of methyl alcohol. The solution was allowed to stand at room temperature for 12 hours, concentrated to dryness under reduced pressure, and the residue was taken into 3 cc. of glacial acetic acid solution. After filtration to remove undissolved solid, 22 cc. of glacial acetic acid and 0.2 g. of zinc dust was added and the mixture was refluxed for 2.5 hours, cooled, and filtered. The filtrate was made just basic with ammonium hydroxide and extracted with four 40-cc. portions of chloroform. The combined chloroform extracts were dried, filtered, concentrated and triturated under ether to yield 1-bromodesoxycodeine-C (XIV), as a crystalline solid, 90 mg. (48%), m.p. 167–175°. Recrystallization from ethanol raised the m.p. to 179–181°. It gives a negative ferric chloride test. Its infrared absorption spectrum showed no carbonyl absorption, but a weak double bond absorption maximum at 6.02μ (1663 cm.$^{-1}$).

Anal. Calcd. for $C_{18}H_{20}NO_2Br\cdot H_2O$: C, 56.85; H, 5.83. Found: C, 56.89; H, 5.90.

Sublimation (oil-pump, 185°) yields anhydrous material, m.p. 210°, reported[20] 210–212.5°.

The Action of Alkali on *cis*-1,7-Dibromodihydrocodeinone Hydrobromide (XI). (−)-1-Bromosinomeninone (XII).—*cis*-1,7-Dibromodihydrocodeinone hydrobromide (XI) (200 mg.) was added to 25 cc. of 4 *N* potassium hydroxide. A transient colorless solid precipitated but redissolved after heating for 30 minutes at 40°. The solution was cooled, filtered and extracted three times with 75-cc. portions of ether. The alkaline raffinate was then neutralized with acetic acid, made slightly basic with dilute ammonia, and extracted with five 75-cc. portions of ether. The ether extracts were washed twice with water, dried over sodium sulfate, filtered, and concentrated to dryness under diminished pressure to yield 113 mg. (79%), of a crystalline compound, m.p. 224° dec., undepressed on admixture with authentic (−)-1-bromosinomeninone.

Conversion of *cis*-1,7-Dibromodihydrocodeinone Hydrobromide (XI) to *cis*-1-Bromocodeinone 2,4-Dinitrophenylhydrazone.—Two hundred milligrams of XI was dissolved in 10 cc. of glacial acetic acid, treated with 84 mg. of 2,4-dinitrophenylhydrazine, and heated on a steam-bath for 30 minutes. The cooled mixture was diluted with water and made just basic with ammonia. The basic mixture was extracted five times with 50-cc. portions of chloroform. The combined chloroform extracts were washed twice with dilute ammonia, once with water, dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. The residue was chromatographed on 10 g. of Woelm (acid-washed) alumina. Development with alcohol-free chloroform eluted a total of 113 mg. of crystalline dinitrophenylhydrazone, m.p. 214–220°, which after recrystallization from ethyl acetate gave 68 mg. (35%) of **1-bromocodeinone 2,4-dinitrophenylhydrazone**, orange needles, m.p. 221–224°, undepressed by admixture with an authentic sample.[6]

(−)-1-Bromosinomeneine Ketone (XV).—*cis*-1,7-Dibromodihydrocodeinone hydrobromide (XI) (200 mg.) was dissolved in 15 cc. of dimethyl sulfoxide, allowed to stand at room temperature for 25 hours, then poured into 50 cc. of ice-water and extracted with five 100-cc. portions of ether. The combined ether extracts were dried over sodium sulfate, filtered, and concentrated to yield a light-yellow residue, which was recrystallized from methyl alcohol; 43 mg. (31%), m.p. 196–197°; reported[28] for its enantiomorph, 198°.

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[28] K. Goto and T. Nambo, *Bull. Chem. Soc. Japan*, **5**, 165 (1930)

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Mechanisms of Acid Hydrolysis of Carboxylic Acid Esters and Amides

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In light of the Bunnett *w* criteria, this paper suggests mechanisms of hydrolysis of carboxylic acid esters and amides. Reasons for preferring a symmetric mechanism of ester hydrolysis and formation are presented. A discussion is given of the determination of *w* from mechanism. An attempt is made to separate simultaneous nucleophilic and proton transfer functions of water contributions to *w*. Separation of these functions in ester hydrolysis and formation indicates that the "γ-butyrolactone enigma" is less serious than previously considered. A useful empirical equation (3) relating the logarithm of the activity of water to the Hammett acidity function for HCl, H_2SO_4 and $HClO_4$ up to about 10 *M* acid is derived. Two applications of this equation are made. An attempt is made to account for the non-linear Bunnett plot obtained in the acid hydrolysis of *o*-nitrophenyl oxalate by a change in rate-determining step to one with different *w* parameters. It is shown that when acid inhibition of a step of a reaction occurs in moderately concentrated acid solutions, extraordinarily high *w*-values are expected. The possibility that the acid hydrolysis of acetylimidazole presents an example of such an inhibited reaction is discussed.

Recently Bunnett[2] has proposed a new criterion for determining reaction mechanism in moderately concentrated acid solutions. In this method of analysis, the logarithm of the pseudo first-order rate constant for the protonated species is plotted against the logarithm of activity of water. Such plots yield straight lines for many reactions, and the slope, *w*, exhibits values useful in elucidating

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[2] J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, (a) 4956, (b) 4968, (c) 4973, (d) 4978 (1961).

mechanisms. Bunnett has suggested that *w*-values may be used to specify the function of water in the rate-determining step as: $w < 0.0$, water is not involved; $+1.2 < w < +3.3$, water acts as a nucleophile; $w > +3.3$, water functions as a proton transfer agent.[2b]

In this paper it is emphasized with examples that simple inspection of the rate-determining step is not in general sufficient to evaluate *w* from mechanism. In addition to describing the determination of *w* from mechanism, an attempt is made to assign separate contributions to *w* due to water acting as a nucleophile and as a proton transfer agent. In suggesting these and other ideas, this paper assumes that the *w* parameter, in spite of all its uncertainties due to differential hydration numbers, unknown activity coefficients and variation of values for the same reaction in different acids, presents a useful criterion of mechanism. Since the requisite data are often easily obtained, it would seem that efforts should be made to interpret kinetic data procured in normal and deuterated acids as a tool in elucidating mechanism. This paper attempts to extend the application of the *w* parameter in several directions in order to enlarge its area of usefulness.

To evaluate the fraction of substrate in protonated or kinetically active form requires knowledge of a pK_a of substrate. Occasionally two groups on a molecule will have similar acid–base strengths so that a constant pK_a value is not obtained over a range of acid to base ratios. In such systems four species exist; for example, AH^+–BH^+, AH^+–B, A–BH^+ and A–B, where A and B are groups on the molecule of not necessarily neutral to plus charge type as indicated here. There are available methods for determining amounts of each species present.[3] In strongly acid solutions the Hammett acidity function is not strictly applicable to at least two of the four microconstants. If protonation of the A group is responsible for reactivity, the two active species AH^+–BH^+ and AH^+–B will generally have different reactivities. Failure to consider these possibilities may lead to incorrect conclusions, as for example in the mechanism of hydrolysis of sulfoazoethers.[4]

In writing mechanisms, simple proton transfers to or from oxygen or nitrogen are not considered rate limiting. Reactions involving such simple proton transfers might be rate limiting if they were to or from an intermediate of sufficiently low concentration, but this type of situation is not considered in this paper.

Hydrolysis and Formation of Esters.—Carboxylic acid esters that hydrolyze according to an A2 mechanism have $w \simeq 5$, while in the one case of synthesis studied in predominantly aqueous solutions $w = 2.2$ for the lactonization of γ-hydroxybutyric acid.[2a] General acid catalysis has been found in the formation of carboxylic acid esters,[5] but whether the hydrolysis reaction is general instead of specific acid-catalyzed is doubtful.[6] Mechanism I for hydrolysis and formation of esters is symmetrical except for the substitution of alcohol (XH) for water.

Mechanism I

$$\mathrm{RCOX} + \mathrm{H}^+ \rightleftarrows \mathrm{RC(OH)X}^+;\ K_1 = (\mathrm{RCOX})h_0/(\mathrm{RC(OH)X}^+)$$

$$\mathrm{RC(OH)X}^+ + \mathrm{H_2O} + \mathrm{B} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathrm{RC(OH)_2X} + \mathrm{HB}$$

$$\mathrm{RC(OH)_2X} + \mathrm{HB} \underset{k_4}{\overset{k_3}{\rightleftarrows}} \mathrm{RC(OH)_2}^+ + \mathrm{XH} + \mathrm{B}$$

$$\mathrm{RC(OH)_2}^+ \rightleftarrows \mathrm{RCOOH} + \mathrm{H}^+;\ K_2 = (\mathrm{RCOOH})h_0/(\mathrm{RC(OH)_2}^+)$$

where B and HB represent conjugate base and acid forms of a catalyst, and the Hammett acidity function $-H_0 = \log h_0$. Even though B will be only water for most of the cases under discussion in this paper, we shall denote the proton acceptor as B and use the symbol H_2O only for water acting as a nucleophile. This distinction is important for some of the discussions that follow. Carboxylic acid esters and probably also the acids undergo predominant carbonyl oxygen protonation,[7] and evidently this species is the kinetically reactive one.[8] Mechanisms in this paper are not balanced according to charges because in different cases reactants and catalysts of different charge types may occur.

The first and last steps of mechanism I are not considered rate determining because proton transfers are known to occur much faster than hydrolysis. For carboxylic acids and esters values of K_1 and K_2 are of the order of 10^7. This result implies that one rate constant is 10^7 times the other. If the rate constant for proton loss from protonated ester is diffusion controlled, $k \simeq 10^{10}$ sec.$^{-1}$, the rate constant for protonation of ester is about 10^3 M^{-1} sec.$^{-1}$ and is still much faster than hydrolysis rate constants of about 10^{-4} M^{-1} sec.$^{-1}$.

When the steady state approximation is made for the tetrahedral intermediate $\mathrm{RC(OH)_2X}$, the initial rate of disappearance of ester (E) in an original solution containing only reactants is

$$-\frac{\mathrm{d(E)}}{\mathrm{d}t} = \frac{k_1k_3(\mathrm{EH}^+)(\mathrm{H_2O})(\mathrm{B})}{k_2 + k_3} = \frac{k_1k_3(\mathrm{E})(\mathrm{H_2O})(\mathrm{HB})K_\mathrm{B}}{(k_2 + k_3)K_1} \quad \text{(I-1)}$$

where $K_\mathrm{B} = (\mathrm{H}^+)(\mathrm{B})/(\mathrm{HB})$. Similarly, in a solution containing acid (A) and alcohol (XH) but no ester, we obtain for the initial rate of appearance

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(3) J. T. Edsall, R. B. Martin and B. R. Hollingworth, *Proc. Natl. Acad. Sci.*, 44, 505 (1958).

(4) J. F. Bunnett and E. Buncel, *J. Am. Chem. Soc.*, 83, 1117 (1961). Examination of the pK_a data reveals that a constant pK_a is not obtained over a range of acid to base ratios for either compound studied. When an analysis[3] is made for the presence of two basic groups, the striking result obtained is that protonation of one group promotes protonation of the other. Such results usually indicate molecular changes during the course of the titration. Effects of *cis–trans* isomerizations may be important and are known to influence profoundly the spectra. Since the observed $w = 3.1$ (omitting two points at low acidities which may indicate a second reactive species) for the naphthyl ether is so near a borderline in the criteria of mechanism and the ionization constant used can only accidentally be correct, incorrect conclusions might have been drawn. It is possible that $w > 3.3$ for both compounds.

(5) A. C. Rolfe and C. N. Hinshelwood, *Trans. Faraday Soc.*, 30, 935 (1934).

(6) R. P. Bell, "Acid–Base Catalysis," Oxford University Press, Oxford, Eng., 1941.

(7) G. Fraenkel, *J. Chem. Phys.*, 34, 1466 (1961).

(8) G. Aksnes and J. E. Prue, *J. Chem. Soc.*, 103 (1959).

of ester

$$+\frac{\mathrm{d(E)}}{\mathrm{d}t} = \frac{k_2k_4\,(\mathrm{AH^+})(\mathrm{XH})(\mathrm{B})}{k_2 + k_3} \qquad \text{(I-2)}$$

Both ester disappearance and formation exhibit general acid catalysis according to eq. I-1 and I-2. In the moderately concentrated acid solutions considered here, HB is a hydrated proton so that general acid catalysis would be difficult to detect. If the B and HB catalysts were eliminated from mechanism I, no (B) term would appear in the numerator of eq. I-1 and only a $+1.2 < w < +3.3$ value would be predicted in contrast to observed $w > +3.3$.

The small equilibrium concentrations of $\mathrm{EH^+}$ may be held against mechanism I. For $K_1 = 10^7$, $(\mathrm{EH^+}) = 10^{-10}M$ at pH 3 where acid catalysis sets in. This concentration may not be too low for a reactive species like $\mathrm{EH^+}$. Hydroxide ion catalysis begins for some reactions as low as pH 4 where $(\mathrm{OH^-}) = 10^{-10}M$. Any objections on these grounds however may be met by mechanism II, also symmetric.

Mechanism II

$$\mathrm{RCOX + H_2O + HB} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{RC(OH)(OH_2{}^+)X + B}$$

$$\mathrm{RC(OH)(OH_2{}^+)X} \rightleftharpoons \mathrm{RC(OH)_2XH^+};$$
$$K_\mathrm{D} = [\mathrm{RC(OH)(OH_2{}^+)X}]/[\mathrm{RC(OH)_2XH^+}]$$

$$\mathrm{RC(OH)_2XH^+ + B} \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \mathrm{RCOOH + XH + HB}$$

Application of the steady-state assumption to both tetrahedral intermediates that appear in K_D, yields for the initial rate of ester disappearance

$$-\frac{\mathrm{d(E)}}{\mathrm{d}t} = \frac{k_1k_3(\mathrm{E})(\mathrm{H_2O})(\mathrm{HB})}{k_2K_\mathrm{D} + k_3} \qquad \text{(II-1)}$$

and for the initial rate of appearance of ester in a solution with no ester originally

$$+\frac{\mathrm{d(E)}}{\mathrm{d}t} = \frac{k_2K_\mathrm{D}k_4(\mathrm{A})(\mathrm{XH})(\mathrm{HB})}{k_2K_\mathrm{D} + k_3} \qquad \text{(II-2)}$$

Mechanisms I and II yield equations of the same kinetically indistinguishable form. The rate constants of each mechanism have a different significance however. Insertion of approximate numerical values into eq. I-1, I-2, II-1 and II-2 yields possible values for the various rate constants. The following discussion on esters is equally applicable to mechanisms I or II, but in order to be specific the constants quoted will be those of mechanism I.

Equation I-1 for ester hydrolysis implies $w > 3.3$ because water acts as a proton transfer agent in the (B) term in addition to a contribution of about 2 to w for $\mathrm{H_2O}$ acting as a nucleophile. Since neither $(\mathrm{H_2O})$, (B) or (HB) appears in the denominator of eq. I-1 and I-2, the inferred w-value is independent of the relative magnitudes of k_2 and k_3. In ester hydrolysis if $k_2 >> k_3$, the k_3 reaction is rate determining, while if $k_3 >> k_2$ the k_1 reaction is rate limiting. In the acid-catalyzed hydrolysis of ethyl benzoate[9] $k_3/k_2 = 2.6$. Thus the partitioning of the tetrahedral intermediate is nearly equally divided between reactants and products, and two reactions are jointly involved in limiting the rate. This result, in addition to equilibrium constants for ester formation near 4 and probably similar values of K_1 and K_2, implies that all corresponding constants in the forward and reverse directions of mechanism I have similar values. It is this close correspondence throughout that favors some kind of symmetrical mechanism for ester hydrolysis and formation.

Comparison of eq. I-1 and I-2 reveals that ester hydrolysis should have a greater w-value than synthesis by 1-3 units due to the additional nucleophilic water $(\mathrm{H_2O})$ term in eq. I-1. In the one reaction studied in aqueous solutions in both directions $w = 2.2$ for the lactonization of γ-hydroxybutyric acid while $w = 6.1$ and 8.5 (in HCl and $\mathrm{HClO_4}$, respectively) for the reverse reaction.[2a] The difference of 4–6 units for hydrolysis and synthesis of γ-butyrolactone is greater than the 1–3 units expected by both mechanisms I and II. Bunnett referred to the discrepancy of 4–6 units as the "γ-butyrolactone enigma" and ascribed the large difference to unusual hydration changes. The preceding analysis indicates that we should expect a w-value 1–3 units greater for hydrolysis anyway so that the enigma is reduced by up to 3 units to 1–3 units of w. Thus the magnitude of the effect necessary to ascribe to unusual hydration changes is decreased considerably.

Unfortunately only the above esterification reaction has been studied in predominantly aqueous solutions. The reversible hydration of fumaric to malic acid yields $w = 5$ in both directions.[10] Values of w for hydration of crotonaldehyde[11] and crotonic acid[12] are greater than 3.3 and greater in the hydration than in the reverse direction.

Hydrolysis of Amides.—In formulating a mechanism for the hydrolysis of amides, a symmetrical mechanism is unnecessary because the reaction is much less reversible than the hydrolysis of esters. Ordinary amides have $w = 1.2$ to 2.6, indicative of water acting as a nucleophile.[2a] Some amides yield higher values of w and are mentioned later. A general mechanism for amide hydrolysis is

Mechanism III

$$\mathrm{RCOX + H^+} \rightleftharpoons$$
$$\mathrm{RC(OH)X^+};\ K_1 = (\mathrm{RCOX})h_0/(\mathrm{RC(OH)X^+})$$

$$\mathrm{RC(OH)X^+ + H_2O} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{RC(OH)_2XH^+}$$

$$\mathrm{RC(OH)_2XH^+ + (B)} \overset{k_3}{\rightleftharpoons} \mathrm{RCOOH + XH + HB}$$

In the last step the catalyst B may not always be necessary. The tetrahedral intermediate $\mathrm{RC(OH)_2X}$ is much more basic than the corresponding intermediate in ester hydrolysis, making mechanism I unnecessary for amide hydrolysis. Application of the steady state approximation to $\mathrm{RC(OH)_2XH^+}$ yields

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[9] M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951); M. L. Bender, R. D. Ginger and J. P. Unik, *ibid.*, **80**, 1044 (1958).

[10] L. T. Rozelle and R. A. Alberty, *J. Phys. Chem.*, **61**, 1637 (1957).

[11] S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, **59**, 1461 (1937); R. P. Bell, J. Preston and R. B. Whitney, *J. Chem. Soc.*, 1166 (1962).

[12] D. Pressman and H. J. Lucas, *J. Am. Chem. Soc.*, **61**, 2271 (1939).

$$-\frac{d(RCOX)}{dt} = \frac{k_1k_3[RC(OH)X^-](H_2O)(B)}{k_2 + k_3(B)} \quad (III-1)$$

In all amides that have been studied, the partitioning of the intermediate strongly favors the products[13] so that $k_3(B) > 100k_2$. Eq. III-1 becomes

$$-d(RCOX)/dt = k_1[RC(OH)X^+](H_2O) \quad (III-2)$$

which corresponds to $w \simeq 2$. In this case it cannot be determined whether base is required in the third reaction. Since $K_1 \simeq 10$ for ordinary amides, the range of acidities studied passes through the region where the amide is becoming protonated. The complete expression for $[RC(OH)X^+] = h_0C_A/(h_0 + K_1)$, where C_A is the total concentration of amide, is required in eq. III-2. In conjunction with the declining activity of water, the maximum observed in the hydrolysis curves of amides can be accounted for in quantitative terms.

The observed first-order rate constant for amide hydrolysis according to eq. III-2 is

$$k' = k_1 a^{w}_{H_2O}\, h_0/(h_0 + K_1) \quad (1)$$

At the maximum in a plot of k' *versus* H_0, $dk'/dh_0 = 0$. Differentiating eq. 1 and setting the derivative equal to zero, we obtain

$$K_1/w(h_0 + K_1) = d \log a_{H_2O}/dH_0 \quad (2)$$

A plot of the $\log a_{H_2O}$ *versus* H_0 for HCl, $HClO_4$ and H_2SO_4 reveals that from 0.5 to about 10.0 *M* acid the points lie on a single curve for all three acids.[14] This curve is adequately represented by the parabolic function

$$-\log a_{H_2O} = 0.034(-H_0)^2 + 0.018(-H_0) + 0.01 \quad (3)$$

Substitution of eq. 3 into eq. 2 yields

$$K_1/w(h_0 + K_1) = 0.068(-H_0) + 0.018 \quad (4)$$

at the maximum in a plot of observed first-order rate constant *versus* acidity. For the particular case of acetamide in HCl, $w = 2.47$[2a] and the maximum[16] occurs at about 3.05 *M* acid where[14] $-H_0 = 1.06$ and $h_0 = 11.5$. Substitution of these values into eq. 4 yields $K_1 = 3.3$, a result nearly identical with the measured equilibrium value[17] of 3.0.

It is now generally agreed that O- rather than N-protonation is predominant in amides.[19] Some investigators,[2b] though admitting predominant O-protonation, have preferred to consider the N-protonated species as the kinetically active species in hydrolysis and other reactions. They argue that the greater value of the equilibrium constant for N-protonation is more than offset by higher reactivity of N- over O-protonated amide. Since there is no compelling reason to write the mechanism in terms of the less common protonated species, mechanism III has been written with the O-protonated species kinetically reactive.

Though a rate expression applicable to amides has been used to derive eq. 4, the result is a general one applicable to any rate expression where the rate varies linearly with concentration of protonated substrate and activity of water to some power. For this reason, eq. 4 also applies if the N-protonated species were considered to be the kinetically reactive one. More complex derivatives are required to treat non-linear equations such as eq. III-1.

The *w*-values of hydrolysis of some amides exhibit high values,[2a] $w > 4.7$. In three cases, picolinamide, nicotinamide and isonicotinamide, a plus charge already resides on the molecule so that further protonation is electrostatically inhibited. A higher K_1 value is expected for these amides and no maximum is observed in their rate *versus* H_0 curves. These amides may hydrolyze according to one of the mechanisms suggested for esters (the catalysts in the k_3 steps of mechanisms I and II may not be required if $k_3 > k_2$), or in mechanism III, k_2 might be greater than $k_3(B)$ yielding

$$k' = k_1k_3(H_2O)(B)/k_2 \quad (III-3)$$

When water is the base, $w > 3.3$ for this rate expression which involves the k_3 rather than the k_1 step as the rate-limiting one. The latter alternative has been suggested for the general base-catalyzed hydrolysis of N,N′-diphenylformamidine[20] ($w = 7.75$) while mechanism I with $k_2 > k_3$ has been proposed for the hydrolysis of piperazine-2,5-dione ($w = 5.1$). Mechanism III with $k_2 > k_3$ could be distinguished from mechanisms I or II with $k_3 > k_2$ by oxygen isotope exchange studies. The complete mechanisms I, II and III with $k_2 > k_3$ are not easily distinguishable experimentally.

Acid hydrolysis of thioacetamide yields acetamide and H_2S[21] with $w = 4.2$ and 5.4 for HCl and $HClO_4$, respectively.[2a] This reaction should proceed in a sequence analogous to mechanism I, which accounts for $w > 3.3$. Methyl benzimidate hydrolyzes in acid solution to give methyl benzoate and ammonia with $w = 6.4$. This reaction may also occur in a scheme like mechanism I.

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[13] M. L. Bender and R. D. Ginger, *J. Am. Chem. Soc.*, **77**, 348 (1955). C. A. Bunton, T. A. Lewis and D. R. Llewellyn, *Chemistry & Industry*, 1154 (1954).

[14] Values of acidity function taken from M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957), and of logarithm activity of water from ref. 15. The relationship of eq. 3 has been discussed another way; see P. A. H. Wyatt, *Disc. Faraday Soc.*, **24**, 162 (1957).

[15] Appendix of ref. 2a.

[16] D. Rosenthal and I. T. Taylor, *J. Am. Chem. Soc.*, **79**, 2684 (1957); J. T. Edward, H. P. Hutchison and S. C. R. Meacock, *J. Chem. Soc.*, 2520 (1955).

[17] N. F. Hall, *J. Am. Chem. Soc.*, **52**, 5115 (1930). The values estimated from ultraviolet absorption spectra (A. R. Goldfarb, A. Mele and N. Gutstein, *ibid.*, **77**, 6194 (1955)) are unacceptable. In separate experiments on some of these amides and others in H_2SO_4 and $HClO_4$ we have confirmed that a single pK_a value will not fit the data. Measurements are performed at 200 or 205 mμ on steep slopes of absorption curves because the maxima occur further into the ultraviolet. Readings taken on steep slopes are subject to displacements as the character of the solvent is changed. This interpretation is supported by the tendency of the ratio $\epsilon_{BH_2^+}/\epsilon_{BH^+}$ of Goldfarb, *et al.*, to approach unity as ϵ_B increases. Similar studies on protonation of benzamides reveal pronounced solvent effects.[18] As the solvent blank changes, recording spectrophotometers with automatically varying slit width introduce an additional variable. By assuming the extinction of the protonated form to be near zero and considering only readings taken in the most dilute acid solutions, we obtain results for acetamide consistent with the potentiometric results of Hall. We feel no such explanation as Goldfarb, *et al.*, offer is required. Until measurements can be performed at the maxima, ultraviolet absorption analysis of pK_a values made on slopes of absorption curves in solutions of markedly changing solvent composition must be suspect.

[18] J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2000 (1957).

[19] G. Fraenkel, A. Lowenstein and S. Meiboom, *J. Phys. Chem.*, **65**, 700 (1961); A. R. Katritzky and R. A. Y. Jones, *Chemistry & Industry*, 722 (1961); R. Stewart and L. J. Muenster, *Can. J. Chem.*, **39**, 401 (1961); M. J. Janssen, *Spectrochim. Acta*, **17**, 475 (1961); D. Herbison-Evans and R. E. Richards, *Trans. Faraday Soc.*, **58**, 845 (1962).

[20] R. H. De Wolfe, *J. Am. Chem. Soc.*, **82**, 1585 (1960).

[21] E. A. Butler, D. G. Peters and E. H. Swift, *Anal. Chem.*, **30**, 1379 (1958).

Values of w from Mechanism.—A variant of eq. III-3 provides an example of the principle enunciated in the introduction that the rate expression may indicate a greater w-value than would be expected from simple inspection of the rate-determining step. If no base were required in the k_3 step, then spontaneous decomposition of the intermediate would by inspection of mechanism III predict $w < 0$. A check with eq. III-3 reveals, however, that without (B) the value of w is that for water acting as a nucleophile or $+1.2 < w < +3.3$.

In the Bunnett criterion of mechanism, water acting as a nucleophile shows up only when no proton transfer occurs to smother the former effect by its greater contribution to w(or w^*). It would seem that it might be possible to break up the total into at least two parts representing water acting as a nucleophile and as a proton transfer agent. This division was implied in the discussion of ester hydrolysis where the observed w was interpreted as the sum of nucleophile and proton transfer contributions. By virtue of this division a greater w-value is expected for ester hydrolysis than for formation because no nucleophilic water contribution appears in the latter.

It may also prove useful to subdivide the contribution to w of water acting as a proton transfer agent into two parts: that of water acting as a proton acceptor and as a proton donor. Only one water molecule is required to accept a proton, but a hydrated proton is thought to be associated with four water molecules.[22] This subdivision may be performed without violation of the principle of microscopic reversibility in an acid–base-catalyzed reaction if hydration differences between proton acceptor and donor are mirrored in acidic and basic forms of substrate with the result that the same transition state occurs for the reactions in either direction. Let the following symbols designate the apparent power of the activity of water for the following functions of water: p, nucleophile; q, proton acceptor; and r, proton donor. In any mechanism an expected experimental w-value may be calculated by adding all p, q and r for forward reactions and subtracting for reverse reactions until the forward direction of the rate-limiting step is just included. Any mechanism which upon this treatment yields a net w containing r must be given special attention because h_0 now appears in the rate expression. One such special case is treated in the last section.

Hydrolysis in mechanisms I or II with a rate-limiting k_1 step yields $w = p + q$, while if the k_3 step is rate limiting, $w = p + q - r + r = p + q$ again. Synthesis gives $w = q$ for either the k_2 or k_4 step rate limiting. The difference between hydrolysis and synthesis is p units or that expected of water acting as a nucleophile. Mechanism III for the hydrolysis of amides yields $w = p$ for a rate-limiting k_1 step and $w = p + q$ if the k_3 step is rate determining in agreement with eq. III-1 through III-3.

Logically the next step is to assign values to p, q and r. Even for a set of similar substrates accurate assignments are not possible until the effects on w of temperature and different acids are better understood. For substrates of a different kind than considered here, other values of p and especially q and r may be required. It may not always be advisable to separate the effects of water acting as a proton transfer agent into q and r contributions if changes in protonated and unprotonated substrate hydration values are not equal to $r - q$. To be specific, however, we may choose p and q as about $+2$ and r as $+4$. These values yield w values of $+4$ and $+2$ for ordinary ester and amide hydrolysis respectively.

It is necessary, in general, to determine w from mechanism and not solely from the rate limiting step. Division of w into nucleophile, p, and proton transfer functions seems desirable. Further subdivision of the proton transfer functions into proton acceptor, q, and proton donor, r, contributions is primarily one of convenience in quickly ascertaining the w-dependence of a given mechanism without having to derive the complete steady-state expression. If r contributions do not cancel and appear in the final net w expression, a dependence on h_0 exists and special treatment is required.

Hydrolysis of *o*-Nitrophenyl Oxalate.—The hydrolysis of *o*-nitrophenyl oxalate passes through a maximum in about 1.5 M HCl,[23] and a Bunnett plot yields a curve of increasing slope as acidity increases.[15] This case may be accounted for by a modification of the full eq. III-1 where there is a change in the rate-limiting step as k_2 overtakes k_3(B) as the acid concentration increases. Let us assume that hydrolysis occurs when the anionic form (S^-) of *o*-nitrophenyloxalate becomes protonated on the carbonyl ester oxygen (SH) and that protonation of the ionized carboxyl group (S′H) yields a species that competitively inhibits hydrolysis because additional protonation at the carbonyl ester oxygen (SH_2^+) requires a much higher acidity than for the kinetically active (SH). Then we have the relationships

$$S^- + H^+ \rightleftarrows S'H;\; K' = (S^-)h_0/(S'H)$$

$$S^- + H^+ \rightleftarrows SH;\; K_1 = (S^-)h_0/(SH)$$

$$SH + H_2O \underset{k_2}{\overset{k_1}{\rightleftarrows}} D$$

$$D + B \xrightarrow{k_3} \text{products}$$

In this mechanism, D may be considered a tetrahedral intermediate which does not require a base for formation because D^- is quite basic. This situation is analogous to that of amides. Application of the steady state approximation to D yields

$$\frac{dP}{dt} = \frac{k_1k_3K'C_sh_0(H_2O)(B)}{[k_2 + k_3(B)][h_0 + K']K_1}$$

where C_s is the sum of (S^-) + (S′H) and (SH) is negligible. When the base B is water, the apparent first-order rate constant may be written as

$$k' = \frac{k_2k_3K'h_0a^{p}{}_{H_2O}a^{q}{}_{H_2}}{[k_2 + k_3a_{H_2O}{}^{q}][h_0 + K']K_1}$$

where p denotes water acting as a nucleophile and q water acting as a proton acceptor. The

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(22) K. N. Bascombe and R. P. Bell, *Disc. Faraday Soc.*, 24, 158 (1957).

(23) M. L. Bender and Y. L. Chow, *J. Am. Chem. Soc.*, 80, 5380 (1958).

ordinate of a Bunnett plot is given by

$$y = \log k' - \log \frac{h_0}{h_0 + K'} = \log \frac{k_1 K'}{K_1} + \log \frac{k_3 a_{H_2O}{}^{p} a_{H_2O}{}^{p}}{k_2 + k_3 a_{H_2O}{}^{q}}$$

Note that $K'(\simeq 0.6)$ and not the much larger K_1 is involved in the ordinate plot. Because y is a complex function of a_{H_2O}, a Bunnett plot will not yield a straight line in the region where k_2 and k_3 are comparable. At low acidities where $k_3\ a_{H_2O}{}^{q} > k_2$, the last term on the right is $\log a_{H_2O}{}^{p}$ and a slope of about 1-3 is expected. At sufficiently high acidities the last term becomes $\log\ [k_3 a_{H_2O}{}^{p+q}/k_2]$ and a slope greater than 4 is predicted. The two points at highest acidities[23] yield a Bunnett slope of 4. If p and q are taken as 2 and 3, respectively, a value of k_3/k_2 of about unity accommodates the data. More exact fitting was not attempted due to lack of data at sufficiently high acidities. Extension of the studies to higher acidities and oxygen isotope exchange experiments over a range of acid concentrations would provide tests for the proposed interpretation.

Though presented in terms of a specific case, rate equations of the same form as those of this section may be of more general applicability. A reaction obeying a mechanism such as that offered for the hydrolysis of *o*-nitrophenyl oxalate, where w consists of different contributions from p and q depending upon the rate-limiting step, may yield deviations from a Bunnett plot which are more informative than a reaction where a linear dependence of pseudo first-order rate constant on water activity is observed.

Acid Inhibition of Hydrolysis.—There is a set of reactions, to be individually discussed at the end of this section, where a proton is liberated in one of the steps of the mechanism. A simple scheme is

Mechanism IV

$$SH^+ + H_2O + B \underset{k_2}{\overset{k_1}{\rightleftarrows}} D + HB$$

$$D \overset{k_3}{\rightleftarrows} \text{products}$$

where SH^+ is a protonated substrate and D is an intermediate. In weakly acid solutions the k_1 step may be rate limiting, while in solutions of sufficient acidity an equilibrium will prevail in the first reaction with the result that the k_3 step becomes rate limiting. Application of the steady state assumption to the intermediate D yields for the initial rate of disappearance of protonated substrate

$$-\frac{d(SH^+)}{dt} = \frac{k_1 k_3 (SH^+)(H_2O)(B)}{k_2(HB) + k_3} \qquad \text{(IV-1)}$$

An important question arises as to the behavior of reactions with acid-inhibited steps when they take place in concentrated acid solutions. A reaction with a rate obeying eq. IV-1 will yield a straight line in a Bunnett plot only when $k_3/k_2 >> h_0$. When $h_0 >> k_2/k_2$, a straight line could be obtained if $\log k' - H_0$ is plotted against $\log a_{H_2O}$. Since this function is seldom plotted, it is of interest to investigate the effect of plotting only the logarithm of the first-order rate constant $\log k'$ *versus* $\log a_{H_2O}$ for the case where $h_0 >> k_3/k_2$. (A more complicated situation prevails when h_0 and k_3/k_2 are comparable and successive trials of k_3/k_2 could be attempted.)

For the case where $h_0 >> k_3/k_2$, the apparent first-order rate constant from eq. IV-1 is given by

$$k' = k_1 k_3 a_{H_2O}{}^{p} K_B / k_2 h_0 \qquad \text{(IV-2)}$$

where $K_B = (B)h_0/(HB)$. Differentiation of eq. IV-2 yields

$$\frac{d \log k'}{d \log a_{H_2O}} = p + \frac{dH_0}{d \log a_{H_2O}} \qquad \text{(IV-3)}$$

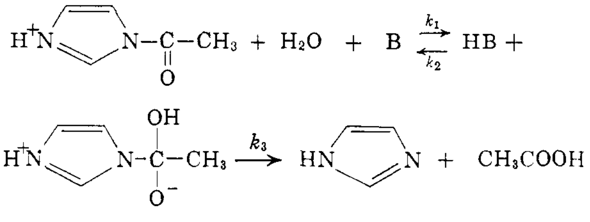
The last term on the right may be estimated by substitution of eq. 3 into eq. IV-3

$$\frac{d \log k'}{d \log a_{H_2O}} = p + \frac{1}{0.068(-H_0) + 0.018} \qquad \text{(IV-4)}$$

Equation IV-4 indicates the slope of a Bunnett plot for a reaction described by a rate equation of the form of eq. IV-1 when $h_0 >> k_3/k_2$. The slope is not a straight line but is a function of H_0. For H_0 values near zero the slope is markedly dependent on H_0, being about 60 when $H_0 \simeq 0$. Even for $-H_0 = 1.0$, 2.5 *M* $HClO_4$, the slope is about 12 + p. Only when $- H_0 > 4$ does the magnitude of the last term in eq. IV-4 become similar to p.

The foregoing analysis reveals that when values of w greater than about +9 are obtained, mechanisms yielding rate equations with a higher power of h_0 in the denominator than in the numerator should be considered. If the h_0 term is predominant in the denominator, a plot of $\log k' - H_0$ *versus* $\log a_{H_2O}$ should yield a straight line. In a similar fashion large negative w-values are expected for reactions abetted by an unbalanced proton reaction in the forward direction in addition to equilibrium protonation of substrate.

Though complicated by salt effects, the rate of hydrolysis of acetylimidazole[24] decreases as the acid strength is increased, Bunnett plots do not yield straight lines, and the initial values of w are as high as 19.6 for $HClO_4$. With $pK_a = 3.6$, acetylimidazole is predominantly in the conjugate acid form in the moderately concentrated acid solutions considered here. In perchloric acid the data are fairly well accommodated by postulating an acid-inhibited step ($k_?$) in acid solutions analogous to that of mechanism IV.



Equation IV-1 is also applicable to this mechanism and accounts for the data up to about 1 *M* in $HClO_4$, where the activity of water is still nearly unity, by setting $k_1 = 2.9$ min.$^{-1}$ and $k_3/k = 1.2$. In more dilute acid solutions $k_3/k_2 >$ (HB); eq. IV-1 predicts general base catalysis, which has been observed.[25] At higher concentrations of $HClO_4$ the observed rate is greater than that predicted by eq. IV-1. This difference may be due

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to participation of mechanism III already presented for amides or to salt effects. All other acids studied yield greater rates than equivalent concentrations of $HClO_4$.

A plot of log $k' - H_0$ *versus* log a_{H_2O} yields a curve which exhibits a negative w decreasing in magnitude as acidity increases. A straight line is not expected at low acidities where, according to the above analysis, $h_0 \simeq k_3/k_2$. At higher acidities the method of analysis overcompensates, due to an additional mode of hydrolysis or salt effects as mentioned before. The effect of salts may be operative through the part they play in B and HB. The variation in effects of salts observed in acetylimidazole hydrolysis may be a more general phenomenon unappreciated because few studies exist of comparable scope on other compounds. Qualitatively the high $w = 19.6$ value of acetylimidazole hydrolysis in perchloric acid is accounted for by mechanism IV. This mechanism predicts the occurrence of oxygen isotope exchange with acetylimidazole at high acidities.

A reaction scheme similar to mechanism IV was used to account for acid inhibition in thiazoline[26a,b] and oxazoline[26c] compounds. In the case of some of the thiazoline compounds such as 2-methylthiazoline where the value of $k_3/k_2 = 0.1$ is small, extraordinary powers of the activity of water would be required to account for the decrease in hydrolysis rate by the decrease in water activity. For 2-(1-acetamino-2-methylpropyl)-thiazoline[26b] and 2-methyloxazoline a value of $k_3/k_2 = 1.2$ was obtained, the same as that for acetylimidazole. The identical value for these three compounds is probably coincidental but is nevertheless suspicious and indicates that some common factor, such as a decrease in the activity of water, might account for the results. In such borderline cases it is difficult to assign with certainty the mode of decomposition. By analogy with other thiazoline derivatives[26b] where $k_3/k_2 = 0.1$ to 0.3, the first compound probably decomposes according to mechanism IV. This conclusion is less certain for 2-methyloxazoline. More studies are required on both compounds with a greater variety of acids and salts. Least certain is the mechanism of hydrolysis of acetylimidazole. Even for this compound we favor mechanism IV with the reservations already discussed.

$$TH^+ + H_2O + B \rightleftharpoons D + HB$$

$$D + HB \rightleftharpoons NH^+ + B$$

$$D \rightleftharpoons S$$

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[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY, UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, N. C., AND THE METCALF CHEMICAL LABORATORY, BROWN UNIVERSITY, PROVIDENCE, R. I.]

The Mechanism of Acid-catalyzed Hydrolysis of Azoaryl Ethers[1]

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The phenolic products of hydrolysis of 4-(*p*-sulfophenylazo)-1-naphthyl methyl ether (Ic) and 4-(*p*-sulfophenylazo)-anisole (II) in oxygen-18-labeled water carry the oxygen-18 label in the phenolic hydroxy group. However, 4-(*p*-sulfophenylazo)-phenol (IV) exchanges oxygen with the medium under the same conditions. Etherification of 4-phenylazo-1-naphthol (IIIa) and transetherification of 4-phenylazo-1-naphthyl methyl ether (Ia) are accomplished by refluxing with ethanol under acid catalysis. The kinetics of hydrolysis of II in 1–6 M $HClO_4$ solutions have been determined, and w and w^* values computed. For several of these reactions a mechanism of nucleophilic displacement at aromatic carbon is required, and for the rest it seems very likely. The protonated azo linkage is a strong activating group for aromatic nucleophilic substitution.

4-(Phenylazo)-1-naphthyl methyl ether (Ia) and related ethers are exceptionally sensitive to acid-catalyzed hydrolytic cleavage, as represented in eq. 1. Hydrolysis is quite rapid, for example, in 0.1 M hydrochloric acid at 46°. Witt and Schmidt,[3] who discovered this phenomenon in 1892, describe it as "gewiss bemerkenswerth." Although several other chemists took note of this phenomenon,[4-8] it escaped general recognition. Recent studies[9,10] have dealt with the conditions, kinetics and mechanism of such cleavages.

Several features of this reaction suggest that it differs in kind from ordinary ether cleavage as commonly effected by hydrobromic or hydroiodic acid. The reaction occurs readily in dilute acid, it does not require highly nucleophilic anions such

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