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Kinetics of Reactions in Moderately Concentrated Aqueous Acids. IV. Application of the Empirical Criterion to Diverse Reactions<sup>1</sup>

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Mechanisms deduced from  $w$ - and  $w^*$ -values are generally in accord with other evidence. For hydrolysis of epoxides, hydrolysis of sulfite esters and dehydration and oxygen exchange of tertiary alcohols, the empirical criterion resolves seeming inconsistencies with other evidence of mechanism. For hydrolysis of cyanamide, hydrolysis of certain glycosides and oxygen exchange-racemization of secondary alcohols, it calls for reconsideration of generally accepted views. When applied straightforwardly to hydrolysis of methyl dihydrogen phosphate, hydrolysis of certain strongly basic amides and the  $\gamma$ -hydroxybutyric acid  $\rightleftharpoons$   $\gamma$ -butyrolactone interconversion, it leads to apparently inconsistent conclusions; unusual hydration of substrates or transition states is thought to be the interfering factor. The empirical criterion is judged to give valuable indications of mechanism, but not to specify mechanisms accurately in all cases. It appears to be disturbed by unusual hydration (or activity coefficient behavior) of certain substrates or transition states.

In the three preceding papers, a new system for classification of reactions in moderately concentrated mineral acids,<sup>2</sup> an empirical criterion of mechanism<sup>3</sup> and a theory of interpretation<sup>4</sup> have been developed. Application to diverse reactions is now undertaken.<sup>5</sup>

When a more precise and more fundamental generalization is introduced into a field previously interpreted with respect to a less adequate one, several consequences are to be expected: confirmation of some conclusions previously drawn, revision (perhaps deep-seated) or refinement of others, resolution of some controversies or seeming inconsistencies, and the recognition of new problems of greater sophistication. All of these expectations are fulfilled in the present instance.

**Epoxide Hydrolyses.**—To a large extent because plots of  $\log k_d$  vs.  $-H_0$  were linear with slopes about 0.86, hydrolyses of epichlorohydrin and some related epoxides were assigned<sup>6,7</sup> a mechanism of rate-determining unimolecular change in  $\text{SH}^+$ . However, this conclusion was challenged<sup>8</sup> on the basis of other criteria which indicate that reaction of water with  $\text{SH}^+$  is rate determining. Slopes of 0.86 correspond<sup>9</sup> to  $w$ -values of about +2 to +3, and are by the new criterion indicative of participation by water as a nucleophile in the slow step. The dependence of rate on acid concentration is no longer at odds with other criteria of mechanism.

**Glycoside Hydrolyses.**— $w$ -Values for several glycoside hydrolyses, mostly from data of Bunton, Vernon and co-workers at University College, London, fall (with one exception) into two ranges suggestive of different rate-determining processes<sup>10</sup>

(1) Presented in part to the Eighth Conference on Reaction Mechanisms, Princeton, N. J., Sept., 1960.

(2) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956 (1961).

(3) J. F. Bunnett, *ibid.*, **83**, 4968 (1961).

(4) J. F. Bunnett, *ibid.*, **83**, 4973 (1961).

(5) It should be noted that this new approach is applicable only to reactions in aqueous acids, and not to reactions in mixed solvents. Arbitrarily, reactions in media containing more than 5% of an organic component have been excluded from consideration.

(6) J. G. Pritchard and F. A. Long, *J. Am. Chem. Soc.*, **78**, 2667 (1956); F. A. Long, J. G. Pritchard and F. E. Stafford, *ibid.*, **79**, 2362 (1957).

(7) F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 935 (1957).

(8) J. Koskikallio and E. Whalley, *Trans. Faraday Soc.*, **55**, 815 (1959); H. Kwart and A. L. Goodman, *J. Am. Chem. Soc.*, **82**, 1947 (1960).

(9) Unfortunately, the data were not published as such, but only graphically, and they cannot be read from the graph with sufficient accuracy for computation of  $w$ -values.

$w$  suggestive of unimolecular change in  $\text{SH}^+$

<i>t</i> -Butyl $\beta$ -D-glucopyranoside (12b)	-5.0
Methyl $\beta$ -2-deoxy-D-glucopyranoside (12e)	-1.6
Methyl $\alpha$ -2-deoxy-D-glucopyranoside (12d)	-1.8
Sucrose (13) (average of several temps.)	-0.6
Methyl $\alpha$ -D-mannopyranoside (12f)	+0.4

$w$  suggestive of nucleophilic attack of water on  $\text{SH}^+$

Methyl $\alpha$ -D-glucopyranoside (9)	+1.7
Methyl $\beta$ -D-glucopyranoside (10)	+1.6
Phenyl $\alpha$ -D-glucopyranoside (11)	+3.0
Phenyl $\beta$ -D-glucopyranoside (12a)	+1.4
Lactose (12h)	+3.0
Maltose (12g)	+3.0

$w$  intermediate

<i>o</i> -Hydroxymethylphenyl $\beta$ -D-glucopyranoside (12c)	+1.1
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The English authors<sup>11</sup> have, however, concluded that all these reactions occur *via* carbonium ions generated unimolecularly from  $\text{SH}^+$ .

The implications from  $w$ -values are accepted with some reservation because of uncertainty as to how the abundance of hydrophilic hydroxy groups in sugar molecules might affect differences in hydration between substrates and transition states.<sup>4</sup> The implied difference in mechanism is perhaps most difficult to accept in the case of the two epimers, methyl  $\alpha$ -D-glucopyranoside and methyl  $\alpha$ -D-mannopyranoside. The similarity in constitution seems to leave little scope for a change in hydrolysis mechanism.

Yet the closely related epimeric pair, 2,3,4,6-tetra-O-methyl- $\alpha$ -D-glucopyranosyl chloride and 2,3,4,6-tetra-O-methyl- $\alpha$ -D-mannosyl chloride, differ significantly in their manner of reaction with methanol (solvolysis) and with sodium thiophenoxide in *n*-propyl alcohol.<sup>12</sup> The glucosyl chloride gives the  $\beta$ -methoxy and  $\beta$ -thiophenoxy products, respectively, which represent inversion at carbon 1. The mannosyl chloride, in contrast, gave nearly equal parts of the  $\alpha$ - and  $\beta$ -methoxy products, and with thiophenoxide in *n*-propyl alcohol a mixture of products in which the two *propyl* mannoses appeared to predominate. The kinetics also corresponded to the predictions of an  $\text{S}_{\text{N}}2$

(10) Numbers in parentheses refer to the location of reactions in Table I, ref. 2.

(11) (a) C. A. Bunton, T. A. Lewis, D. R. Llewellyn and C. A. Vernon, *J. Chem. Soc.*, 4419 (1955); (b) C. Armour, C. A. Bunton, S. Patai, L. H. Selman and C. A. Vernon, *ibid.*, 412 (1961).

(12) A. J. Rhind-Tutt and C. A. Vernon, *ibid.*, 4037 (1960).

mechanism for the glucosyl chloride and SN1 for the mannosyl chloride.

The differing behavior of the glycosyl chlorides and the parallelism with the indications from  $w$ -values raise confidence in the latter. Moreover, the appearance of certain sugars in the first category with respect to others in the second is reasonable. *t*-Butyl  $\beta$ -D-glucopyranoside hydrolyzes with *t*-butyl-oxygen scission and doubtless proceeds via *t*-butyl carbonium ions.<sup>11b</sup> The two methyl 2-deoxy-D-glucopyranosides, because they lack the electron-attracting 2-hydroxy groups of the parent glucosides, should be more prone to carbonium ion formation.<sup>11b</sup> The sucrose structure presents the possibility of forming an  $\alpha$ -alkoxy secondary carbonium ion, whereas only  $\alpha$ -alkoxy primary carbonium ions could be formed from the other sugars. In view of the stability of secondary carbonium ions with respect to primary, etc., it is reasonable that sucrose hydrolysis should occur by a mechanism of greater carbonium ion character. This implies that it is the fructose-oxygen bond of sucrose which suffers initial scission.

While the evidence from  $w$ -values perhaps does not yet warrant the *conclusion* that some of these reactions involve rate-determining nucleophilic attack of water on SH<sup>+</sup>, it does at least call for reconsideration of the view that they all occur by a carbonium ion mechanism. An intermediate view is that their mechanisms stand somewhere in a gradual series ranging from the pure SN2 to the pure SN1 extreme, with a good deal of carbonium ion character on carbon 1 in the transition states for all the sugars. Conceivably another criterion would draw the boundary between "SN1" and "SN2" at a different point. At any rate, the present criterion suggests that many of these reactions involve enough participation of water as a nucleophile so that the designation SN2 is not out of place.<sup>13</sup>

**Alcohol Oxygen Exchange, etc.**—In *ca.* 1 *M* perchloric acid, oxygen exchange in butanol-2 (reaction 18,<sup>10</sup>  $w + 0.8$  in HClO<sub>4</sub>) occurs exactly half as fast as racemization (reaction 19,  $w + 1.3$  in HClO<sub>4</sub>). This shows that each act of exchange occurs with complete inversion of configuration.<sup>14</sup> Elimination to 2-butene was negligible in an open system at *ca.* 1 *M*, but at higher acidities became an ever-stronger competitor of substitution<sup>14</sup>; elimination therefore has a lower  $w$ -value. In the ampoules used for kinetics, elimination was followed by re-addition and thus constituted an alternative path of racemization or exchange. The observed  $w$ -values are a weighted average of those for the two reactions, and the true  $w$ 's for substitution are higher than those observed, probably cleanly in the range characteristic of nucleophilic participation by water in the slow step.

Earlier discussions<sup>14-16</sup> have proposed a carbonium ion mechanism, but a highly qualified one to

(13) I wish to thank Mr. C. A. Vernon for discussions on this matter, as well as for the privilege of using unpublished data.

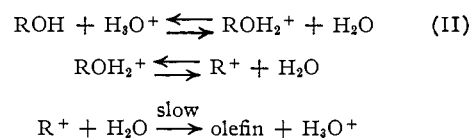
(14) C. A. Bunton, A. Konasiewicz and D. R. Llewellyn, *J. Chem. Soc.*, 607 (1955); C. A. Bunton and D. R. Llewellyn, *ibid.*, 3402 (1957).

(15) R. H. Boyd, R. W. Taft, Jr., A. P. Wolf and D. R. Christman, *J. Am. Chem. Soc.*, **82**, 4729 (1960).

account for the precise stereochemical result. Part of the argument involved the Zucker-Hammett hypothesis (slopes of 1.02 and 0.97 in plots of  $\log k_{\psi}$  vs.  $-H_0$ ). The present criterion calls for a mechanism of the SN2 type, which moreover gives a straightforward account of the stereochemical inversion. It remains possible that the carbon atom at the site of substitution carries considerable positive charge in the transition state, that is, that the SN2 mechanism leans considerably toward the SN1.<sup>17</sup>

Oxygen exchange in *t*-butyl alcohol (20) has  $w$  of  $-2.3$  in sulfuric acid, indicative of a carbonium ion mechanism in which the rate-determining step is dissociation of ROH<sub>2</sub><sup>+</sup> into R<sup>+</sup> and H<sub>2</sub>O. By the principle of microscopic reversibility this should be equivalent to the reverse process, R<sup>+</sup> + H<sub>2</sub>O → ROH<sub>2</sub><sup>+</sup>, in its demand for water; that is, in its  $w$ -value with respect to ROH as substrate.

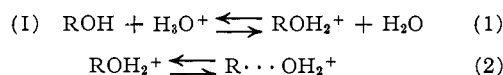
Dehydration of *t*-butyl alcohol occurs only 1/27 as fast as oxygen exchange in 0.45 *M* sulfuric acid,<sup>18</sup> and mechanism II<sup>19</sup> has been offered.<sup>15</sup> In this



mechanism, *proton removal* from R<sup>+</sup> is rate determining. A  $w$ -value some two or three units higher than for oxygen exchange would be expected, corresponding to the usual difference between water acting as a nucleophile and as a proton transfer agent.<sup>3</sup> In fact, the  $w$ -values for *t*-amyl alcohol dehydration (21) are  $-0.4$  (H<sub>2</sub>SO<sub>4</sub>) and  $+0.5$  (HNO<sub>3</sub>). Mechanism II is supported.

Measurements on the rates of hydration of trimethylethylene (to *t*-amyl alcohol), and of similar reactions, as a function of acid concentration have been made.<sup>20</sup> Unfortunately the data are not suitable for calculation of  $w$ -values. No fault is imputed; the difficulty is that correction for solubility of the (gaseous) olefins in the acid media must be made. While the corrections applied are apparently valid, they are not considered precise enough to warrant calculation of sensitive  $w$ -values. The  $w$ 's are evidently in the vicinity of zero, and are therefore compatible with the foregoing discussion.

An alternative mechanism for tertiary alcohol exchange and dehydration was also entertained<sup>15</sup>



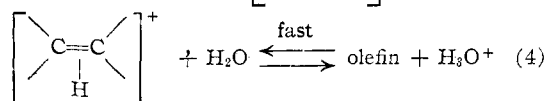
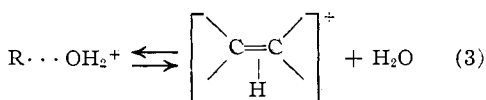
(16) H. L. Goering and R. E. Dilgren, *ibid.*, **82**, 5744 (1960); J. Manassen and F. S. Klein, *J. Chem. Soc.*, 4203 (1960).

(17) That elimination has a lower  $w$  than substitution points to a carbonium ion (E1) mechanism for the former. The E1 reaction should be accompanied by SN1; that is, at higher acidities some of the substitution may occur via carbonium ions, further contributing to a lowering of  $w$  for the total reaction. Whether the shift from SN2 to SN1 is discontinuous or gradual is a moot point.

(18) I. Dostrovsky and F. S. Klein, *J. Chem. Soc.*, 791 (1955).

(19) The numbering is that of ref. 15.

(20) R. W. Taft, Jr., *J. Am. Chem. Soc.*, **74**, 5372 (1952); R. W. Taft, Jr., E. L. Purlee, P. Riesz and C. A. DeFazio, *ibid.*, **77**, 1584 (1955).

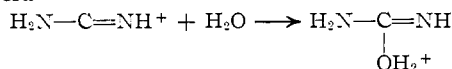


Step 2 is slow for exchange but fast for dehydration, for which step 3 is rate determining. The vital step in dehydration is conversion of one unfamiliar intermediate into another, and one does not know what kind of water requirement it would have. Should it be considered as a proton transfer reaction? Assignment even of relative  $w$ -values would be sheer guesswork. Mechanism I cannot be judged with respect to the new criterion.

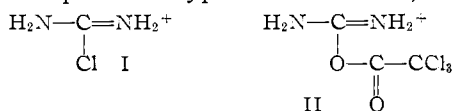
Because mechanism II comprises familiar transformations between well recognized intermediates, and is rational with respect to the  $w$  criterion, whereas I comprises unfamiliar transformations between strange species, the former is strongly preferred.<sup>21</sup>

**Hydrolysis of Carboxylic Acid Derivatives. Cyanamide.**—The hydrolysis of cyanamide to urea was one of the few reactions for which good data were available at the time the Zucker-Hammett hypothesis was formulated.<sup>23</sup> For reactions in nitric acid up to 5  $M$ ,  $\log k_{\psi}$  was approximately linear with  $-\bar{H}_0$ , and a mechanism not requiring water in the rate-determining step was implied. Later work confirmed the correlation with  $H_0$  in nitric acid and revealed amazing specific effects of particular acids.<sup>24</sup> These were not the usual sort of general acid catalysis; thus trichloroacetic acid was a better catalyst than oxonium ion while hydrochloric and hydrobromic acids at higher concentrations strongly retarded the formation of urea. The interpretations offered by Kilpatrick<sup>25</sup> have not been entirely accepted.<sup>7</sup>

For nitric acid-catalyzed hydrolysis,  $w$ -values of +0.8, +1.4 and +1.5 are computed (87); the latter two values are from the more recent work. These indicate that the rate-determining step is nucleophilic attack of water on the conjugate acid



The complications in other acids stem, it seems, from competing nucleophilic attack by better nucleophiles. In hydrohalic acids, hydrolysis-resistant species of type I are formed<sup>26</sup>; this was



(21) A further special assumption required for mechanism I is that the  $\pi$ -complex (step 3 or 4) be different from the transition state (of nearly identical composition and geometry) in rearrangement of isobutyldiazonium ion to *t*-butyl carbonium ion.<sup>22</sup>

(22) L. G. Cannell and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **78**, 5812 (1956).

(23) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 273.

(24) M. J. Sullivan and M. L. Kilpatrick, *J. Am. Chem. Soc.*, **67**, 1815 (1945).

(25) M. L. Kilpatrick, *ibid.*, **69**, 40 (1947).

(26) The conjugate acid of the (basic) original adduct is shown.

proposed by Kilpatrick<sup>25</sup> and supported cogently.<sup>27</sup> The corresponding process in trichloroacetic acid would form intermediate II. While this undoubtedly would have equal resistance to hydrolytic attack on its cyanamide carbon, it is ideally constituted for scission to urea and trichloroacetic acid via attack of water on the trichloroacetate carbonyl carbon.

Hydrolyses of *N,N'*-diphenylformamidine (84), thioacetamide (85) and methyl benzimidate (86) have high  $w$ -values (+4.2 to +7.8) indicative of proton transfer in rate-determining steps. In paper II,<sup>3</sup> four generalized mechanisms for substitution at unsaturated carbon involving proton transfer concerted with the making or breaking of C-O or C-N bonds were outlined. Of these, mechanisms a and b seem the most probable for the present cases; mechanism b for *N,N'*-diphenylformamidine hydrolysis is given in detail in that paper.

If one knew exactly why nucleophilic attack of water on  $SH^+$  is rate determining for hydrolysis of ordinary amides, he would be in a position to choose between mechanisms a and b for these three related reactions. The reasoning is somewhat lengthy and is withheld. So also is the argument which disfavors mechanisms c and d.

The high  $w$ -value (+5.1 in HCl) for piperazine-2,5-dione hydrolysis (42) suggests general acid catalysis of leaving group departure in the rate-determining step. The probable mechanism was sketched in paper II.<sup>3</sup> It is unlikely that attack of water is rate determining (as with most amides) since the leaving group is part of a ring structure and therefore less prone to depart. If this deduction is correct, this hydrolysis reaction, unlike most acid-catalyzed amide hydrolyses, should show oxygen exchange between carbonyl oxygen and the medium in the course of hydrolysis.

**The  $\gamma$ -Butyrolactone Enigma.**—The hydrolysis of  $\gamma$ -butyrolactone (74)<sup>5</sup> and the reverse reaction, lactonization of  $\gamma$ -hydroxybutyric acid (83), became something of a stumbling block in application of the Zucker-Hammett hypothesis.<sup>28</sup> The facts that rates of hydrolysis and lactonization correlated approximately with  $[H_3O^+]$  and  $h_0$ , respectively,<sup>7,29</sup> seemed at first quite reasonable since a common transition state might require a molecule of water for hydrolysis but not for lactonization. However, rationalization with respect to the Zucker-Hammett hypothesis was difficult because of the emphasis usually placed on the activity coefficient of the transition state.<sup>28</sup> When the same transition state is involved for two reactions, its activity coefficient cannot be nearly independent of the medium for one case and quite dependent for the other. Taft, Deno and Skell<sup>28</sup> suggested that the explanation lay in medium-de-

(27) Remarkably, the halide ion complication with ordinary nitriles causes acceleration of hydrolysis. This is reasonable because intermediates of type  $R-C=NH_2^+$  lack the resonance stabilization



which structure I must enjoy.

(28) R. W. Taft, Jr., N. C. Deno and P. S. Skell, *Annual Review of Physical Chemistry*, **9**, 287 (1958).

(29) F. A. Long, F. B. Dunkle and W. F. McDevit, *J. Phys. Colloid Chem.*, **55**, 829 (1951).

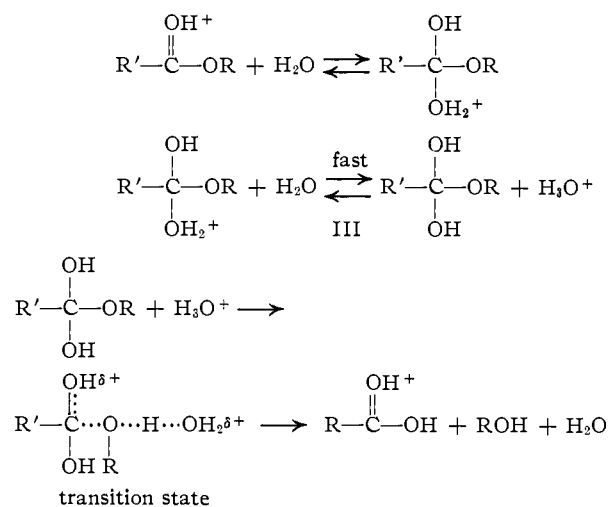
pendence of substrate activity coefficients. They implied that the activity coefficient of the lactone varied abnormally.

A similar problem arises in connection with the new approach.  $w$  for hydrolysis (+6.1 in HCl, +8.5 in HClO<sub>4</sub>) exceeds that for lactonization (+2.2 in either acid) by some four to six units whereas an excess of only one unit (the water molecule consumed in hydrolysis) might have been expected. How are the other three to five units to be accounted for?

An explanation is given by the hydration theory of  $w$ -values,<sup>4</sup> which holds  $w$  to be indicative of the difference in hydration between transition state and substrate on a scale set by the water balance in protonation of indicator bases. If a substrate has unusually high hydration, but the transition state is "normal," a low  $w$ -value is to be expected. In the present case, it is reasonable that  $\gamma$ -hydroxybutyric acid with its excellent hydrogen-bonding hydroxy and carboxy groups should have more water molecules of hydration than does the lactone.<sup>30</sup>

**Carboxylic Esters.**—Measurements of oxygen isotope exchange in the course of ester hydrolysis<sup>32</sup> indicate that rate determination is shared between attack of water on carbon and expulsion of the alkoxy group from a tetrahedral intermediate. If the former were altogether rate determining, exchange would not be observed; if the latter were the slow step, carbonyl oxygen-18 would be entirely "washed out" in the course of hydrolysis.

If alkoxy group departure is general acid catalyzed, the following mechanism is probable for oxonium-catalyzed hydrolysis (starting with protonated substrate)



(30) This is equivalent to attributing the known<sup>31</sup> dependence of the equilibrium constant,  $K = [\text{lactone}]/[\text{acid}]$ , on acid concentration largely to a difference in hydration of the two organic species. A plot of  $\log K$  in hydrochloric acid against  $\log a_{\text{H}_2\text{O}}$  has slope  $-4.3$ . After correction for the molecule of water liberated on lactonization, and on the assumption that the activity coefficient ratio for the hydrated molecules<sup>4</sup> is virtually independent of mineral acid concentration, this indicates the hydroxy acid to have about three more waters of hydration than the lactone.

(31) F. A. Long, W. F. McDevit and F. B. Dunkle, *J. Phys. Colloid Chem.*, **55**, 813 (1951).

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

The two rate-determining steps should have different  $w$  requirements:  $w$  for nucleophilic attack is commonly +2 to +3, and for general acid catalysis of leaving group ejection from a covalent hydrate intermediate about +6. When rate determination is shared between the two, an intermediate  $w$ -value should result. In fact,  $w$ -values for common ester hydrolyses are about +4 to +5.

**Strongly Basic Carboxylic Amides.**—The  $w$ -values for hydrolysis of four amides having strongly basic centers apart from the amide nitrogen (acetylhydrazide (43) and the three pyridine-carboxamides (38–40)) are about +5, much higher than the range of +1.2 to +2.6 for hydrolysis of ordinary amides. A possible explanation is that these  $w$ -values represent unusual hydration changes or activity coefficient behavior related to the special charge character of these reactions (monopositive substrates  $\rightarrow$  dipositive transition states), superimposed on the usual mechanism of amide hydrolysis. Another way of saying the same thing is that the  $H_+$  function may differ significantly from  $H_0$  for these substrates. Alternatively, there may be an actual change to a mechanism in which proton transfer occurs during the slow step.

**Hydrolysis of Inorganic Esters. Sulfites.**—Bunton, de la Mare and Tillett<sup>33</sup> found, for hydrolysis of several open and cyclic dialkyl sulfites in perchloric acid, a dependence on acidity intermediate between the two classical Zucker–Hammett categories. With some discomfort, they based their postulate of mechanism (rate-determining nucleophilic attack of water on sulfur of the conjugate acids) on other (cogent) evidence and in effect bent the Zucker–Hammett hypothesis to fit the facts. No special adjustments are needed, however, with respect to the new criterion since the  $w^*$ -values for hydrolyses of dimethyl (46), diethyl (47) and trimethylene (52) sulfites ( $-2.5$  to  $-3.8$ ) are in the range characteristic of the mechanism indicated by the other evidence.

$w^*$ -Values are higher ( $-1.5$  to  $-2.3$ ), however, for hydrolysis of several sulfite esters of 1,2-glycols (48–51), suggesting that proton transfer may take some part in rate determination in these cases. It is reasonable that when leaving group expulsion ruptures a five-membered ring, it should be slower, perhaps slow enough to enable it to share in rate determination. Two experiments in ca. 0.1  $M$  perchloric acid indicated ethylene sulfite does not exchange oxygen with the medium during hydrolysis,<sup>34</sup> in disagreement with this idea. Such experiments would be of greatest interest, however, at high acid concentrations in which leaving group expulsion would be expected to have, if any, a greater share in rate determination.

**Phosphates.**— $w$  and  $w^*$  for hydrolysis of the mono- and dimethyl esters of phosphoric acid, and for oxygen exchange in phosphoric acid, are

	$w$	$w^*$
H <sub>3</sub> PO <sub>4</sub> , oxygen exchange (98)	+3.4	-0.7
Methyl dihydrogen phosphate (53)	+4.0	-0.1
Dimethyl hydrogen phosphate (54)	+4.6	-1.9

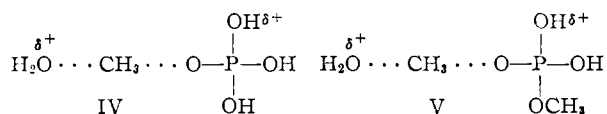
(33) C. A. Bunton, P. B. D. de la Mare and J. G. Tillett, *J. Chem. Soc.*, 4754 (1958); 1766 (1959).

(34) C. A. Bunton, P. B. D. de la Mare, P. M. Greaseley, D. R. Llewellyn, N. H. Pratt and J. G. Tillett, *ibid.*, 4751 (1958).

Methyl dihydrogen phosphate hydrolysis was studied over a broad range of acid concentration, and the  $w$  plot is significantly curved while the  $w^*$  plot is straight.<sup>2</sup> For the other two reactions either type of plot has about the same standard deviation of slope. Discussion in terms of  $w^*$ -values is to be preferred.

For methyl dihydrogen phosphate hydrolysis, the magnitude of  $w^*$  is characteristic of general acid catalysis and, there being no authentic example of such for displacement at saturated carbon in moderately concentrated acids, suggests a mechanism of substitution at phosphorus.<sup>35</sup> However, hydrolysis in oxygen-18-rich water 5  $M$  in perchloric acid produced methanol whose isotopic content indicated, after correction for exchange between methanol and the medium, 73% of C-O bond scission.<sup>36,37</sup> Moreover, oxygen exchange in phosphoric acid, the mechanism of which is presumably similar to that of  $\text{CH}_3\text{OPO}_3\text{H}_2$  hydrolysis at phosphorus, has a  $w^*$ -value little lower than that for the total monomethyl ester hydrolysis reaction. Therefore  $w^*$  for hydrolysis at carbon must be close to that for the over-all reaction.

Thus a reaction which assuredly involves rate-determining nucleophilic attack of water on the substrate conjugate acid has a  $w^*$ -value (about -0.1) much greater than expected (about -3.8 to -2.0) for this mechanism. The empirical criterion of mechanism is not valid here. Why? Possibly because the present reaction involves unusual hydration changes on activation. Perhaps the transition state, best represented as IV, has exceptionally high hydration about the three



highly acidic hydroxy groups of the phosphate moiety. Even though the two acidic hydrogens of methyl dihydrogen phosphate are themselves considerably hydrated, this exceptional hydration may cause an extraordinary increase in hydration in forming the transition state and therefore an exalted  $w^*$ -value.

This rationalization is strengthened by the behavior of dimethyl hydrogen phosphate hydrolysis, in which C-O scission is even more predominant.<sup>38,40</sup> The  $w^*$ -value (-1.9) is nearly normal for water acting as a nucleophile. In the transition state (V), one of the three good sites for hydrogen bonding with water molecules has been lost.

(35) J. F. Bunnett, *J. Am. Chem. Soc.*, **82**, 499 (1960).

(36) C. A. Bunton, D. R. Llewellyn, K. G. Oldham and C. A. Vernon, *J. Chem. Soc.*, 3574 (1958).

(37) Haake and Westheimer<sup>38</sup> reckoned 52 to 76% P-O scission from their experiments on the same reaction under similar conditions. These authors determined oxygen-18 content of the phosphoric acid product, but did not correct for exchange between  $\text{H}_2\text{PO}_4$  and the medium, which has since been shown to be considerable.<sup>39</sup> The value of Bunton, *et al.*,<sup>36</sup> is therefore preferred.

(38) P. C. Haake and F. H. Westheimer, *J. Am. Chem. Soc.*, **83**, 1102 (1961).

(39) C. A. Bunton, D. R. Llewellyn, C. A. Vernon and V. A. Welch, *J. Chem. Soc.*, 1636 (1961).

(40) C. A. Bunton, M. M. Mhala, K. G. Oldham and C. A. Vernon, *ibid.*, 3293 (1960).

Until this interpretation is more firmly substantiated, or replaced by a better one, one must withhold judgment on reactions of other substrates containing the  $-\text{PO}_3\text{H}_2$  group. Thus one is not sure whether the unexpectedly high  $w$ -values (+1.8 in  $\text{HClO}_4$ , +3.3 in  $\text{H}_2\text{SO}_4$ ) for  $\alpha$ -D-glucose-1-(dihydrogen)phosphate hydrolysis (55) represent the above special hydration factor superimposed on unimolecular heterolysis in the protonated substrate,<sup>41</sup> or whether water acts as a nucleophile in the slow step as the unadjusted empirical criterion would suggest. The detailed mechanism of oxygen exchange in phosphoric acid<sup>39</sup> is also obscure.

**Evaluation.**—In the foregoing “field test,” the new criterion of mechanism has in three cases (hydrolysis of epoxides; hydrolysis of sulfite esters; tertiary alcohol dehydration and oxygen exchange) confirmed other good evidence of mechanism although the Zucker-Hammett hypothesis had contributed confusion or discomfort. In three further instances (hydrolysis of cyanamide; hydrolysis of certain glycosides; *sec*-butyl alcohol racemization and oxygen exchange) it calls for mechanisms compatible with other evidence but which had been passed by largely because of the Zucker-Hammett hypothesis. Finally in three cases (hydrolysis of methyl dihydrogen phosphate; hydrolysis of strongly basic amides; the  $\gamma$ -hydroxybutyric acid  $\rightleftharpoons$   $\gamma$ -butyrolactone interconversion), straightforward application of the empirical criterion leads to inconsistent conclusions; these seeming inconsistencies have been rationalized by invoking special postulates of unusual substrate or transition state hydration which, though reasonable, lack force.

The empirical criterion has, by and large, served quite well in this application to diverse data. However, it clearly falls short of the ideal of giving direct and unequivocal answers without any attention to the system under study. That special postulates are necessary in a few cases in order to resolve internal or external inconsistencies is disturbing, not only with respect to these cases, but also with respect to others where there is no present evidence of conflict. How is one to know when the criterion can be applied without reservation and when special adjustments need be made? With our present state of knowledge in this field, postulates of unusual hydration (or, alternatively, of unusual activity coefficient behavior) are necessarily qualitative and subjective. They could serve, unwittingly, to shape experimental results to fit a pet theory.

A balanced judgment is that the criterion, in its present state of development, gives indications rather than specifications of mechanism. As empirical experience is extended, or as more is learned of factors determining hydration and/or activity coefficients of species in acidic solutions, confidence in these indications will increase. Indeed, already the deduction of mechanism from  $w$ - or  $w^*$ -values is relatively safe in systems (*e.g.*, most oxygen derivatives of hydrocarbons) where

(41) C. A. Bunton, D. R. Llewellyn, K. G. Oldham and C. A. Vernon, *ibid.*, 3588 (1958).

one can infer by analogy that regular behavior is to be expected.

Because of the frequent ease with which reaction rates can be measured as a function of mineral acid concentration, because of the present considerable accuracy of the empirical criterion of mechanism and the probability that it will become more accurate with the passage of time, kinetic response to changing acid concentration deserves a restoration of status as a criterion of mechanism.

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## Structure of Salts of N,N-Dimethylacetamide and N,N-Di(*n*)butylacetamide<sup>1</sup>

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The infrared spectra of N,N-dimethylacetamide, N,N-di(*n*)butylacetamide, their hydrochlorides and deuteriochlorides have been measured. The spectra are interpreted on the assumption that the proton goes to oxygen.

### Introduction

Pauling<sup>2</sup> calculated that the basic dissociation constant of amides would be  $1 \times 10^{-20}$  if the proton goes to nitrogen and commented "the value for the base constant  $1 \times 10^{-20}$  is so small as to be without significance, except to show that the amides do not form salts with acids by adding a proton to the amino group." This calculation did not take into account the inductive effect of the carbonyl group

which should be considered. The  $pK_a$  of  $\text{CH}_3\text{-C}(=\text{O})\text{-NH}_2^+$  can be estimated by analogy to be 5.0 from the

values for acetic acid, 4.76; glycolic, 3.83; acetoacetic, 3.38; ammonium ion, 9.25; and hydroxyammonium ion, 5.96. The corresponding  $K_b$  for

$\text{CH}_3\text{-C}(=\text{O})\text{-NH}_2$  without resonance would be  $10^{-9}$ . Since acetamide has 21 kcal. resonance energy the  $K_b$  of the compound would be  $RT \ln 10^{-9}/21,000 = 10^{-24.3}$ , a smaller value than that above, making N-protonation in amides even more unlikely.

It has been concluded from a number of n.m.r. studies<sup>3-7</sup> that the proton goes mainly on oxygen in agreement with this calculation, but some of these studies<sup>6,7</sup> have found a fast proton ex-

change on nitrogen but with the concentration of the N-protonated species undetectably small.

Other studies using ultraviolet and infrared<sup>8-10</sup> and dissociation constant<sup>11</sup> data have concluded the proton goes on the nitrogen.

Since the previous evidence was on urea or unsubstituted or monosubstituted amides with one or more hydrogens on the nitrogen, it was of interest to measure N-disubstituted amides where only one proton or deuteron would be present in the hydrochloride or deuteriochloride.

### Results

The spectra of N,N-dimethylacetamide and N,N-di(*n*)butylacetamide, together with their hydrochlorides and deuteriochlorides shown in Fig. 1, indicate that the spectra of the salts are quite different from those of the free amides particularly in the 4.0 to 6.5  $\mu$  region. Conclusions from the infrared spectra, including our own, that the proton goes to nitrogen have been based largely on the assumption that the band around 6  $\mu$  in the salts arises from a carbonyl vibration.

While it is probably an oversimplification to consider any single vibration of a pair of atoms in the -CO-NH system as being exclusively re-

(1) Presented in part at the 137th National Meeting of the American Chemical Society at Cleveland, Ohio, April, 1960.

(2) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., Third Edition, 1960, p. 281.

(3) W. D. Phillips, *J. Chem. Phys.*, **23**, 1363 (1955).

(4) H. S. Gutowsky and C. H. Holm, *ibid.*, **25**, 1228 (1956).

(5) G. Fraenkel and C. Niemann, *Proc. Natl. Acad. Sci.*, **44**, 688 (1958).

(6) A. Berger, A. Loewenstein and S. Meiboom, *J. Am. Chem. Soc.*, **81**, 62 (1959).

(7) G. Fraenkel and C. Franconi, *ibid.*, **82**, 4478 (1960).

(8) S. Mizushima, T. Simanouti, S. Nagakura, E. Kuratani, M. Tsuboi, H. Baba and O. Fujioka, *ibid.*, **72**, 3420 (1950). We have repeated this work on N-methylacetamide and like these workers find a band at 2695 Å. in 5 N HCl. However, when the compound was carefully purified as reported by Bello (J. Bello, *J. Phys. Chem.*, **60**, 1341 (1956)) no band was found. The band therefore results from an impurity and gives no evidence that the proton is on nitrogen in the salt of N-methylacetamide.

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(11) J. T. Edward, H. S. Chang, K. Ajatia and R. Stewart, *Can. J. Chem.*, **38**, 1518 (1960).