of 6.76 reported by Hertel and Lebok[13] in benzene solution.

p-Aminoacetophenone has a greater molar refraction and absorbs at a longer wave length (in the ultraviolet) in a mixture of dioxane and chloroform than in either pure solvent. This is attributed to solvent interaction at both ends of the solute molecule OC_4H_8O - - - $H_2NC_6H_4CRO$ - - - $HCCl_3$. It was thought that this compound might also show a greater moment in a dioxane–*trans*-dichloroethylene mixture than in dioxane. The value obtained, however, is 0.06 debye less than in dioxane, indicating that the dichloride is a weaker "acceptor" solvent than chloroform, and that its weak interaction does not quite compensate for the decreased concentration of dioxane molecules in the vicinity of the amino group.

The moment of *p*-methoxycinnamonitrile in benzene, 5.14, shows the expected increase over the value, 4.82, observed for anisonitrile. In the light of these values, the moments reported by Weizmann[14] for *p*-dimethylaminobenzaldehyde, 5.6, and *p*-dimethylaminocinnamaldehyde, 5.4, appear somewhat anomalous.

This study of solute-solvent interaction on the electric moments of amines is being continued to determine the effect of extension of the conjugated chain.

Summary

Electric moments have been determined for mono-*n*-butylamine and some para-substituted anilines in benzene and dioxane, for *p*-methoxybenzonitrile in benzene, for *p*-methoxycinnamonitrile and *p*-dimethylaminobenzaldehyde in benzene and *trans*-dichloroethylene, and for *p*-nitrosodimethylaniline in *trans*-dichloroethylene.

The large moments observed for the substituted anilines in dioxane are interpreted as indicating increased contribution of highly polar resonance structures in this solvent resulting from the stabilization of these structures by intermolecular hydrogen bonding. A weaker solute–solvent interaction is observed in *trans*-dichloroethylene.

NOTRE DAME, INDIANA RECEIVED MARCH 2, 1950

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[13] Hertel and Lebok, *Z. physik. Chem.*, **B47**, 315 (1940).

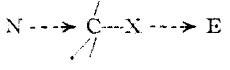
[14] Weizmann, *Trans. Faraday Soc.*, **36**, 329 (1940).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Concerted Displacement Reactions. V. The Mechanism of Acid-Base Catalysis in Water Solution[1]

BY C. GARDNER SWAIN

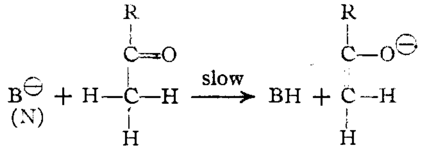
Previous studies of the displacement reactions of organic halides have demonstrated that *in benzene solution* there must always be both a nucleophilic or pushing reagent to attack carbon and an electrophilic or pulling reagent to attack halogen in the rate determining step in order to effect any reaction, regardless of whether the displacement is of the Walden inversion[2] or carbonium ion[3] type.



It has been considered by some that only nucleophilic attack is involved in the Walden inversion and only electrophilic attack in the carbonium ion mechanism. The concerted, push-pull character of the rate determining steps in benzene seemed to shed doubt on this concept of a sharp duality of mechanism.

Naturally one wonders about the generality of this conclusion, *i. e.*, whether both nucleophilic and electrophilic attack are also generally required for polar reactions *in water solution*. In most displacements in water solution, including halide displacements, water is too reactive in one or both roles relative to the other species present to permit unambiguous conclusions to be reached experimentally, but it appears that an affirmative answer can be found among reactions involving carbonyl groups, such as enolization, mutarotation and carbonyl addition. The evidence will be presented in this paper.

For the enolization of ketones it is currently accepted that there are two different mechanisms: base catalyzed and acid catalyzed.[4] In the base catalyzed mechanism only a base, or nucleophilic reagent, is involved.



In the acid catalyzed mechanism only an acid, or electrophilic reagent, is involved.

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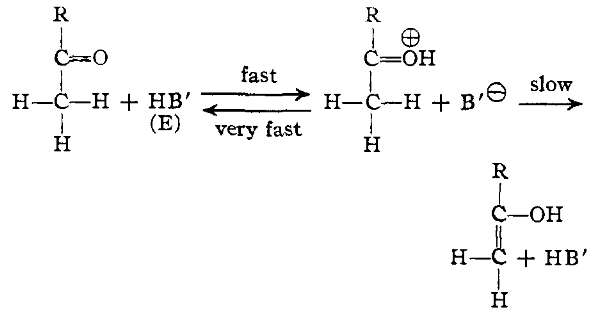
(1) Paper presented in the Acid–Base Symposium at the Atlantic City Meeting of the American Chemical Society, Sept. 21, 1949. For paper IV, see Swain, THIS JOURNAL, **72**, 2794 (1950).

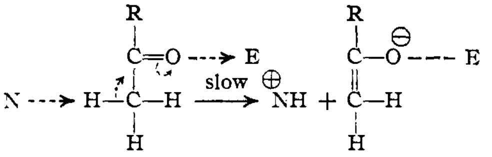
(2) Methyl halides with pyridine, Swain and Eddy, THIS JOURNAL, **70**, 2989 (1948).

(3) Triphenylmethyl halides with methanol, Swain, *ibid.*, **70**, 1119 (1948).

(4) See, for example, Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., N. Y., 1940, pp. 229–237; Wheland, "Advanced Organic Chemistry," John Wiley and Sons, New York, N. Y., 1949, p. 255.



Instead of these two different mechanisms one can imagine that there might be only a *single mechanism*, a concerted or push-pull mechanism, which holds in all cases, requiring the united action on the ketone in the rate determining step of both a nucleophilic reagent and an electrophilic reagent, *i. e.*, two separate attacking molecules.



It is this latter view which will be adopted to see what new information or predictions may be gleaned. The nucleophilic reagent N might be either uncharged (as shown) or negatively charged: it might be HO^-, AcO^-, H_2O or any other base. The electrophilic reagent E might be either uncharged (as shown) or positively charged: it might be Cu^{++}, H_3O^+, HOAc, H_2O, or any other acid or species capable of solvating an anion. The product would be either the solvated enolate anion (as shown) or an enol or enol derivative depending on the structure of the electrophilic reagent E, *i. e.*, on whether or not it (or a fragment from it such as H^+) covalently bonds to the oxygen atom. The strongest kind of pull is one that does lead to the formation of a covalent bond between oxygen and the electrophilic reagent, but an electrostatic solvation (as shown) will suffice.[5]

If this concerted mechanism operates, the relative reactivity of different nucleophilic reagents capable of attacking the hydrogen should be to a first approximation constant and independent of what electrophilic reagent is attacking the oxygen, and, conversely, the relative reactivity of different electrophilic reagents at the second center should be independent of what nucleophilic reagent is attacking at the first center. Therefore, we ought to be able generally to express the first order rate constant, k_1, as follows

$$k_1 = v/[\mathrm{C}] = k_0 (\sum_{\mathrm{N}} r_{\mathrm{N}}[\mathrm{N}])(\sum_{\mathrm{E}} r_{\mathrm{E}}[\mathrm{E}]) \qquad (1)$$

where v is the rate of reaction, C is the compound undergoing displacement (here, $RCOCH_3$), N may be any species which can attack the first center, and E is any species which can attack the second center, and r_N and r_E are the relative reactivities for any given N or E with respect to a fixed standard, such as water. Both r_N and r_E will be set equal to 1.00 for water.

The Enolization of Ethyl Acetoacetate.—Pedersen experimentally found the following expression for the enolization of ethyl acetoacetate.[6]

$$k_1 = 1.9 \times 10^{-2} + 8.2[\mathrm{AcO}^-] + 2.7[\mathrm{Cu}^{++}] + 1.14 \times 10^3[\mathrm{Cu}^{++}][\mathrm{AcO}^-]$$

His data fit equation (1) excellently, as may be seen by factoring this experimental expression into three parts (k_0 and two summations).

$$k_1 = 6.2 \times 10^{-6}([\mathrm{H_2O}] + 2.4 \times 10^4[\mathrm{AcO}^-])([\mathrm{H_2O}] + 7.8 \times 10^3[\mathrm{Cu}^{++}]) \quad (2)$$

Here the concentration of water $[H_2O]$ is 55 *M*, N is either water or acetate ion, and E is either water or cupric ion. Ability to factor in this way to obtain equation (2) is due to the fact that the relative reactivities are indeed perfectly constant within the experimental error, cupric ion, for example, being 7800 times as reactive an electrophilic reagent as water regardless of whether the nucleophilic reagent is water or acetate ion.[7] With 0.10 *M* cupric and 0.10 *M* acetate ion, the third order term involving both cupric and acetate ions represents 91% of the total rate. Cupric ion is known to form coördinate bonds with enolate anions, but there is no evidence of bonding with non-enolic ketones. Hence a concerted mechanism, in which it bonds with the oxygen only as the α-hydrogen is removed and not before, appears to be the simplest way to explain these results.

The Mutarotation of Glucose.—The same kind of concerted attack of nucleophilic and electrophilic reagents might be involved in the mutarotation of α-D-glucose.

This would give the open chain aldehyde form of the sugar as an intermediate which could then rapidly recyclize to give either the original α-form or the β-form. This concerted, push-pull mechanism of catalysis was proposed by Lowry and Faulkner in 1925 to explain their results on 2,3,4,6-tetramethylglucose in non-aqueous solvents.[8] They found that this compound mutarotated only slowly in either pure pyridine solution or pure cresol solution, but far faster in an equimolar mixture of the two. Therefore, they proposed that

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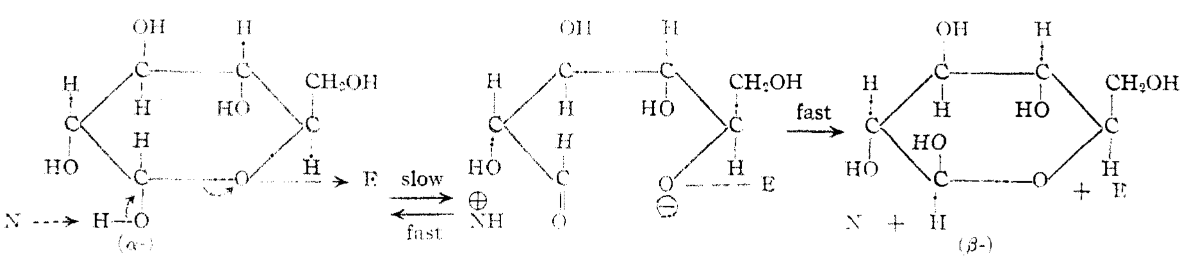
(5) There are no doubt solvent molecules farther out involved in solvating N and E. However, this is a constant factor if only rates run in the same solvent, *viz.*, water, are compared.

(6) Pedersen, *Acta Chem. Scand.*, **2**, 252 (1948).

(7) Actually, it is surprising that the positively charged copper ion is not at least two to ten times more reactive when the negatively charged acetate ion is involved, due to an electrostatic effect. The electrostatic effect may be compensated in this case by a second effect which operates independently of charge type, *viz.*, the tendency for discrimination between different nucleophilic reagents (*i. e.*, the spread of r_N values) to be somewhat less as stronger electrophilic reagents are used. Similarly, the electrostatic advantage of acetate ion over water in the reaction involving cupric ion may be offset by a tendency for all r_E values (including $r_{Cu^{++}}$) to be slightly less when a reagent of high r_N (like AcO^-) is used.

(8) Lowry and Faulkner, *J. Chem. Soc.*, **127**, 2883 (1925).



both a base (N) and an acid (E) were required. This is certainly a very clear-cut experiment. Yet Pedersen and later workers have tended to consider that this mechanism was limited to nonaqueous solvents, and in the case of water solution to favor instead the idea of two different bimolecular mechanisms, base and acid catalyzed respectively, because in water solution third order terms are not found in the rate expression.

Brönsted and Guggenheim experimentally found the following expression for the mutarotation of α-D-glucose in water solutions containing strong acids or bases or acetate buffers.[9]

$$k_1 = 8.8 \times 10^{-5} + 4.4 \times 10^{-4}[\mathrm{AcO^-}] + 1 \times 10^{2}[\mathrm{HO^-}] + 4 \times 10^{-5}[\mathrm{HOAc}] + 2.4 \times 10^{-3}[\mathrm{H_3O^+}] \quad (3)$$

There are second order terms involving the base acetate ion or the acid acetic acid, but no third order term involving both acetate ion and acetic acid.

To understand the reason for this we shall start with the concerted, push-pull picture of Lowry and calculate the magnitude that the third order term should have. Equation (1) applied to this case would have the form

$$k_1 = k_0([\mathrm{H_2O}] + r_{\mathrm{AcO^-}}[\mathrm{AcO^-}] + r_{\mathrm{HO^-}}[\mathrm{HO^-}])([\mathrm{H_2O}] + r_{\mathrm{HOAc}}[\mathrm{HOAc}] + r_{\mathrm{H_3O^+}}[\mathrm{H_3O^+}]) \quad (4)$$

Thus there are nine cross combinations of nucleophilic and electrophilic reagents that we must consider. These are shown in Table I.

TABLE I

COMBINATIONS OF NUCLEOPHILIC AND ELECTROPHILIC REAGENTS CONTRIBUTING TO EACH KINETIC ORDER

	$k_0r_N[N]r_E[E]$	Expected kinetic order
1	$k_0[\mathrm{H_2O}]^2$	$= K_1$
2	$k_0r_{\mathrm{AcO^-}}[\mathrm{AcO^-}][\mathrm{H_2O}]$	$= K_2\,[\mathrm{AcO^-}]$
3	$k_0r_{\mathrm{HO^-}}[\mathrm{HO^-}][\mathrm{H_2O}]$	$= K_3\,[\mathrm{HO^-}]$
4	$k_0[\mathrm{H_2O}]r_{\mathrm{HOAc}}[\mathrm{HOAc}]$	$= K_4\,[\mathrm{HOAc}]$
5	$k_0r_{\mathrm{AcO^-}}[\mathrm{AcO^-}]r_{\mathrm{HOAc}}[\mathrm{HOAc}]$	$= K_5\,[\mathrm{AcO^-}][\mathrm{HOAc}]$
6	$k_0r_{\mathrm{HO^-}}[\mathrm{HO^-}]r_{\mathrm{HOAc}}[\mathrm{HOAc}]$	$= K_2'\,[\mathrm{AcO^-}]$
7	$k_0[\mathrm{H_2O}]r_{\mathrm{H_3O^+}}[\mathrm{H_3O^+}]$	$= K_6\,[\mathrm{H_3O^+}]$
8	$k_0r_{\mathrm{AcO^-}}[\mathrm{AcO^-}]r_{\mathrm{H_3O^+}}[\mathrm{H_3O^+}]$	$= K_4'\,[\mathrm{HOAc}]$
9	$k_0r_{\mathrm{HO^-}}[\mathrm{HO^-}]r_{\mathrm{H_3O^+}}[\mathrm{H_3O^+}]$	$= K_1'$

The first term in Table I would be due to one water molecule serving as N and a second water molecule serving as E. One can never determine the kinetic order with respect to the solvent, because the solvent is in large excess and its concentration does not change appreciably on a percentage basis as the reaction progresses nor from one run to another. Hence kinetically the water would not appear in the experimental expression and this term would be first order with the square of the water concentration, [55 M],[2] lumped into the rate constant K_1. However, the experimental first order term might also be due, at least in part, to combination 9 with hydroxide serving as N and hydronium ion as E. This is possible because the product of hydroxide and hydronium ion concentrations is a constant, the water constant, which would also be concealed within the rate constant. Similarly the acetate ion term could be due either to acetate ion as N and water as E (combination 2), or to hydroxide ion as N and acetic acid as E (combination 6). Also the experimental acetic acid term must include both the combination of water as N and acetic acid as E (4), and acetate ion as N and hydronium ion as E (8).

In the past these kinetic ambiguities have not been clearly recognized. The experimental coefficient for the so-called "uncatalyzed" term, 8.8×10^{-5}, must therefore be set equal to $K_1 + K_1'$; the experimental coefficient for the acetate ion term, 4.4×10^{-4}, must be set equal to $K_2 + K_2'$; the experimental coefficient for the acetic acid term, 4×10^{-5} must be set equal to $K_4 + K_4'$; and in addition we know that $1 \times 10^2 = K_3$ and $2.4 \times 10^{-3} = K_6$. These five simultaneous equations prove to be perfectly compatible and capable of solution to give the following expressions.[10]

$$\begin{aligned} k_1 &= 2.9 \times 10^{-8}([\mathrm{H_2O}] + 2.8 \times 10^{2}[\mathrm{AcO^-}] + 6.3 \times 10^{7}[\mathrm{HO^-}])([\mathrm{H_2O}] + 2.5 \times 10^{1}[\mathrm{HOAc}] + 1.5 \times 10^{3}[\mathrm{H_3O^+}]) \\ &= 8.8 \times 10^{-5} + 4.4 \times 10^{-4}[\mathrm{AcO^-}] + 1 \times 10^{2}[\mathrm{HO^-}] + 4 \times 10^{-5}[\mathrm{HOAc}] + 2.4 \times 10^{-3}[\mathrm{H_3O^+}] + 0.2 \times 10^{-3}[\mathrm{AcO^-}][\mathrm{HOAc}] \quad (5) \end{aligned}$$

The second of these calculated expressions agrees exactly with the original experimental expression (3) of Brönsted and Guggenheim, except for the presence of the final third order acetate ion–acetic acid term, which was not included in their experimental expression. Table II shows why this term escaped detection experimentally. It shows the extent to which each of the nine combinations of reagents contributes to the total rate under the particular set of experi-

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[9] Brönsted and Guggenheim, THIS JOURNAL, **49**, 2554 (1927).

[10] Calculated using $[\mathrm{H_2O}] = 55\ M$, $K_w = 1.0 \times 10^{-14}$ and $K_A = 1.9 \times 10^{-5}$, the proper values for this salt concentration.[9]

TABLE II

EXTENT OF PARTICIPATION OF DIFFERENT REAGENTS UNDER TYPICAL EXPERIMENTAL CONDITIONS[a]

Kinetic term	Reagents N	Reagents E	Per cent. of total rate: Mutarotation of glucose	Per cent. of total rate: Enolization of acetone
"Uncatalyzed"	H_2O	H_2O	64	0.7
	HO^-	H_3O^+	0.000	.2
$[AcO^-]$	AcO^-	H_2O	32	38
	HO^-	HOAc	0.002	0.1
$[HO^-]$	HO^-	H_2O	0.04	0.2
[HOAc]	H_2O	HOAc	2.9	0.3
	AcO^-	H_3O^+	0.02	45
$[H_3O^+]$	H_2O	H_3O^+	0.033	0.8
$[AcO^-]$[HOAc]	AcO^-	HOAc	1.4	14

a For the mutarotation of glucose, 55 *M* H_2O, 0.10 *M* AcO^-, 0.10 *M* HOAc, 1.9×10^{-5} *M* H_3O^+, 5.3×10^{-10} *M* HO^-; for the enolization of acetone, 55 *M* H_2O, 0.20 *M* AcO^-, 0.20 *M* HOAc, 2.6×10^{-5} *M* H_3O^+, $4.6 \times^{-10}$ *M* HO^-.

mental conditions used by Brönsted and Guggenheim which would have given the *maximum* contribution of this third order term. Even here it contributes only 1.4% to the total rate. The five other terms, on the other hand, could each be made to contribute a relatively large amount to the total rate by proper choice of experimental conditions, conditions such as were used by these investigators. *E.g.*, in alkaline solution the hydroxide ion term was the only important term, in strong acid the hydronium ion term dominated, etc.

This resolves the mystery of why no third order term showed up experimentally. Water is in such high concentration relative to the other reagents, *viz.*, 55 *M vs.* 0.1 *M*, that it was always involved, as one of the reagents at least, in every important combination.

The Enolization of Acetone.—Dawson and Spivey obtained the following experimental expression for the iodination of acetone in water solution.[11]

$$k_1 = 6 \times 10^{-9} + 3.3 \times 10^{-6}[AcO^-] + 7[HO^-] + 1.3 \times 10^{-6}[HOAc] + 5.6 \times 10^{-4}[H_3O^+] + 3.5 \times 10^{-6}[AcO^-][HOAc] \quad (6)$$

Here a third order term involving both acetate ion and acetic acid does turn up experimentally. However, in 1934 Pedersen concluded that the third order term was 220-fold smaller than could be predicted on the concerted, push-pull basis of Lowry, and later investigators have generally concurred with this view.[12] This has been used by them as the crushing argument to dispose of the concerted mechanism. However, the discrepancy of 220-fold arises from failure to recognize the ambiguities in some of the kinetic terms, which we mentioned above, *i.e.*, the fact that the so-called "uncatalyzed" term might be due to either one water molecule serving as N and another as E or to hydroxide ion as N and hydronium ion as E; also that the acetic acid term might be due either to water serving as N and acetic acid as E or to acetate ion as N and hydronium ion as E; etc. By applying the same method that was used above on the mutarotation of glucose, which takes into account these kinetic ambiguities, calculated expressions can be obtained.[13]

$$k_1 = 2.5 \times 10^{-12}([H_2O] + 1.5 \times 10^4[AcO^-] + 3 \times 10^{10}[HO^-])([H_2O] + 1 \times 10^2[HOAc] + 2.5 \times 10^6[H_3O^+])$$

$$= 9.8 \times 10^{-9} + 2.1 \times 10^{-6}[AcO^-] + 4.1[HO^-] + 2.4 \times 10^{-6}[HOAc] + 3.4 \times 10^{-4}[H_3O^+] + 3.7 \times 10^{-6}[AcO^-][HOAc] \quad (7)$$

This time the agreement with the experimental expression (6) is poorer, but corresponding terms in equations (7) and (6) all have the same powers of ten and actually all agree within a factor of two. The less than two-fold deviations which remain are probably due to the fact that the relative reactivities of the different nucleophilic reagents are not completely independent of what electrophilic reagent is involved even though the electrophilic reagent is reacting at a different center, because the two reaction centers in the acetone molecule are not infinitely far apart. We feel that a discrepancy of a factor of two is about what would be expected from this cause,[14] and in any case is considerably less troublesome than the discrepancy of 220-fold which previously existed.

The calculated third order term actually agrees within a factor of two with that experimentally observed. No distortion or throwing out of balance of the other coefficients in the calculated equations was necessary to secure this agreement. Quite the contrary, the fit of the first and second order terms is within 1% of being the optimum agreement that could have been obtained by ignoring completely the experimental value of the third order term when solving for the relative reactivities. In fact it appears that if one were to assume that most of the enolization did occur by bimolecular processes such as the base catalyzed mechanism shown at the start (not involving water) or such as the following cyclic process in the case of acetic acid catalysis

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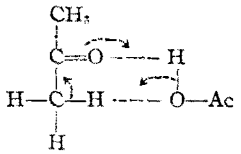
[11] Dawson and Spivey, *J. Chem. Soc.*, 2180 (1930).

[12] Pedersen, *J. Phys. Chem.*, **38**, 590 (1934); Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 236–237; Bell, "Acid-Base Catalysis," Oxford, 1941, p. 133; Wheland, "Advanced Organic Chemistry," John Wiley and Sons, New York, N. Y., 1949, p. 255.

[13] Calculated using H_2O = 55 *M*, $K_W = 1.2 \times 10^{-14}$ and $K_A = 2.6 \times 10^{-5}$, the proper values for this salt concentration.[11] The six simultaneous equations in five unknowns are not perfectly compatible, but were solved by successive approximation to make the final agreement between calculated and experimental coefficients as close as possible. Equal weight was given to all coefficients.

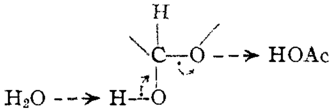
[14] Here the first effect mentioned in footnote (7) is slightly more than offset by the second effect. Further study of this latter effect leads us to believe that the value of HO^--H_3O^+ contribution in Table II (0.2) may be too large due to changing relative reactivities, but that the other estimated contributions are not seriously in error since there is reasonably good compensation of the two opposing effects.



then one would inevitably calculate a coefficient for the third order term too *small* (rather than too large) to agree with experiment. When the kinetic ambiguities are properly considered, it appears that it is the bimolecular mechanisms rather than the single, concerted, push-pull process which is discredited by the experimental facts.

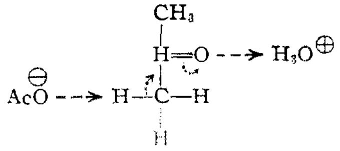
Conclusions from Table II.—On the basis of this analysis we can again say what combination of reagents is responsible for each of the kinetic terms in the rate expression (*cf.* Table *II*). Under a typical set of reaction conditions, the third order term contributes as much as 14% to the total rate. The most surprising conclusion concerns the nature of the acetic acid term. In the mutarotation, over 99% of this term was due to water serving as N and acetic acid as E. Here the situation is just reversed and over 99% of the acetic acid catalysis is due to the combined action of acetate ion and hydronium ion. This is due to the fact that the whole scale of relative reactivities (r_N and r_E) is generally more expanded in the enolization of acetone than in the mutarotation of glucose. This causes the stronger nucleophilic and electrophilic reagents to be relatively more effective, and terms not involving water have more chance to be important.

The above analysis indicates that in the mutarotation of glucose the bulk of the catalysis by acetic acid is due to operation of the mechanism

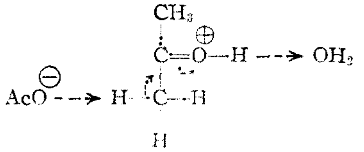


Were proton transfer from the acetic acid to the oxygen to occur in a fast equilibrium step prior to the rate determining step, specific hydronium ion catalysis would be observed instead of general acid catalysis. Hence it is not the conjugate acid of glucose which reacts with the nucleophilic reagent, which in this case is a water molecule, but it is glucose itself which reacts.

In the enolization of acetone catalyzed by acetic acid, N is acetate ion and E is hydronium ion. This still leaves two possibilities open. It might be a concerted reaction in which the proton from the hydronium ion is transferred to the carbonyl oxygen only as the α-hydrogen is removed by acetate ion

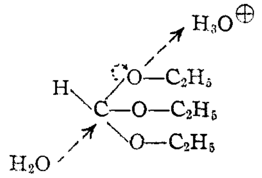


or the proton from the hydronium ion might be transferred to the carbonyl oxygen to give the conjugate acid in a fast equilibrium step ahead of the rate determining step.

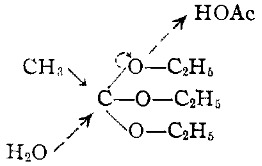


We favor the first, or concerted, picture because this is analogous to what must happen in the case of mutarotation, where the conjugate acid was not involved, and because this single, concerted picture is adequate for all other simple enolizations and mutarotations regardless of solvent as far as one can tell experimentally at the present time.

Among closely related compounds showing acid catalysis, the most stable ones should show the greatest discrimination between the various reactants, *i.e.*, the steepest slope on a Brönsted catalysis law plot. Hence it is not surprising that hydrolysis of ethyl orthoformate is catalyzed effectively only by hydronium ion



whereas ethyl orthoacetate, which can relinquish its ethoxyl group and bonding electron pair more easily due to greater electron supply from the methyl group than from a hydrogen atom, exhibits general acid catalysis by a wider range of acids.



In halide displacements in hydroxylic solvents, the solvent rather than any solute generally plays the role of electrophilic reagent. From this we may conclude that here there is even less discrimination between electrophilic reagents than in the case of mutarotation of glucose or hydrolysis of ethyl orthoacetate.

The Effect of *p*H.—The minimum in rate of mutarotation or enolization that is observed at intermediate values of *p*H follows naturally from the high values of r_N for hydroxide ion and r_E for hydronium ion relative to water.

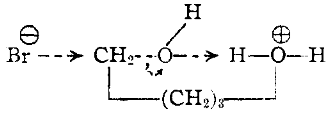
Scope of Concerted Mechanisms.—Isolated bits of evidence indicate the requirement of attack by both a nucleophilic reagent and an electrophilic reagent in the rate determining step in several other systems.

Optically active piperitone, a terpene ketone, racemizes slowly in pure water solution but rapidly in either alkaline solution or in dilute acids, *e.g.*, saturated aqueous sulfur dioxide. However, it can be recovered unracemized from homogeneous solution in 90% sulfuric acid, an enormously stronger acid.[15] Evidently water or some other base is required for enolization. In sulfuric acid more concentrated than 84%, all of the water has been converted to hydronium ion, and apparently hydronium ion, bisulfate ion and sulfuric acid are all ineffective as nucleophilic reagents in this reaction.

The fact that esterification[16] and semicarbazone formation[17] show general acid catalysis is suggestive that carbonyl addition reactions may also be concerted, push-pull processes.

It has long been recognized that the methyleneazomethine rearrangement proceeds by a concerted process requiring both a nucleophilic and an electrophilic reagent in the rate determining step.[18]

It is even possible that the rate-determining steps of most polar reactions of uncharged organic compounds in solution may be concerted processes of this sort. The first line of Fig. 1 depicts what may well be the usual situation, with a nucleophilic reagent N attacking compound C at one center, denoted by an x, while some electrophilic reagent E attacks at another definite center, marked by another x. Of course special cases arise where N and C are parts of the same molecule (second line), *i.e.*, the cases of neighboring group participation studied so thoroughly by Winstein and co-workers. There should also be cases where C and E are parts of the same molecule (third line), although these have received relatively little attention.[19] It is possible that enzymes owe a large share of their catalytic powers to the fact that N and E are combined in the same molecule (fourth line) just the proper distance apart for optimum interaction with the substrate C.



$$\overset{\ominus}{\mathrm{Br}} \dashrightarrow \underbrace{\mathrm{CH_2}\cdots\overset{\overset{\mathrm{H}}{/}}{\mathrm{O}}}\dashrightarrow \mathrm{H{-}}\overset{\oplus}{\mathrm{O}}\mathrm{{-}H} \qquad \text{—}(\mathrm{CH_2})_3\text{—}$$

In reactions in homogeneous solution, the first situation involving three separate molecules is probably the most usual one. The reason that third order terms seldom appear in reactions in water solution is then simply that few solutes are sufficiently more reactive than water to more than make up for the hundred-fold or greater difference in concentrations. Hence water participates instead in the role of nucleophilic reagent or electrophilic reagent or both simply because it is in so much higher concentration. It is only in cases where water is unusually ineffective in both roles that third order terms can be expected to appear.

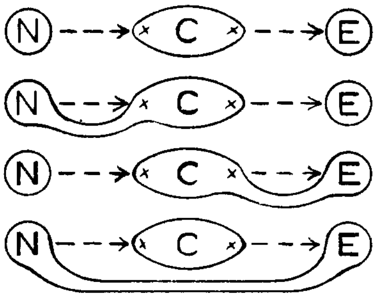


Fig. 1.—Concerted displacement reactions.

Summary

The currently accepted hypothesis of two competing bimolecular mechanisms, one acid catalyzed and the other base catalyzed, is difficult to reconcile with data on the enolization of acetone in water solution. Instead there appears to be only a single mechanism, which is a concerted, push-pull process requiring attack by both an acid and a base (two separate species) in the rate determining step. This mechanism permits more definite identification of reacting species than was possible with the Pedersen concept of a duality of mechanism, and more definite predictions of rate. This concerted picture is compatible also with data on the mutarotation of glucose in water solution and appears necessary to explain metal ion catalysis of enolization in water solution and various carbonyl reactions in non-aqueous solvents.

Thus the enolization of acetone in water solution and the displacement reactions of organic halides in benzene solution are similar in this respect of requiring attack by *both* a nucleophilic reagent and an electrophilic reagent in the rate determining step.

CAMBRIDGE 39, MASSACHUSETTS

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[15] Read and Smith, *J. Chem. Soc.*, **123**, 2267 (1923).

[16] Rolfe and Hinshelwood, *Trans. Faraday Soc.*, **30**, 935 (1934).

[17] Conant and Bartlett, THIS JOURNAL, **54**, 2881 (1932).

[18] Hsü, Ingold, Raisin, Salas and Wilson, *J. chim. phys.*, **45**, 233, 241 (1948).

[19] Such a case may be the reaction of tetramethylene glycol with hydrogen bromide in phenol solution, which is abnormally fast compared to homologous glycols; cf. Bennett and Reynolds, *J. Chem. Soc.*, 134 (1935).