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

A Transition from Specific Oxonium-ion Catalysis to General Acid Catalysis[1]

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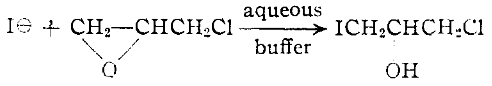
RECEIVED DECEMBER 10, 1951

It is suggested that reactions classified as examples of specific oxonium-ion catalysis in the region *p*H 2–7 may be made to exhibit general acid catalysis experimentally simply by using higher buffer concentrations. One can calculate the approximate buffer concentration required. This suggestion is tested and verified on a typical example of a specific oxonium-ion catalyzed reaction, a displacement reaction on an ethylene oxide. Experimental results exclude the Pedersen mechanism for general acid catalysis (involving the free oxonium ion of the ethylene oxide, *i.e.*, the conjugate acid of the substrate, as an intermediate), but agree with a concerted mechanism in which the nucleophilic reagent attacks the carbon atom *while* an electrophilic reagent (either hydronium ion, acetic acid or water) is protonating the oxygen atom (leaving group) of the ethylene oxide. In this mechanism there is no ionic intermediate, *i.e.*, the substrate never becomes a charged ion at any stage.

It is generally accepted[2] that certain reactions are subject to catalysis only by oxonium ions (*e.g.*, hydronium ion in water solution), whereas others are catalyzed generally by a wide range of un-ionized acid molecules as well. The first class, showing "specific oxonium-ion catalysis," is considered to include reactions of ethylene oxide,[3] hydrolysis of ethyl orthoformate,[4] and formation and hydrolysis of acetals.[4,5] The second class, showing "general acid catalysis," includes formation and hydrolysis of esters[6] and semicarbazones,[7] hydrolysis of ethyl orthoacetate,[4] enolization of ketones[8] and the hemiacetal decomposition illustrated by the mutarotation of glucose.[9]

To test the validity of the *experimental basis* for this classification we selected a typical example of "specific oxonium-ion catalysis" to see if it could be made to exhibit "general acid catalysis" simply by using a slightly higher buffer concentration. We chose the reaction of iodide ion with a substituted ethylene oxide, *viz.*, epichlorohydrin, as one that could be easily and accurately followed in water solution at 25°.



$$I^{\ominus} + \underset{O}{CH_2—CHCH_2Cl} \xrightarrow[\text{buffer}]{\text{aqueous}} ICH_2\underset{OH}{CH}CH_2Cl$$

Displacement reactions on ethylene oxides have been reported to be catalyzed by hydronium ion but not by undissociated acids such as acetic acid.[3] For example, doubling the concentration of acetic acid in 0.01 M acetic acid–0.02, 0.05 or 0.1 M sodium acetate buffers had no effect on the second-order rate constant for reaction of acetate ion with epichlorohydrin. The highest concentration of acetic acid used with each concentration of sodium acetate was 0.02 M.

To understand why only "specific oxonium-ion" catalysis was observed, we first *calculated* the approximate concentration of undissociated acetic acid which would be necessary to double the rate of displacement reactions on epichlorohydrin. The experimental value of c in

$$\log r_{HOAc} = c \log r_{H_3O^+}$$

where r_{HOAc} and $r_{H_3O^+}$ are reactivities of acetic acid and hydronium ion relative to water is 0.44 for mutarotation of glucose at 18° ($\log r_{H_3O^+} = 3.2$) and 0.31 for enolization of acetone at 25° ($\log r_{H_3O^+} = 6.4$).[10] From the average value of 0.37 ± 0.07, $\log r_{HOAc}$ can be calculated to be 1.6 ± 0.3 for epichlorohydrin ($\log r_{H_3O^+} = 4.3$). Thus even assuming no important effect on r_{HOAc} from changing medium or dielectric constant or concentration of acetic acid, the concentration of acetic acid needed to double the rate would be 1.2 M. In view of the variation in c and the possible association of acetic acid in concentrated solution, the necessary molarity might easily be as high as 4 M.

To keep catalysis by hydronium ion below the negligible value of 1% of the total rate, the *p*H must be at or above $4.3 - \log 0.02 - \log 55 = 4.3$. Accordingly we selected 4:1 acetic acid–sodium acetate buffers (*p*H 4.3). We expected the reaction to be accelerated about two- to fourfold on changing from 0.4 M acetic acid–0.1 M sodium acetate to 4 M acetic acid–1 M sodium acetate.

Results.—The relative initial rates, given in Table I, bear out this prediction. The rate of reaction of iodide ion with epichlorohydrin was accelerated by a factor of 2.2 (*cf.* runs 4 and 5) by the added acetic acid.

TABLE I

REACTION OF 0.150 M SODIUM IODIDE WITH 0.129 M EPICHLOROHYDRIN AT 25°

Run	HOAc, M	NaOAc, M	$NaClO_4$, M	Ionic strength, M	Relative rate
4	0.40	0.10	0.90	1.15	1.000
5	4.0	1.0	.00	1.15	2.2 ± 0.2
9	0.40[a]	0.10	.90	1.15	0.85 ± .09[a]
6	.40[b]	.10	.90	1.15	0.79 ± .08[b]
7	.40	.10	.00	0.25	1.18 ± .12
10	.40	.10	1.80	2.05	0.98 ± .10

[a] Dioxane (3.6 M) added in place of extra 3.6 M acetic acid in run 5. [b] Acetamide (3.6 M) added in place of extra 3.6 M acetic acid in run 5.

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(1) This is paper IX in the series "Concerted Displacement Reactions." For VIII, see C. G. Swain and J. F. Brown, Jr., THIS JOURNAL, **74**, 2538 (1952). This work was supported by the Office of Naval Research under Contract N5ori-07838, Project NR-056-198.

(2) K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1950, Chap. 10; L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 220, 241, 275.

(3) J. N. Brönsted, M. Kilpatrick and M. Kilpatrick, THIS JOURNAL, **51**, 428 (1929).

(4) J. N. Brönsted and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929).

(5) J. N. Brönsted and C. Grove, THIS JOURNAL, **52**, 1394 (1930); A. J. Deyrup, *ibid.*, **56**, 60 (1934).

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(7) J. B. Conant and P. D. Bartlett, THIS JOURNAL, **54**, 2881 (1932.)

(8) H. M. Dawson and E. Spivey, *J. Chem. Soc.*, 2180 (1930).

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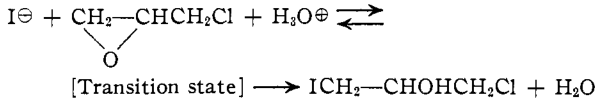
(10) C. G. Swain, *ibid.*, **72**, 4578 (1950).

To be sure that this acceleration was not due to a medium effect, we added other organic solutes in other experiments instead of the additional acetic acid. With either added dioxane (less polar than acetic acid) or added acetamide (more polar than acetic acid) the rate was depressed rather than accelerated.

To be sure that the acceleration was not due to a salt effect, we varied total ionic strength over the range 0.25–2.05 *M* in three runs (4, 7, 10). This had relatively little effect. Nevertheless, as a safeguard, the ionic strength was kept constant at 1.15 *M* in all other runs.

To be sure that the acceleration was not due to an increased concentration or activity of hydronium ions in the more concentrated buffer, we studied a phenolate ion-phenol equilibrium in the different media, since this equilibrium is similar in charge type to a hydronium ion-catalyzed reaction.

$$\text{ArO}^{\ominus} + \text{H}_3\text{O}^{\oplus} \rightleftharpoons \text{ArOH} + \text{H}_2\text{O}$$

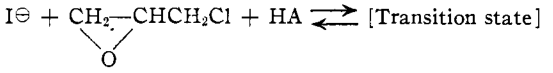


$$\text{I}^{\ominus} + \underset{\diagdown\,\text{O}\,\diagup}{\text{CH}_2\text{—CHCH}_2\text{Cl}} + \text{H}_3\text{O}^{\oplus} \rightleftharpoons$$

$$[\text{Transition state}] \longrightarrow \text{ICH}_2\text{—CHOHCH}_2\text{Cl} + \text{H}_2\text{O}$$

The results showed that the ratio of 2,4-dinitrophenol to 2,4-dinitrophenolate ion changes less than twofold, and in the wrong direction to serve as an explanation for the acceleration observed (see Experimental section).

The only remaining explanation for the 2.2-fold acceleration in rate appears to be general acid catalysis by acetic acid. Thus one must conclude that the reaction involves



$$\text{I}^{\ominus} + \underset{\diagdown\,\text{O}\,\diagup}{\text{CH}_2\text{—CHCH}_2\text{Cl}} + \text{HA} \rightleftharpoons [\text{Transition state}]$$

where HA may be H_2O, HOAc or H_3O^+. Thus no pre-equilibrium between oxide and the free (dissociated) oxonium salt of the oxide is involved in the main reaction which yields iodohydrin, since the concentration of the oxonium salt would depend only on *p*H and be otherwise independent of the concentration of acetic acid. Neither can one invoke the Pedersen interpretation[11] of the general acid catalysis here, *i.e.*, that it involves reaction of the conjugate base (acetate ion) with the oxonium salt of the substrate (oxide), because this would have given a stable product (glycol monoacetate) which was neither formed in appreciable amount nor included in the per cent. reaction figures derived from the titrations (see Experimental section).

Thus the Lowry mechanism[12] for general acid catalysis may be considered preferable to the Pedersen mechanism in the region *p*H 2–7 not only for enolization of ketones[10] (nucleophilic displacements on hydrogen) but also for the reaction of iodide ion with an ethylene oxide (nucleophilic displacements on carbon).

Thus "specific oxonium-ion catalysis" for ethylene oxide reactions is a behavior observed only at buffer concentrations which are so low that neither the undissociated buffer acid nor the buffer base participates detectably. It may be generally possible in other reactions to make the buffer participate by raising its concentration. Indeed, in acetal hydrolysis there is evidence for general acid catalysis in the presence of a sufficiently acidic and concentrated buffer acid: 0.5–4 *M* trichloroacetic acid gives abnormally rapid hydrolysis of sucrose compared to sulfuric acid solutions of equivalent H_0.[13]

Experimental

Reagents.—The epichlorohydrin was redistilled Eastman Kodak No. 507, b.p. 114.2–115.2°. The 2,4-dinitrophenol was Eastman Kodak No. 102, recrystallized from water, m.p. 114.4–115.2° (cor.). The sodium perchlorate was the monohydrate from G. Frederick Smith Chemical Company. All other reagents were analyzed reagent grade.

Reaction Products.—Over 93% of the total reaction in all kinetic runs was with iodide ion and less than 7% with acetate ion or water, since at least 93% of the theoretical iodide ion was always consumed based on the initial weight of epichlorohydrin used. Since the titration with mercuric nitrate measures any chloride ion along with iodide ion, these end-points also demonstrate that little or no displacement of chloride from the epichlorohydrin occurs.

Procedure.—Run 4 illustrates the method. Epichlorohydrin (1.191 g.), 5.0 ml. of 8.0 *M* acetic acid–2.0 *M* sodium acetate, 25 ml. of 3.6 *M* sodium perchlorate, 25 ml. of 0.60 *M* sodium iodide and distilled water to a total of 100 ml. were added to a volumetric flask, and the contents quickly mixed and transferred to a glass-stoppered erlenmeyer flask clamped in a 25.00 ± 0.05° bath. Aliquot samples (2.0 or 5.0 ml.) were titrated with 0.0373 *N* $Hg(NO_3)_2$ to the first purple color using *sym*-diphenylcarbazide as indicator. Data are given for run 4 in Table II. A second-order plot is linear, but a few per cent. of the reaction is with acetate ion and water (k_{I^-}, k_{AcO^-} and $k_{H_2O}[H_2O]$ are reported[8] to be $2.3 \times 10^{-3} M^{-1}\text{sec.}^{-1}$, $1.2 \times 10^{-5} M^{-1}\text{sec.}^{-1}$ and $5.3 \times 10^{-5}\text{sec.}^{-1}$ for epichlorohydrin at 20°). Consequently, only the relative initial rates are reported in Table I. It was found to make no practical difference whether the times compared in obtaining these relative rates were up to 20, 35 or 50% iodide consumed, since the final iodide consumed was so nearly the same in all runs (total range was only from 93.2 in runs 5 to 96.4 in run 9).

TABLE II

REACTION OF 0.150 *M* SODIUM IODIDE, 0.129 *M* EPICHLOROHYDRIN, 0.40 *M* ACETIC ACID AND 0.10 *M* SODIUM ACETATE AT 25°. RUN 4

Time, min.	0.0373 *N* Hg-$(NO_3)_2$, ml.[a]	I^-, *M*	I^- consumed, % of 0.129 *M*	Time, min.	0.0373 *N* Hg-$(NO_3)_2$, ml.[a]	I^-, *M*	I^- consumed, % of 0.129 *M*
5	7.60	0.1418	6.3	117	3.82	0.0713	61.0
8	7.35	.1371	10.0	133	3.60	.0671	64.3
16	6.85	.1278	17.2	145	8.45[a]	.0630	67.5
25	6.30	.1175	25.2	201	7.24	.0540	74.4
36	5.75	.1073	33.1	216	6.88	.0513	76.5
46	5.44	.1015	37.6	3110	3.65	.0272	95.2
59	5.01	.0935	43.8	5860	3.72	.0278	94.7
76	4.65	.0867	49.1	10300	3.71	.0277	94.8
94	4.20	.0783	55.6				

[a] Aliquot samples 2.00 ml. for points at 133 min. or less, 5.00 ml. for 145 min. or more.

Phenolate–Phenol Equilibrium.—Solutions of 2,4-dinitrophenol ($10^{-4}M$) in (1) 0.10 *M* hydrochloric acid, (2) 0.10 *M* sodium carbonate, (3) 0.40 *M* acetic acid, 0.10 *M* sodium acetate, 0.90 *M* sodium perchlorate, (4) 4.0 *M* acetic acid, 1.0 *M* sodium acetate and (5) 0.40 *M* acetic acid, 0.10 *M* sodium acetate were analyzed on a Cary model 11MS ultraviolet recording spectrophotometer.[14] It was

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[11] K. J. Pedersen, *J. Phys. Chem.*, **38**, 581 (1934).

[12] T. M. Lowry and I. J. Faulkner, *ibid.*, **127**, 2883 (1925).

[13] L. P. Hammett and M. A. Paul, THIS JOURNAL, **56**, 830 (1934).

[14] We are indebted to Miss Laura E. Kaiser of the Microchemical Laboratory for determining these visible and ultraviolet absorption spectra.

assumed that no phenolate ion was present in the first solution and no phenol in the second. The average ratios of phenol to phenolate ion based on three wave lengths (3560, 4000 and 2550 Å.) were 1.2, 0.8 and 0.7 for (3), (4) and (5), corresponding to runs 4, 5 and 7, respectively.

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[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE AND THE DEPARTMENT OF CHEMISTRY OF SARAH LAWRENCE COLLEGE]

The Hydrolysis of Substituted Benzoic Anhydrides[1]

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RECEIVED FEBRUARY 4, 1952

The rates of hydrolysis of substituted benzoic anhydrides in 75% dioxane have been determined at two temperatures. The differences in rates are determined mainly by differences in activation energies and the reaction follows the Hammett equation. The mechanism of anhydride hydrolysis is discussed.

Although the hydrolysis of aromatic esters, acid chlorides and amides has been frequently studied with regard to substituent effects, no corresponding study is available for the hydrolysis of substituted benzoic anhydrides. Such an investigation seemed desirable, because the anhydrides form a logical part of the series of benzoic acid derivatives ArCOR on which hydrolytic cleavages can be performed. Only the hydrolysis of unsubstituted benzoic anhydride is reported,[2] whereas numerous studies have been carried out on aliphatic anhydrides, particularly acetic anhydride.[3] In the following are reported data for the hydrolysis of nine substituted benzoic anhydrides in dioxane–water mixtures at two temperatures.

Experimental

Materials.—Aniline (Reagent Grade) was distilled under reduced pressure in the presence of zinc dust. When stored in a wax-sealed bottle, it could be kept colorless for a period of several months. Dioxane was purified by a standard procedure.[4] It was twice distilled from sodium, and the fraction boiling at 100.5–101° was collected and stored over sodium. All anhydrides, except for the commercially available benzoic anhydride, were prepared by a modification of the method of Autenrieth and Thomae.[5] The appropriate acid was treated with approximately fifteen times the theoretical amount of acetic anhydride. For six hours, periods of reflux were alternated with periods of slow removal of the solvent by distillation. The remainder of the solvent was then removed by distillation *in vacuo*, and the crude anhydrides, with the exception of the two nitro derivatives, were distilled. The nitro derivatives were purified by repeated crystallization. In general two crystallizations of each of the distilled anhydrides yielded a pure product. Relevant data pertaining to the anhydrides are shown in Table I.

TABLE I[a]

SUBSTITUTED BENZOIC ANHYDRIDES

Substituent	M.p., °C.	B.p., °C.	B.p., Mm.	Solvent	Anhydride,[b] %
None	42-44[c]	204-207	8	Benzene-ligroin	99.8
p-Methyl	94.3-94.8	229-230	13	Benzene-ligroin	99.8
m-Methyl	70.0-71.5[c]	195-197	5	Benzene-ligroin	99.9
p-Methoxy	98.5-98.8	304-310	10	Benzene-ligroin	100.0
m-Methoxy	65-66[c]	236-240	2	Benzene	99.7
p-Nitro	192.5-193.0	.....		Benzene-acetone	100.0
m-Nitro	161-162[c]	.....		Benzene-acetone	99.9
p-Chloro	192.9-193.4	248	5	Benzene	99.7
p-*t*-Butyl[d]	78.7-79.0	220	3	Petroleum ether	99.8

[a] All melting points are corrected unless otherwise stated. [b] Accurately weighed samples of the anhydride were dissolved in dioxane, treated with aniline, and the liberated acid was titrated with standard base. [c] Uncorrected melting point. [d] *Anal.* Calcd. for $C_{22}H_{26}O_3$: C, 78.08; H, 7.74. Found: C, 78.22; H, 7.90. Analysis by Miss K. Weiss and Miss L. Carmichael.

The *p*-methoxy-, *m*-methoxy and *p*-chlorobenzoic acid were best commercial products and were used without further purification. The two nitrobenzoic acids were commercial products crystallized to constant melting point. The two toluic acids were prepared from the corresponding toluidines, followed by hydrolysis of the nitriles.[6] The para isomer melted at 179–180° (aqueous ethanol) and the meta isomer at 112–114° (benzene). The *p*-*t*-butylbenzoic acid was obtained from *p*-bromo-*t*-butylbenzene (prepared in 71% yield[7]) by carbonation of the Grignard reagent. The yield of once crystallized acid (m.p. 159–160°, uncor., from aqueous ethanol) was 55%; neutral equivalent 177.6 (theoret. 178.2).

Rate Measurements.—The analytical procedure involved a modification of the method introduced by Menschutkin and Wassilieff.[8] Anhydride solutions (0.015–0.045 *M*) were made up by dissolving accurately weighed amounts of solute in anhydrous dioxane and diluting to the mark in a 200-ml. volumetric flask. Aliquot samples (15 ml.) were brought to temperature in a thermostat held constant to ±0.03°. The hydrolysis was initiated by pipetting into each sample 5.0 ml. of water at room temperature, and agitating to ensure homogeneity. Blank tests established that isothermal conditions were invariably restored within less than two minutes after initiation of the introduction of the water. This lapse of time introduced no detectible error into any of the runs except for those of the three most reactive anhydrides. In these latter cases, the first-order linear graph failed to touch the theoretical zero point. The substitute reading for the initial point was the average of three titers, agreeing to within at least 0.04 ml., and obtained from triplicate samples which were prepared for titration at the end of four minutes.

Kinetic points were obtained after measured time periods by pipetting 5 ml. of aniline into the hydrolyzing mixture, which was then shaken and removed from the thermostat, to be stored in a dark place at room temperature. The time necessary for complete reaction of the remaining anhydride with aniline had been determined in advance as follows: solutions containing *p*-nitro-, *m*-nitro- and *p*-chlorobenzoic anhydride were allowed to stand for at least two minutes; solutions of benzoic and *m*-methoxybenzoic anhydride were

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(1) Taken from a dissertation submitted by Mrs. L. Holljes Altschul to the Graduate School of Bryn Mawr College in partial fulfillment of the requirements for the Ph.D. degree.

(2) B. H. Wilsdon and N. V. Sidgwick, *J. Chem. Soc.*, **103**, 1959 (1913); S. C. J. Olivier and G. Berger, *Rec. trav. chim.*, **46**, 609 (1927); S. E. Vles, *ibid.*, **52**, 809 (1933).

(3) For a recent literature survey see V. Gold, *Trans. Faraday Soc.*, **44**, 506 (1948).

(4) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Company, New York, N. Y., 2nd ed., 1941, p. 368.

(5) W. Autenrieth and G. Thomae, *Ber.*, **57**, 431 (1924).

(6) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 514; *ibid.*, Coll. Vol. II, 1943, p. 588.

(7) A. E. Tchitchibabine, S. Elgasine and V. Lengold, *Bull. soc. chim.*, [4] **43**, 238 (1928).

(8) N. A. Menschutkin and M. Wassilieff, *J. Russ. Chem. Soc.*, **21**, 188 (1889) [*J. Chem. Soc. Abs.*, **58**, 359 (1890)]. See also S. E. Vles, ref. 2