ORGANIC AND BIOLOGICAL CHEMISTRY

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Acid–Base Catalysis in Non-dilute Aqueous Acid. The "Decarbonylation" of 2,4,6-Trimethoxybenzaldehyde[1]

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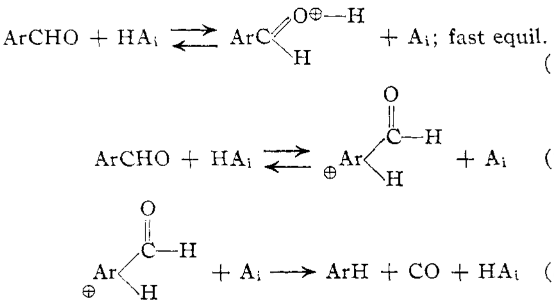
2,4,6-Trimethoxybenzaldehyde is a relatively strong oxygen base in aqueous mineral acid media, having a pK_{BH^+} of -2.1. It decomposes in these media to yield 1,3,5-trimethoxybenzene and formic acid quantitatively. First-order rate constants for the decomposition in 1–54% $HClO_4$, 1–31% HCl and 2–48% HBr have been measured and show a maximum in the intermediate mineral acid percentages. The reaction exhibits general acid catalysis behavior which approaches the extreme of specific oxonium ion catalysis more closely than it does dependence on the Hammett acidity function, h_0. A mechanism of successive bimolecular steps similar to that assigned to the decarbonylation of 2,4,6-trialkylbenzaldehydes is presented.

The decarbonylation reaction of 2,4,6-trialkylbenzaldehydes, an example of electrophilic substitution by hydrogen, has found use in a study of acid–base catalysis in mineral acid solutions of relatively high strength, *e.g.*, 50–100% H_2SO_4.[2] An extensive study of the rate of decarbonylation of hydrogen and deuterioaldehydes (ArCDO) in various percentages of sulfuric acid and deuteriosulfuric acid has led to an assignment of the following general acid–base catalysis mechanism of successive bimolecular proton transfer steps



$$\mathrm{ArCHO + HA_i \rightleftharpoons ArC}\begin{smallmatrix}\diagup \mathrm{O^{\oplus}\!-\!H}\\ \diagdown \mathrm{H}\end{smallmatrix} + \mathrm{A_i;\ fast\ equil.} \qquad (1)$$

$$\mathrm{ArCHO + HA_i \rightleftharpoons {}_{\oplus}Ar}\begin{smallmatrix}\diagup \overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{-H}\\ \diagdown \mathrm{H}\end{smallmatrix} + \mathrm{A_i} \qquad (2)$$

$$\underset{\oplus}{\mathrm{Ar}}\begin{smallmatrix}\diagup \overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{-H}\\ \diagdown \mathrm{H}\end{smallmatrix} + \mathrm{A_i \longrightarrow ArH + CO + HA_i} \qquad (3)$$

The symbol HA_i refers to a general acid (*e.g.*, $H_3O^{\oplus}$ and H_2SO_4 in strong sulfuric acid solution) and A_i to general base (*e.g.*, H_2O, $HSO_4^{\ominus}$). Depending upon the specific structure of the substrate and the percentage sulfuric acid, either step 2 forward or step 3 can be rate controlling or both steps 2 forward and 3 can be rate controlling steps of comparable magnitude. Furthermore, a change in substrate structure (from 2,4,6-trimethyl- to 2,4,6-triisopropylbenzaldehyde) produced a deviation toward relatively more oxonium ion catalysis.[2] The decarboxylation of alkyl benzoic acids in 70–100% H_2SO_4 appears to follow a similar mechanistic course, although a study of this reaction was somewhat complicated by extensive equilibrium formation of acylonium ion $(\mathrm{Ar\overset{\oplus}{C}O})$ in greater than 90% H_2SO_4.[3]

An investigation of the decarbonylation reaction of 2,4,6-trimethoxybenzaldehyde was undertaken with the objective of extending these studies to mineral acids of lower percentages. Previously, the decarboxylation of 2,4,6-trimethoxybenzoic acid had been investigated with this same objective in mind. However, interpretation of the kinetics of this reaction was complicated by the occurrence of a side equilibrium to acylonium ion in as low as 35% $HClO_4$.[4]

Experimental

Preparation of Materials.—2,4,6-Trimethoxybenzaldehyde, prepared by a known method, was recrystallized several times from ethanol or water, m.p. 117.5–118°.[5] Perchloric and hydrochloric acid solutions of various strength were made by appropriate dilution of analytical reagent grades of the concentrated acids. Reagent grade 47% hydrobromic acid was distilled before dilution. The concentration of each solution prepared was checked by base titration of weighed samples.

Kinetic Method.—As in the example of 2,4,6-trialkylbenzaldehydes, the decomposition of 2,4,6-trimethoxybenzaldehyde in mineral acid is quantitative and manifests itself in an appreciable change in the ultraviolet spectrum with time. By the method previously described, this change in spectrum was used to determine the first-order rate constant of solutions about 10^{-4} molar in 2,4,6-trimethoxybenzaldehyde.

Zero-time Spectra.—The ultraviolet spectrum of 2,4,6-trimethoxybenzaldehyde was determined at room temperature in a number of the mineral acid solutions. For mineral acid solutions in which decomposition of the aldehyde was negligibly slow at this temperature, this spectrum was used directly in determining $pK_{BH^{\oplus}}$. For mineral acid solutions in which the decomposition of the aldehyde at room temperature was noticeable, readings at two or more time intervals were taken and zero-time spectra determined by extrapolation.

Product Identification.—No gas was evolved when 2,4,6-trimethoxybenzaldehyde (*ca.* 10^{-2} molar) was decomposed in 14% HCl, 25% HCl and 40% $HClO_4$, respectively. Formic acid was identified through its derivative, benzimidazole, as a product of the reaction in 14, 20 and 47% HBr, 40 and 55% $HClO_4$, and 25% HCl. A typical experiment will be described. A solution of 2,4,6-trimethoxybenzaldehyde (202 mg.) in 47% HBr was heated at 80° for 18 minutes (*ca.* 7 half-lives). While cooled in an ice-bath, the solution was made basic (*p*H 12) by the addition of NaOH pellets. The mixture was steam distilled to remove volatile non-acidic materials. The residue was acidified to *p*H 2 with sulfuric acid and distilled. A sample of the acidic distillate reduced aqueous $KMnO_4$ and produced a gray precipitate with mercuric oxide.[6] The remaining distillate was made basic with NaOH and evaporated to dryness.

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[1] Supported in part by the National Science Foundation and a grant from the Socony Mobil Oil Co.

[2] (a) W. M. Schubert and H. Burkett, THIS JOURNAL, **78**, 64 (1956); (b) W. M. Schubert and P. C. Myhre, *ibid.*, **80**, 1755 (1958).

[3] W. M. Schubert, J. Donohue and J. D. Gardner, *ibid.*, **76**, 9 (1954).

[4] W. M. Schubert, R. E. Zahler and J. Robins, *ibid.*, **77**, 2293 (1955).

[5] J. Herzing, F. Wenzel and H. Gehringer, *Monatsh.*, **24**, 866 (1903).

[6] S. P. Mulliken, "The Identification of Pure Organic Compounds," Ed. 1, Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1904, p. 79.

TABLE I

COMPARISON OF OBSERVED AND CALCULATED RATE CONSTANTS IN PERCHLORIC ACID

$HClO_4$,[a] M	h_0[b]	a_{H_2O}[c]	$[S]/[S]_{st}$[d]	$k_{obsd} \times 10^3$, sec.$^{-1}$ (80°)	$0.452 \frac{[S]}{[S]_{st}} h_0$[e]	$57.4 \frac{[SH^{\oplus}]}{[S]_{st}} a_{H_2O}$[e]	$0.505 \frac{[S]}{[S]_{st}} M$[e]
0.103	0.115	0.994	0.999	0.052	0.052	0.052	0.052
1.03	1.78	.959	.986	0.60	0.79	0.76	0.51
2.32	8.51	.884	.937	1.62	3.62	3.20	1.10
3.83	44.7	.750	.738	2.99	15	11.3	1.44
4.60	107	.664	.540	3.22	26	17.5	1.25
5.38	282	.556	.309	2.71	39	22.1	0.84
5.43	302	.546	.294	2.66	40	22.3	0.81
6.71	2400	.368	.0499	1.10	54	20.1	0.17
6.79	2820	.356	.0428	1.09	55	19.7	0.15
7.94	20000	.206	.00627	0.45	56	11.7	0.025

[a] Molarity. [b] Data of M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957). [c] Data of J. N. Pierce and A. F. Nelson, THIS JOURNAL, **55**, 3075 (1933). [d] Calculated using $pK_{SH^{\oplus}} = -2.1$. [e] The proportionality constants were chosen to give agreement with $k_{obsd} \times 10^3$ in 0.103 *M* $HClO_4$.

TABLE II

COMPARISON OF OBSERVED AND CALCULATED RATE CONSTANTS IN HYDROCHLORIC ACID

HCl,[a] M	h_0[b]	a_{H_2O}[c]	$[S]/[S]_{st}$[d]	$k_{obsd} \times 10^3$, sec.$^{-1}$ (80°)	$0.457 \frac{[S]}{[S]_{st}} h_0$[e]	$58.6 \frac{[SH^{\oplus}]}{[S]_{st}} a_{H_2O}$[e]	$0.583 \frac{[S]}{[S]_{st}} M$[e]
0.36	0.457	0.989	0.996	0.21	0.21	0.21	0.21
1.41	2.63	.945	.980	1.08	1.20	1.13	.80
1.44	2.75	.941	.979	1.17	1.23	1.18	.83
2.36	6.61	.894	.950	2.45	2.88	2.62	1.31
2.81	9.55	.864	.930	3.24	4.06	3.46	1.53
2.98	10.72	.852	.922	3.87	4.52	3.93	1.61
4.15	28.84	.770	.814	7.11	10.7	8.36	1.97
4.93	54.95	.706	.696	9.80	17	12.4	2.00
5.01	58.9	.701	.681	10.9	18	13.1	1.99
6.10	138	.608	.477	16.2	30	18.6	1.70
7.06	316	.523	.285	18.5	41	21.8	1.17
7.13	347	.512	.266	19.0	42	21.9	1.11
8.75	1413	.382	.0818	18.5	53	20.5	0.42
9.14	1950	.353	.0606	17.9	54	19.4	.32
9.80	3390	.306	.0359	15.3	56	17.3	.20

[a] Molarity. [b] Data of M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957). [c] Data of M. Randall and L. E. Young, THIS JOURNAL, **50**, 989 (1928). [d] Calculated using $pK_{SH^{\oplus}} = -2.1$. [e] The proportionality constants were chosen to give agreement with $k_{obsd} \times 10^3$ in 0.36 *M* HCl.

The method of Phillips was used to convert the sodium formate residue to benzimidazole, m.p. 170–171°, no depression in m.p. with an authentic sample.[7] In one instance (an experiment in 25% HCl) formic acid was identified as its *p*-phenylphenacyl ester, m.p. 73–75°.[8]

Isolation of 1,3,5-trimethoxybenzene as a product of the decomposition of 2,4,6-trimethoxybenzaldehyde was made for reactions in 5, 10, 20 and 39% of HBr, 55% $HClO_4$ and 14 and 25% HCl. A typical experiment is described. A solution of 2,4,6-trimethoxybenzaldehyde (30 mg.) in 25 ml. of 39% HBr was heated at 80° for four minutes (*ca.* 2 half-lives). An equal volume of water was added and the mixture steam distilled. The distillate was chilled in an ice-bath and the white precipitate collected by centrifuging and decanting, m.p. 51–52°, no depression in m.p. with authentic 1,3,5-trimethoxybenzene.

That 1,3,5-trimethoxybenzene is an initial product of the decarbonylation was first shown spectrally. In low strength mineral acids, the final spectrum of the reaction solution was identical with that of 1,3,5-trimethoxybenzene. In medium strength mineral acids (*e.g.*, 31% HCl, 48% $HClO_4$) the spectrum after initial decarbonylation corresponded to that of 1,3,5-trimethoxybenzene, but suffered a further slow change and gradually became identical to the spectrum of phloroglucinol. Apparently the initially formed trimethoxybenzene was undergoing slow ether cleavage. This was verified by noting the changes undergone by authentic 1,3,5-trimethoxybenzene in the same media. In the highest acid percentage, 60.5% $HClO_4$, ether cleavage of trimethoxybenzene was so rapid that the spectrum obtained after initial decarbonylation was directly that of phloroglucinol. Because of the subsequent ether cleavage reaction, rate constants for decarbonylation were measured at wave lengths at which the spectra of 1,3,5-trimethoxybenzene and phloroglucinol are of low intensity and practically identical.

Results

Rate Constants.—The first-order plots of log $(D - D_\infty)$ *vs.* time were linear within ±0.05 unit of log $(D - D_\infty)$ except for an occasional stray point. The plot was made at three or more wave lengths for each run and the reported first-order rate constant is an average of the results from the different wave lengths. In all cases the reaction was followed beyond two half-lives. A typical run is plotted in Fig. 1. Values of k_{obsd} for various percentages of perchloric, hydrochloric and hydrobromic acid are given in Tables I, II and III.

Basicity of 2,4,6-Trimethoxybenzaldehyde.—Zero-time spectra were used to determine the pK_a of this aldehyde in perchloric, hydrochloric and hydrobromic acid by the isosbestic method of Hammett.[9] In Fig. 2 is shown the zero-time spectrum in various concentrations of perchloric acid. The spectrum in 20.6% $HClO_4$, 19.8% HCl and

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[7] M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

[8] R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," Ed. III, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 157.

[9] L. P. Hammett, C. A. Flexser and A. Dingwall, THIS JOURNAL, **57**, 2103 (1935).

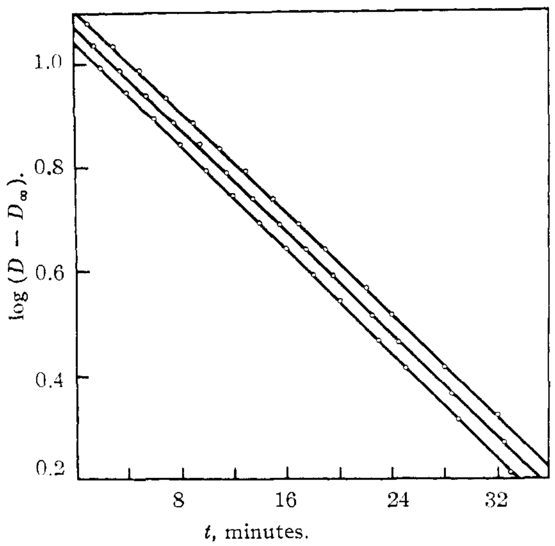

Fig. 1.—First-order plot for the decarbonylation of 2,4,6-trimethoxybenzaldehyde in 53.98% perchloric acid at 90°, plotted for the data at 315, 320 and 325 mμ, respectively, beginning with the upper line.

12.5% HBr was considered to be that of the free base in each of these mineral acids. The spectrum in 48.8% $HClO_4$ and 47.9% HBr was considered to be that of the conjugate acid. Table IV gives the detailed results for perchloric acid. The pK_a values determined in each of the three mineral acids are within experimental error of being the same: −2.10 ± 0.11 in $HClO_4$, −2.19 ± 0.08 in HCl and −2.06 ± 0.12 in HBr.

TABLE III

COMPARISON OF OBSERVED AND CALCULATED RATE CONSTANTS IN HYDROBROMIC ACID

HBr,[a] M	h_0[b]	$[S]/[S_{st}]$[c]	$k_{obsd} \times 10^3$, sec.$^{-1}$ (80°)	0.542 $[S]/[S]_{st}$ h_0[d]	0.542 $[S]/[S]_{st}$ M[d]
0.24	0.24	0.998	0.13	0.13	0.13
.54	0.68	.995	.34	.36	.29
.91	1.41	.989	.60	.75	.49
1.25	2.24	.983	.92	1.19	.67
1.69	3.80	.971	1.39	2.00	.89
2.01	5.37	.959	1.79	2.78	1.05
2.53	8.71	.935	2.61	4.42	1.28
3.36	18.2	.874	4.29	8.62	1.59
4.16	38.9	.764	6.46	16.1	1.72
4.35	45.7	.734	7.04	18.2	1.73
4.54	55.0	.696	7.87	20.7	1.71
5 64	162	437	9.69	38.3	1.33
6.60	447	.220	10.20	53.3	0.79
7.94	2040	.0581	9.42	64.3	.25
8.00	2240	.0533	8.98	64.7	.23
8.81	6030	.0205	7.59	67.1	.10

[a] Molarity. [b] Data of M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957). [c] Calculated using $pK_{SH^\oplus} = -2.1$. [d] The proportionality constants were chosen to give agreement with $k_{obsd} \times 10^3$ in 0.24 M HBr.

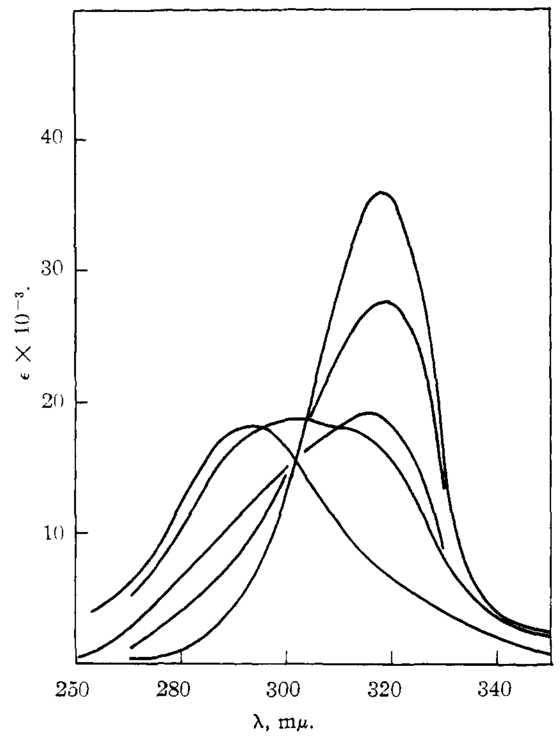

Fig. 2.—Extinction coefficients *vs.* wave length for 2,4,6-trimethoxybenzaldehyde in various concentrations of perchloric acid. Beginning with the upper curve the plots are for 48.82, 41.22, 36.62, 31.55 and 20.61% $HClO_4$, respectively.

TABLE IV

EXTINCTION COEFFICIENTS ($\epsilon \times 10^{-3}$) AND pK_a VALUES FOR 2,4,6-TRIMETHOXYBENZALDEHYDE IN AQUEOUS $HClO_4$[a]

	$HClO_4$, %					
λ, mμ	20.61	31.55	36.62	41.22	48.82	$-pK_a$
310	10.1	18.2[b]	18.5	23.2	28.5	2.09 ± 0.08
315	8.1	17.6	19.3	26.8	34.8	2.09 ± .11
320	6.4	15.7	18.3	27.6	35.7	2.10 ± .12
325	5.0	12.2	15.1	22.5	29.5	2 13 ± 11
330	4.0	8.0	9.5	12.5	17.0	2.10 ± .10
					Av	2.10

[a] The values of ε are those of the spectral curves after being shifted through an isosbestic point at 302 mμ. Note (Fig. 2) that curve for 31.55% $HClO_4$ did not pass near the isosbestic point, probably due to insufficient resolution by the instrument. Reading from column 2 to column 6 the curves were shifted to the right by the following amounts (mμ): 1.5, 1.0, 0, 0, 0. [b] Not used.

Discussion

Basicity of 2,4,6-Trimethoxybenzaldehyde.—The acid-catalyzed decomposition of 2,4,6-trimethoxybenzaldehyde into 1,3,5-trimethoxybenzene and formic acid is sufficiently slow at room temperature to allow measurement of the equilibrium between the free aldehyde and its conjugate acid. The basicity of the aldehyde was determined in the usual way by means of the zero-time ultraviolet spectrum in various strengths of mineral acid (Fig. 2). The spectral changes of Fig. 2 correspond to a simple equilibrium between the aldehyde and its oxygen conjugate acid $ArCHOH^{\oplus}$ (equation 5).[10] No other species could be detected in the zero-time spectra. The behavior of 2,4,6-trimethoxybenzaldehyde as a simple neutral monofunctional base contrasts with the more complex behavior of 2,4,6-trimethoxybenzoic acid. For the latter, the equi-

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[10] The conjugate acid responsible for the spectral changes of Fig. 2 undoubtedly has the added proton on the carbonyl oxygen rather than on an ether oxygen (see reference 4).

librium giving conjugate acid is overlapped by an equilibrium giving acylonium ion ($ArCO^{\oplus}$).[4] The value of $pK_{BH^{\oplus}}$ for 2,4,6-trimethoxybenzaldehyde was found to be -2.1 ± 0.1 in each of three mineral acids: perchloric, hydrochloric, hydrobromic. Thus this aldehyde is a strong oxygen base. Apparently the conjugate acid is stabilized relative to the free base by internal hydrogen bonding as well as by resonance with the *o*- and *p*-methoxyl groups.[4]

Kinetics of the Decarboxylation.—Plots of the observed rate constant *vs.* mineral acid molarity are given in Figs. 3, 4 and 5 for perchloric, hydrochloric and hydrobromic acids, respectively. Certain features of these plots are to be noted particularly. The rates in all three acids are identical within experimental error up to a concentration of about two molar but differ significantly in higher molarities. In each mineral acid the rate constant reaches a maximum in media in which protonation to oxygen conjugate acid (equation 5) becomes appreciable and then declines as mineral acid molarity is increased further.

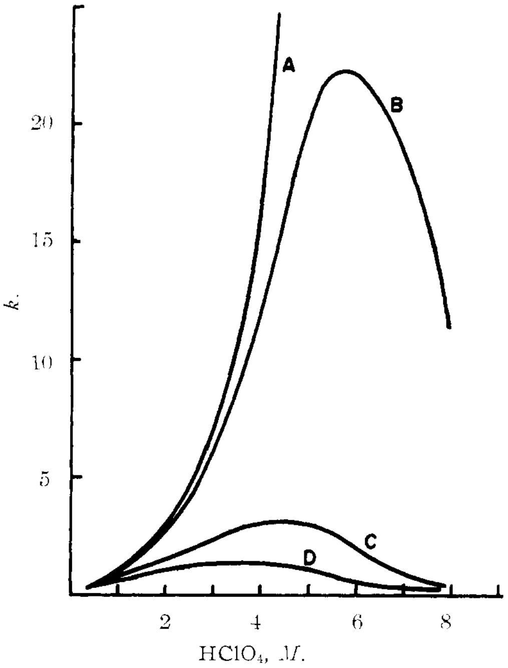

Fig. 3.—Plot of observed and calculated rate constants *vs.* molarity $HClO_4$: (A) 0.452 $h_0[S]/[S]_{stoich}$; (B) $57.4a_{H_2O}\cdot[SH^+]/[S]_{stoich}$; (C) $k_{obsd} \times 10^3$ sec.$^{-1}$ (80°); (D) 0.505 *M* $[S]/[S]_{stoich}$. The proportionality constants are chosen so as to give intersection of all curves at 0.103 *M* $HClO_4$.

Three criteria of mechanism have been applied to the data, one for the Hammett "unimolecular" mechanism and two different criteria for specific oxonium-ion catalysis. For the Hammett mechanism, in which the rate-controlling step is the unimolecular decomposition of either the oxygen conjugate acid, $SH^{\oplus}$, or some other conjugate acid of the substrate base S, equation 4 should be followed.[11,2]

$$k_{obsd} = k\,\frac{[SH^{\oplus}]}{[S]_{stoich}}\,\frac{f_{SH^{\oplus}}}{f_{tr^{\oplus}}} = \text{const}\,\frac{[S]}{[S]_{stoich}}\,h_0\,\frac{f_S f_{BH^{\oplus}}}{f_{tr^{\oplus}} f_B} \quad (4)$$

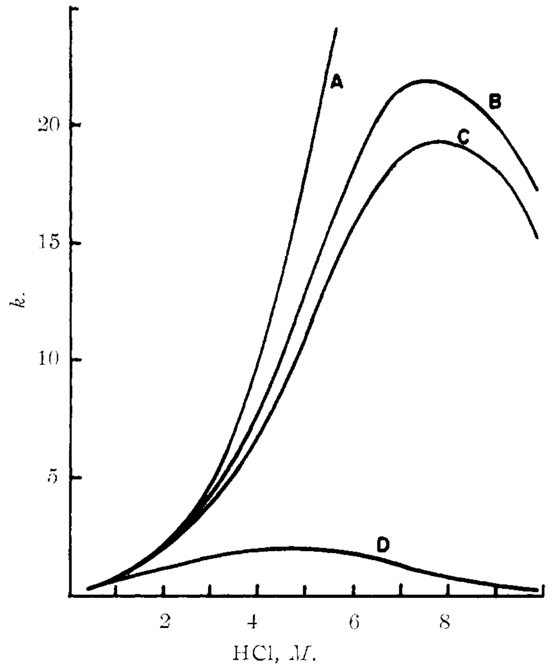

Fig. 4.—Plot of observed and calculated rate constants *vs.* molarity HCl: (A) 0.457 $h_0[S]/[S]_{stoich}$; (B) 58.9 $a_{H_2O}[SH^+]/[S]_{stoich}$; (C) $k_{obsd} \times 10^3$ sec.$^{-1}$ (80°); (D) 0.583 *M* $[S]/[S]_{stoich}$.

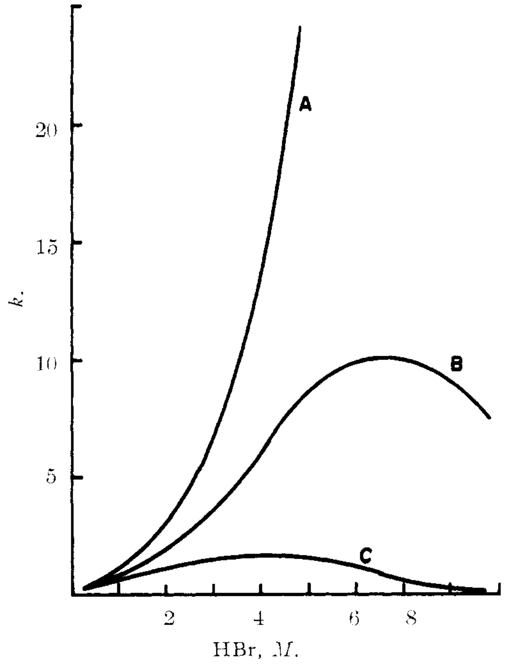

Fig. 5.—Plot of observed and calculated rate constants *vs.* molarity HBr: (A) 0.542 $h_0[S]/[S]_{stoich}$; (B) $k_{obsd} \times 10^3$ sec.$^{-1}$ (80°); (C) 0.542 *M* $[S]/[S]_{stoich}$.

In equation 4, $f_S, f_{SH^{\oplus}}, f_{tr^{\ominus}}, f_B$ and $f_{BH^{\oplus}}$ are activity coefficients of substrate base, substrate conjugate acid, transition state of the rate controlling step, indicator base and indicator base conjugate acid, respectively. In applying equation 4 as a criterion of mechanism, the assumption is usually made that $f_S f_{BH^{\oplus}}/f_{tr^{\oplus}} f_B$ is constant with changing mineral

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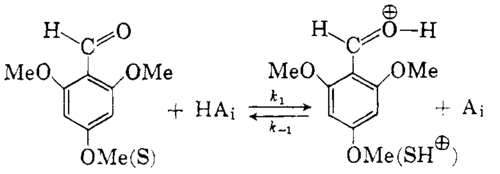
(11) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter IX.

acid molarity.[11-13] Rate constants calculated from equation 4, based on this assumption, are compared with the observed rate constants in perchloric, hydrochloric and hydrobromic acids in Tables I, II and III (see also Figs. 3, 4 and 5). Agreement between observed and calculated rate constants is found only in the lowest acid molarities.[14] As the mineral acid concentration is increased beyond one molar, wide divergences between calculated and observed rate constants are found. These divergences are greatest in perchloric acid and least in hydrochloric acid. In all three mineral acid media, the calculated rate constant first increases much more rapidly with increased mineral acid molarity than does the observed rate constant. In the highest mineral acid percentages, the calculated rate constant levels off to a constant value rather than declining in the manner of k_{obsd}.[16] It is apparent that the Hammett "unimolecular" mechanism safely can be ruled out on the basis of the very wide disagreement between the observed and calculated rate constants. Literally tremendous variations in the activity coefficient ratios of equation 4 would be required to force a fit of the data to this mechanism.

Bimolecular Mechanisms; Specific Oxonium Ion Catalysis.—The substrate free base, 2,4,6-trimethoxybenzaldehyde (S), is known to be in rapid equilibrium with its carbonyl-oxygen conjugate acid, $SH^{\oplus}$. It can be concluded, however, that $SH^{\oplus}$ probably is not involved directly in the decarbonylation reaction (*i.e.*, S, and not $SH^{\oplus}$, is the more immediate precursor of the decarbonylation products). If $SH^{\oplus}$ were involved, the slow step in the decarbonylation would have to be decomposition rather than formation of $SH^{\oplus}$. This follows from the known fact that $SH^{\oplus}$ is formed rapidly and reversibly from S. The slow step cannot be a unimolecular rearrangement of $SH^{\oplus}$ (see previous section) nor can it be further protonation of $SH^{\oplus}$.[14] Furthermore, from a mechanistic standpoint, it is difficult to imagine how attack on $SH^{\oplus}$ by basic species could give a direct path to decarbonylation products.[18] If it is then presumed that S is a more immediate precursor than SH^+, the proton involved in the catalysis must be placed at a site other than the carbonyl oxygen. This is most reasonably the site to which the group being displaced is attached, *i.e.*, as in step 6 forward. This step is the same as has been postulated for other reactions of aromatic electrophilic substitution by hydrogen, more particularly for the decarbonylation of 2,4,6-trialkylbenzaldehydes (see equation 2).[2] The more rapid decarbonylation of 2,4,6-trimethoxybenzaldehyde is in accord with the expected increased activating effect of the methoxyl groups in an electrophilic substitution step of this type. However, the subsequent fate of the carbon conjugate acid $SH^{*\oplus}$ must be different from that in decarbonylation of 2,4,6-trialkylbenzaldehydes. In the decomposition of the trialkylbenzaldehydes, carbon monoxide is formed quantitatively as a direct product of the reaction and, as shown by deuterium isotope effects, attack by base on $SH^{*\oplus}$ is at the aldehydic hydrogen (equation 3).[2,19] In the decomposition of 2,4,6-trimethoxybenzaldehyde, *no* carbon monoxide is formed; formic acid is obtained instead. It is therefore postulated that in this latter instance attack on $SH^{*\oplus}$ by base occurs *at the carbonyl carbon* (equation 7) rather than at the aldehydic hydrogen. This altered course may be due to decreased steric shielding of the carbonyl carbon or to some specific effect by the *o*-methoxyl groups (*e.g.*, hydrogen bonding with an attacking water molecule). For the proposed reaction mechanism, equations 6 and 7, application of the steady state assumption of $SH^{*\oplus}$ leads to the general rate expression 8.[2] This equation applies when the second or third step is rate controlling, or when both are of comparable speed.



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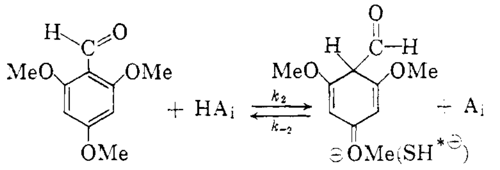
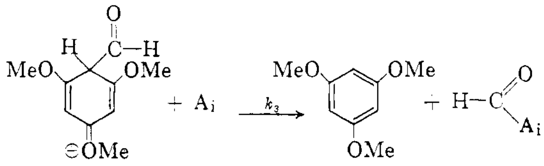


(6)



(7)

$$k_{\text{obsd}} = \frac{[\mathrm{S}]}{[\mathrm{S}]_{\text{stoich}}} \frac{\Sigma k_{2i}[\mathrm{HA_i}] f_{\mathrm{S}} f_{\mathrm{HA_i}}/f_{\mathrm{tr}_{2i}}}{1 + \dfrac{\Sigma k_{-2i}[\mathrm{A_i}] f_{\mathrm{A_i}}/f_{\mathrm{tr}_{2i}}}{\Sigma k_{3i}[\mathrm{A_i}] f_{\mathrm{A_i}}/f_{\mathrm{tr}_{3i}}}} \qquad (8)$$

Under the condition that either the third step (equation 7) or the second step (equation 6) is rate controlling, the rate equation 8 can be simplified into kineticallye quivalent rate expressions of

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

(13) Long and McIntrye (see ref. 12) have obtained evidence that in the hydrolysis of methylal the ratio $f_{\mathrm{S}}/f_{\mathrm{B}}$ suffers small systematic change with acid molarity. They considered the ratio $f_{\mathrm{BH}^{\oplus}}/f_{\mathrm{tr}^{\oplus}}$ to be relatively more constant. It is to be noted that in media in which $[\mathrm{SH}^{\oplus}]/[\mathrm{S}]$ can be measured directly, the substrate in effect functions as its own indicator base and variation in only $f_{\mathrm{SH}^{\oplus}}/f_{\mathrm{tr}^{\oplus}}$ need be considered.

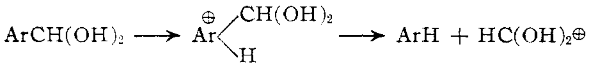
(14) Since divergence of h_0 and $[\mathrm{H_3O}^{\oplus}]$ does not become appreciable until beyond one-molar mineral acid,[12,15] this result indicates only that a single proton is involved in the catalysis.

(15) L. Zucker and L. P. Hammett, THIS JOURNAL, **61**, 2791 (1939).

(16) In the highest acid molarities the equilibrium to oxygen conjugate acid, equation 5, lies far to the right; *i.e.*, $[\mathrm{SH}^{\oplus}] >> [\mathrm{S}]$. Then, $[\mathrm{S}]/[\mathrm{S}]_{\text{stoich}} = [\mathrm{S}]/[\mathrm{SH}^{\oplus}] = K_{\mathrm{SH}^{\oplus}}/h_0$, and equation 4 becomes $k = \text{const.}\, f_{\mathrm{SH}^{\oplus}}/f_{\mathrm{tr}^{\oplus}}$.[17]

(17) W. M. Schubert and H. K. Latourette, THIS JOURNAL, **74**, 1829 (1952).

(18) A conceivable but unlikely path is attack by water on the carbonyl carbon of $\mathrm{SH}^{\oplus}$ followed by loss of a proton to yield the aldehyde hydrate, which could react further as



$$\mathrm{ArCH(OH)_2} \longrightarrow \overset{\oplus}{\mathrm{Ar}}\begin{cases}\mathrm{CH(OH)_2}\\ \mathrm{H}\end{cases} \longrightarrow \mathrm{ArH} + \mathrm{HC(OH)_2}^{\oplus}$$

(19) It has been shown that formic acid cannot be an intermediate in the decarbonylation of 2,4,6-trialkylbenzaldehydes in strong sulfuric acid.[20]

(20) W. M. Schubert and R. E. Zahler, THIS JOURNAL, **76**, 1 (1954).

the form of 9 and 10. The constants k_1 and k'_1 are either rate constants or composites of rate and equilibrium constants.

$$k_{\mathrm{obsd}} = \frac{[\mathrm{S}]}{[\mathrm{S}]_{\mathrm{stoich}}} \Sigma k_{\mathrm{i}}[\mathrm{HA_i}] f_{\mathrm{S}} f_{\mathrm{HA_i}} / f_{\mathrm{tr}_{3\mathrm{i}}} \qquad (9)$$

$$k_{\mathrm{obsd}} = \frac{[\mathrm{SH}^+]}{[\mathrm{S}]_{\mathrm{stoich}}} \Sigma k'_{\mathrm{i}}[\mathrm{A_i}] f_{\mathrm{SH^+}} f_{\mathrm{A_i}} / f_{\mathrm{tr}_{3\mathrm{i}}} \qquad (10)$$

The qualitative appearance of the plots of k_{obsd} against mineral acid molarity (Figs. 3, 4 and 5) suggests that the reaction may be one of specific oxonium ion catalysis. This is particularly indicated by the fact that k_{obsd} decreases in the high molarities, in which $[\mathrm{SH}^{\oplus}] > [\mathrm{S}]$.[21] In specific oxonium ion catalysis, the rate-controlling step is either (1) a proton transfer step to neutral substrate (equation 6) in which $H_3O^{\oplus}$ is the only proton donor, or (2) a proton abstraction from a conjugate acid of the substrate (equation 7) in which H_2O is the only base.[21] Under either of these conditions, equations 9 and 10 reduce further to 11 and 12.

$$k_{\mathrm{obsd}} = \mathrm{const}\frac{[\mathrm{S}]}{[\mathrm{S}]_{\mathrm{stoich}}} [\mathrm{H_3O}^{\oplus}] f_{\mathrm{S}} f_{\mathrm{H}} f_{\mathrm{H_3O^+}} / f_{\mathrm{tr}_3}{}^{\oplus} \qquad (11)$$

$$k_{\mathrm{obsd}} = \mathrm{const}\frac{[\mathrm{SH}^{\oplus}]}{[\mathrm{S}]_{\mathrm{stoich}}} a_{\mathrm{H_2O}} f_{\mathrm{SH}}{}^{\ominus} / f_{\mathrm{tr}_3}{}^{\oplus} \qquad (12)$$

Equations 11 and 12 are essentially the same as applied by Zucker and Hammett to the enolization of acetophenone in 0.2 to 3.6 molar perchloric acid, except that for the weaker base acetophenone the quantity $[\mathrm{S}]/[\mathrm{S}]_{\mathrm{stoich}}$ is practically unity and $[\mathrm{SH}^{\oplus}]/[\mathrm{S}]_{\mathrm{stoich}} \cong h_0/K_{\mathrm{SH}^{\oplus}}$.[15] These authors concluded that the enolization reaction shows specific oxonium ion catalysis on the basis of the fact that the observed rate constant had a fair proportionality to $[\mathrm{HClO_4}]_{\mathrm{stoich}}$, where $[\mathrm{HClO_4}]_{\mathrm{stoich}} \cong [\mathrm{H_3O}^{\oplus}]$. This conclusion required that $f_{\mathrm{S}} f_{\mathrm{H_2O}^{\oplus}} / f_{\mathrm{tr}^{\oplus}}$ for their substrate be reasonably constant with changing perchloric acid molarity; *i.e.*, that medium effects on the product $f_{\mathrm{S}} f_{\mathrm{H_2O}^{\oplus}}$ are cancelled by medium effects on $f_{\mathrm{tr}_3{}^{\oplus}}$, the activity coefficient of the transition state ion. On the basis of the fact that the enolization rate constant did not show a satisfactory proportionality to $h_0 a_{\mathrm{H_2O}}$ it was concluded that the ratio $f_{\mathrm{SH}^{\ominus}} / f_{\mathrm{tr}^{\oplus}}$ is not constant with changing perchloric acid molarity even though both conjugate acid and transition state have the same charge and are similarly constituted, except for a molecule of water in the latter. In general, when the transition state contains a molecule of water, the assumption that $f_{\mathrm{S}} f_{\mathrm{H_3O}^{\oplus}} / t_{\mathrm{tr}^{\ominus}}$ is constant is considered to be more valid than the assumption that $f_{\mathrm{SH}^{\ominus}} / f_{\mathrm{tr}^{\oplus}}$ is constant, *i.e.*, equation 11 (with the assumption of a constant activity coefficient ratio) is considered to be a better criterion for specific oxonium ion catalysis than equation 12.[12]

The application of equation 11 to the decarbonylation of 2,4,6-trimethoxybenzaldehyde, with the assumption that $f_{\mathrm{S}} f_{\mathrm{H_2O}^{\oplus}} / f_{\mathrm{tr}_3{}^{\oplus}}$ is constant and also that $[\mathrm{H_3O}^{\oplus}] \cong [\mathrm{HX}]_{\mathrm{stoich}}$, leads to calculated rate constants in perchloric, hydrochloric and hydrobromic acids given in the last column of Tables I, II and III and plotted in Figs. 3, 4 and 5. Although the rate constants calculated on this basis do show a maximum in the intermediate acid molarities, the calculated rate constants are generally much lower than the observed rate constants. The lack of agreement is greatest in hydrochloric acid and least in perchloric acid. If the assumption that $f_{\mathrm{S}} f_{\mathrm{H_2O}^{\oplus}} / f_{\mathrm{tr}^{\oplus}}$ is constant is valid, it can be concluded that the reaction is only approaching specific oxonium ion catalysis. In other words, if a step involving solvent acids is rate-controlling (*i,e.*, equation 6) there is some catalysis by molecular mineral acid as well as by the oxonium ion in this step. On the other hand, if a step involving solvent bases (equation 7) is rate controlling, then solvent bases other than water also have some degree of effectiveness in this step. From the magnitude of the discrepancies between calculated and observed rate constants it could be concluded further that general catalysis is greatest in hydrochloric acid, next in hydrobromic and least in perchloric acid.[22]

If the alternative assumption is made that the activity coefficient ratio of equation 12 rather than that of equation 11 is constant, then, for specific oxonium ion catalysis, k_{obsd} should be proportional to $a_{\mathrm{H_2O}}[\mathrm{SH}^{\oplus}]/[\mathrm{S}]_{\mathrm{stoich}}$ rather than $[\mathrm{HX}]_{\mathrm{stoich}} \cdot [\mathrm{S}]/[\mathrm{S}]_{\mathrm{stoich}}$. Making this assumption leads to calculated rate constants for perchloric and hydrochloric acids given in the seventh column of Tables I and II and plotted in Figs. 3 and 4. Unfortunately, equation 12 could not be tested against the data in hydrobromic acid since values of $a_{\mathrm{H_2O}}$ are not available. It is seen that the calculated rate constants agree quite well with the observed ones in hydrochloric acid. Thus, *if* the assumption $f_{\mathrm{SH}^{\oplus}} / f_{\mathrm{tr}_3{}^{\oplus}}$ remains constant with changing molarity of hydrochloric acid is valid, this agreement would imply that the decarbonylation in hydrochloric acid shows specific oxonium ion catalysis. By the same token, the fact that the observed rate constants in perchloric acid are considerably less than those calculated from equation 12 would lead to the conclusion the reaction shows *less than* specific oxonium ion catalysis in perchloric acid, a situation difficult to conceive. This result may lend support to the conclusion that equation 11 is a better one to apply to specific oxonium ion catalysis than is equation 12.[12]

One more possible condition should be considered. This is the one in which the velocities of the forward second step and the third step are comparable, due to a close balance between the velocities of the third step and the *reverse* of the second step. In this situation, the general rate expression, equation 8, cannot be simplified except in the unlikely event that v_{-2}/v_3 be constant.[2,21] Since v_{-2}/v_3 would be expected to vary with medium, equation 8 predicts general catalysis with a non-linear dependence on any particular acid species.[21]

In the event that there is some participation by molecular mineral acid in the second step (and hence by anion of the molecular acid in the reverse of this step) but little or no participation by mineral acid

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[21] R. P. Bell, "Acid-Base Catalysis," Oxford Press, New York, N. Y., 1941, Chapter VII.

[22] Part of the discrepancy between calculated and observed rate constants could be attributed to the fact that the ratio $[\mathrm{S}]/[\mathrm{S}]_{\mathrm{stoich}}$ was determined at room temperature whereas k_{obsd} was determined at 80°. This is not likely to lead to a large error, however.[23]

[23] A. I. Gelbstein, G. G. Shcheglova and M. I. Temkin, *Zhur. Neorg. Khim.*, **1**, 282, 506 (1956).

anion in the third step,[24] then a general acid catalysis behavior which approaches specific oxonium ion catalysis could be exhibited.

The general conclusion based upon the effect of changing mineral acid molarity upon k_{obsd} is that the reaction exhibits general acid catalysis behavior which approaches much more closely the extreme of specific oxonium ion catalysis than it does dependence on the acidity function, h_0. Many points remain unanswered, including the question of which step is rate controlling. It is clear that further studies are in order, including an examination of the kinetics of the reaction in dilute aqueous solution and the determination of deuterium isotope effects. If this reaction can be studied effectively in dilute aqueous solution, it may help to bridge the gap between our knowledge of acid–base catalysis in dilute and non-dilute aqueous acids.

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(24) Since the third step is essentially a hydrolysis of a formic acid derivative, it is not unreasonable to expect H_2O to be the only effective base in this step.

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

Electrostatic Catalysis. The Reactivity of an Ester and a Nucleophile of Opposite Charge[1a]

BY MYRON L. BENDER AND YUAN-LANG CHOW[1b]

RECEIVED DECEMBER 31, 1958

Reactions of *o*-nitrophenyl hydrogen oxalate with pyridine, aniline, 2-aminopyridine and 4-aminopyridine occur in buffered aqueous solutions in the region *p*H 3 to 6. The reacting species in the latter cases include both the free aminopyridine and the corresponding monoprotonated species, the aminopyridinium ion. Part of the reaction of the aminopyridines with *o*-nitrophenyl hydrogen oxalate in this *p*H region includes a reaction of a negatively charged substrate and a positively charged nucleophile. There is a difference of thirty in the nucleophilicities of 2-aminopyridinium ion and 2-aminopyridine while there is a difference of fifteen powers of ten in their basicities. The nucleophilicity of 2-aminopyridinium ion is comparable to that of 4-aminopyridinium ion although the basicity of the former is one-tenth as large. The exceptional reactivity of 2-aminopyridinium ion is attributed to the electrostatic stabilization of the quasi cyclic transition state I. This system is considered to be a model reaction for enzymatic processes such as the interaction of acetylcholine and acetylcholinesterase.

Introduction

It is generally believed that the powerful and specific catalysis of the hydrolysis of carboxylic acid derivatives exhibited by proteolytic and hydrolytic enzymes such as chymotrypsin and acetylcholinesterase, respectively, is due to the action of one or more nucleophilic substances on the enzyme, perhaps in conjunction with electrophiles. The source of the nucleophiles is believed to be in the side chain groups of the α-amino acid moieties of the enzymes. For example, the imidazole group (of histidine) and the hydroxymethyl group (of serine) have been implicated in chymotrypsin action.[2–5]

Studies with model systems, involving imidazole or its derivatives alone, have indicated that the enzymatic process is still considerably better than can be accounted for on the basis of a simple nucleophilic attack by an imidazole nitrogen.[6] Attempts have been made to explain the discrepancy between the action of imidazole and the enzyme chymotrypsin. For example, it has been postulated that since enzymatic action proceeds through primary complex formation followed by one or more catalytic steps, enzymatic action may be likened to an intramolecular reaction which would be expected to proceed more readily than the corresponding intermolecular reaction.[7,8] This concept has been amply verified by studies of intramolecular catalysis involving the carboxylate ion,[9] the carboxylic acid group,[10] and the imidazole group[11,12] which has shown impressive similarity to the chymotrypsin system.

While the concept of an intramolecular reaction goes far to explain the enhanced reactivity of enzymes toward carboxylic acid derivatives,[8,12] it does leave unanswered the question of how one obtains the complex between enzyme and substrate that may be considered to lead to an intramolecular process. In the reaction of various substrates with acetylcholinesterase, it has been shown that the "esteratic" site is accompanied by another (anionic) site on the enzyme which interacts electrostatically with a positive site of the substrate, usually the acetylcholine cation. It was therefore conceivable that a system composed of an ester substrate and an amine nucleophile could be constructed in which there would be, adjacent to the reactive centers on each molecule, a second set of centers which would be correctly oriented for electrostatic interaction. It was thought that a considerable rate enhancement might occur under these circumstances and that such a reaction system might provide a better model for enzymatic reaction than

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(1) (a) This research was supported by Grant H-2416 of the National Institutes of Health and by a grant from the Upjohn Co. (b) Royal Institute of Technology, Stockholm 70, Sweden.

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(12) T. C. Bruice and J. M. Sturtevant, *Biochim. et Biophys. Acta*, **30**, 208 (1958).