The Catalysis of the Hydrolysis of Isopropyl Methylphosphonofluoridate in Aqueous Solutions by Primary Amines

Joseph Epstein,* Paul L. Cannon, Jr., and John R. Sowa

Contribution from the Defensive Research Department, Physical Research Laboratory, Research Laboratories, Edgewood Arsenal, Maryland 21010. *Received April 17, 1970*

Abstract: The hydrolysis of isopropyl methylphosphonofluoridate was followed in the presence of ethoxyamine, ethylenediamine, hydrazine, 1,3-propylenediamine, benzylamine, *p*-methoxybenzylamine, 3-methoxypropylamine, and 3-ethoxyethoxypropylamine, isopropyl methylphosphonic acid being the only product. The kinetics were first order in free amino nitrogen concentration. A linear free-energy plot showed no rate discrepancy whether the amine was uncharged, charged, or one which can exhibit an "α" effect. The absence of a "charge" or "α" effect is consistent with general base catalysis as the mechanism of hydrolysis.

For some time our group and others have been investigating the displacement reaction of fluoride ion from the nerve gas isopropyl methylphosphonofluoridate (I) in aqueous medium by oxygen nucleophiles (phenates,[1] catecholates,[1b,2] hydroximates,[3] oximates,[4] anions of hydrogen peroxide,[5] hypochlorous acid,[6] and hydrated aldehydes[4b]). In each case a new phosphorus–oxygen bond is formed, and for each nucleophilic class the linear free-energy equation, $\log k_2 = \beta pK_a + C$, where β is the slope (always positive) and K_a is the ionization constant of the conjugate acid of the nucleophile, adequately describes the quantitative relationship of the reaction rate and the proton basicity of the nucleophile.

Although proton basicity of the nucleophile is important to its reactivity, it is not the only factor of importance. The presence of a hydroxyl group, ortho to the attacking anion, increases the reactivity,[2] and the anions of ketoximes and hydroxamic acids ("α" nucleophiles[7]) are more reactive than, *e.g.*, phenates of the same proton basicities. Differences in reaction rates have also been noted within some classes of nucleophiles when comparing "charged" and "uncharged" nucleophiles.[1,4b] Introduction of cationic substituents in phenates, catecholates, and the anions of hydrated aldehydes causes the nucleophiles to be more reactive than expected from the pK_a's of their conjugate acids. The higher reactivity shown by a positively charged nucleophile (as compared with a nucleophile of the same class but possessing no cationic groups) is thought to be due to a higher basicity to a neutral substrate than is reflected by its pK_a, *i.e.*, its proton basicity. The abnormally high reactivities of the hydroxo species of the hydrated metal ions in the catalytic hydrolysis of I is explained on this basis.[8]

In contrast to oxygen nucleophiles, displacement of fluoride ion from a fully substituted phosphorofluoridate, and presumably phosphonofluoridates, in aqueous solution by nitrogen nucleophiles occurs *via* a general base catalyzed hydrolysis;[9] nucleophilic attack on phosphorus by nitrogen nucleophiles does not contribute to the overall rate due to the formation of a stable zwitterionic intermediate.[10]

In this paper, we report on the hydrolysis rates of I in the presence of primary mono- and diamines. Our purpose was (a) to determine whether "α" and "charged" nitrogen nucleophiles showed a different behavior than did "non-α" and "uncharged" nitrogen nucleophiles with respect to nucleophilic or general base catalysis and (b) to assess the magnitude of the "charge" and "α" effects on the general base catalyzed reaction, if indeed the mechanism for the compounds tested is base catalysis. Data for the construction of a linear free-energy plot were obtained. The reactivities of the "charged" and "α" nucleophiles are compared with those which would be expected from the pK_a's of the conjugate acids.

Experimental Section

Materials and Equipment. The amine and amine hydrochloride titrations and the pH control and enzyme assays were performed with a Radiometer TTTlc automatic titrator, Radiometer SBRc titrigraph, and a Radiometer SBUla syringe buret. The nmr spectra were obtained with a Varian A60 nmr spectrometer.

The amines or their hydrochlorides, the deuterium oxide, and the eel cholinesterase (EC 3.1.1.7)[11] were obtained from commercial sources and, except for the amine hydrochlorides, were used with-

* To whom correspondence should be addressed.

(1) (a) J. Epstein, R. E. Plapinger, H. O. Michel, R. Cable, R. A. Stephani, R. J. Hester, C. Billington, Jr., and G. R. List, *J. Amer. Chem. Soc.*, **86**, 3075 (1964); (b) J. Epstein, H. O. Michel, D. H. Rosenblatt, R. E. Plapinger, and E. Cook, *ibid.*, **86**, 4959 (1964).

(2) (a) B. J. Jandorf, T. Wagner-Jauregg, J. J. O'Neill, and M. Stolberg, *ibid.*, **74**, 1521 (1952); (b) K.-B. Augustinsson, *Acta Chem. Scand.*, **6**, 959 (1952); (c) J. Epstein, D. H. Rosenblatt, and M. M. Demek, *J. Amer. Chem. Soc.*, **78**, 341 (1956).

(3) (a) B. E. Hackley, R. E. Plapinger, M. Stolberg, and T. Wagner-Jauregg, *ibid.*, 77, 3651 (1955); (b) R. Swidler and G. M. Steinberg, *ibid.*, **78**, 3594 (1956); (c) M. A. Stolberg and W. A. Mosher, *ibid.*, **79**, 2618 (1957); (d) A. L. Green, G. L. Sainsbury, B. Saville, and M. Stansfield, *J. Chem. Soc.*, 1583 (1958); (e) G. F. Endres and J. Epstein, *J. Org. Chem.*, **24**, 1497 (1959); (f) R. Swidler, R. E. Plapinger, and G. M. Steinberg, *J. Amer. Chem. Soc.*, **81**, 3271 (1959).

(4) (a) A. L. Green and B. Saville, *J. Chem. Soc.*, 3887 (1956); (b) J. Epstein, P. L. Cannon, Jr., H. O. Michel, B. E. Hackley Jr., and W. A. Mosher, *J. Amer. Chem. Soc.*, **89**, 2937 (1967).

(5) (a) L. Larsson, *Acta Chem. Scand.*, **12**, 723 (1958); see also (b) J. Epstein, M. M. Demek, and D. H. Rosenblatt, *J. Org. Chem.*, **21**, 796 (1956).

(6) J. Epstein, V. E. Bauer, M. Saxe, and M. M. Demek, *J. Amer. Chem. Soc.*, **78**, 4068 (1956).

(7) J. O. Edwards and R. G. Pearson, *ibid.*, **84**, 16 (1962).

(8) J. Epstein and W. A. Mosher, *J. Phys. Chem.*, **72**, 622 (1968).

(9) M. Kilpatrick and M. L. Kilpatrick, *ibid.*, **53**, 1371 (1949).

(10) R. F. Hudson and R. Greenhalgh, *J. Chem. Soc. B*, 325 (1969).

(11) For an explanation of this nomenclature see "Recommendations 1964 of the International Union of Biochemistry," Elsevier, Amsterdam, 1965.

out further purification. Hydrazine dihydrochloride was purified according to Hatt.[12] Ethoxyamine hydrochloride and 1,2-ethanediamine dihydrochloride were recrystallized from isopropyl alcohol. 4-Methoxybenzylamine, which is difficultly soluble in water and tends to absorb carbon dioxide from the air, was also converted to the hydrochloride. Table I shows the amines used in this study

Table I. Theoretical and Experimental Neutralization Equivalents of Amines

Amines	Neutralization equiv Found	Theor
$CH_3CH_2ONH_2 \cdot HCl$	98.2	97.5
$H_3N(CH_2)_2NH_2 \cdot 2HCl$	63.5	66.5
$NH_2NH_2 \cdot 2HCl$	46.3	52.5
$H_2N(CH_2)_3NH_2$	35.4	37.1
$C_6H_5CH_2NH_2$	110.1	107.2
$CH_3OC_6H_4CH_2NH_2 \cdot HCl$	137.2	137.1
$CH_3O(CH_2)_3NH_2$	89.8	89.1
$CH_3CH_2O(CH_2)_2O(CH_2)_3NH_2$	147.3	147.2

and their theoretical and determined neutralization equivalents. Isopropyl methylphosphonofluoridate (I) was obtained from the Chemical Process Laboratory at Edgewood Arsenal. It was 85% pure according to enzymatic assay.[13]

O-Isopropyl *N*-benzylmethylphosphonamidate[14] was prepared by dropwise addition (with stirring) of 2 mol of benzylamine to 1 mol of isopropyl methylphosphonochloridate in anhydrous diethyl ether. The precipitate of benzylamine hydrochloride was filtered off and the diethyl ether removed by distillation. The product was distilled at 0.75–1.0 mm; bp 150.5–151.0°. A 20% solution in D_2O had the following nmr spectrum: aryl 7.19 (s), CH 4.30 (m), benzyl 3.89 (d, 12 Hz), CH_3P 1.34 (d, 18 Hz), and CH_3 1.10 (d, 6 Hz). Isopropyl methylphosphonochloridate was prepared as follows.

To 100 ml of anhydrous diethyl ether in a round-bottomed flask (equipped with a condenser and protected from atmospheric moisture with a desiccant) was added 26.2 g of methyldichlorophosphine oxide. To the cooled solution (ice bath) was added, with stirring, 20.2 g of triethylamine, followed by dropwise addition of 12.0 g of isopropyl alcohol in 50 ml of anhydrous diethyl ether. The resulting mixture was allowed to come to room temperature and then stirred for 1 hr. The amine hydrochloride was filtered off, the ether flash distilled, and the product was distilled at 37.0–38.0° and 0.8–1.0 mm.

Determination of pK_a Values. The compounds were titrated with 0.1 *N* acid or base according to the method previously described.[4b] The pK_a's of monoamines with $pK_a > 7$ and/or diamines with pK_a values <2.7 units apart were computed from titration curves according to Albert and Serjeant.[15]

Determination of Reaction Velocities and Rate Constants. Approximately 0.001 mol of an amine was accurately weighed and diluted to 10.0 ml with 0.1 *M* KCl. Exactly 4 ml of this solution was adjusted to the experimental pH with 5 *N* HCl or 0.01 *N* NaOH in the 25.0 ± 0.1° thermostatted reaction vessel in an humidified N_2 atmosphere. I (50 mg) was dissolved in 1.0 ml of benzene. The benzene solution (10 μl) was shaken vigorously with 10.0 ml of 0.1 *M* KCl. Exactly 1 ml of the 0.1 *M* KCl solution containing I was added to the pH-adjusted amine solution. Exactly 0.1 ml of the reaction mixture was immediately added to 5.0 ml of 0.001 *M* acetic acid (this stops the hydrolysis reaction) and a stopwatch started. At various time intervals 0.1-ml samples of the reaction mixture were added to containers of 5.0 ml of 0.001 *M* acetic acid. The amount of unhydrolyzed I in the acetic acid solution was determined by taking advantage of its ability to inhibit eel cholinesterase. In order to make this determination, 0.1–0.4-ml samples of the acetic acid solution were allowed to react for 1 min with the enzyme. The ability of the resulting solution to hydrolyze acetylcholine chloride was then determined in a manner similar to previously published techniques,[13] except that the concentrations of acetylcholine chloride, the KCl, and the tris(hydroxymethyl)aminomethane buffer were 0.0367, 0.33, and 0.0003 *M*, respectively. A plot of the log of the relative concentration of I, log *c'*, *vs.* sample time is used to calculate the first-order rate constant, k_{obsd}. Where a sufficient number of runs was available (more than 5) only linear regression plots having correlation coefficients ≥0.98 are reported; in no case was a line with a correlation coefficient <0.96 used. The second-order rate constants were calculated from the equation

$$k_2 = \frac{k_{obsd} - k_{hyd}}{[\text{amine active species}]}$$

Nmr Studies. (1) Stability of *O*-Isopropyl *N*-Benzylmethylphosphonamidate in Aqueous Solution. A 20% solution of the amidate in D_2O was saturated with $NaHCO_3$. The nmr spectrum was recorded immediately after the addition of $NaHCO_3$ and several times thereafter for 4 days. There were no changes from the original spectrum under these conditions or after heating to 50°.

(2) Search for Amidate Formation in the Reaction of I with Amines. (a) The following solution was prepared in an nmr tube: 0.1 ml of I, 0.1 ml of benzylamine, 0.3 ml of D_2O saturated with $NaHCO_3$. Spectra were recorded immediately after mixing and at regular intervals thereafter until the hydrolysis reaction was complete. Special note was taken of the region around 3.89 ppm for the appearance of the benzyl doublet due to formation of system $-CH_2-N-P$. It was not observed. (b) A similar experiment as that given above was run except that methoxypropylamine was used. There was no evidence for the formation of a $-CH_2-N-P$ system. In both cases the final spectrum was only that of isopropyl methylphosphonate. The relative chemical shifts of the different methyl groups were pH dependent, varying from 0.35 to 0.0 ppm for the pH range of 3–10: at pH 3, CH_3P 1.60 (d, 18 Hz), CH_3 1.25 (d, 6 Hz), CH 4.55 (m); at pH 10, CH_3P 1.25 (d, 18 Hz), CH_3 1.25 (d, 6 Hz), CH 4.55 (m).

Results and Discussion

The reactions of I under aqueous conditions in the presence of several primary mono- and diamines proceeded faster than in their absence. The kinetics showed dependence on the first power of the amine concentration. Under the reaction conditions, the rate equation is as follows

$$\frac{-d[GB]}{dt} = k_2[GB][\text{amine active species}] + k_{OH}[GB][OH^-]$$

A summary of the data obtained is given in Table II. Table II also includes the second-order rate constants (k_2) which were calculated from the equation $\log k_2 = 0.505pK_a - 4.480$. This equation was obtained from a plot of $\log k_2$ *vs.* pK_a for ethoxyamine,[16] benzyl- and 4-methoxybenzylamine, 3-methoxypropylamine, and 3-(2-ethoxyethoxy)propylamine, the correlation coefficient being 0.9998. The calculated k_2 values for the diamines are from the equation

$$\log k_2/q = 0.505\frac{p}{q}pK_a - 4.480$$

where *p* is the number of dissociable protons from the conjugate acid and *q* the number of equivalent points in the base species at which a proton can be attached.[17] The experimental k_2 values are sufficiently close to those predicted from the equation which used

(12) H. H. Hatt in "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, pp 208–213.

(13) H. S. Aaron, H. O. Michel, B. Witten, and J. I. Miller, *J. Amer. Chem. Soc.*, **80**, 456 (1958).

(14) The procedures for the preparation of this compound and isopropyl methylphosphonochloridate were kindly supplied by Dr. G. T. Davis of these laboratories.

(15) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases; A Laboratory Manual," Wiley, New York, N. Y., 1962, pp 39, 51.

(16) Ethoxyamine is, strictly speaking, an α amine; the justification for its use in construction of the "basic" line is that (a) its omission would not seriously affect the equation and (b) it provides a point of low pK_a.

(17) R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, 1941, pp 83–85.

Table II. Calculated and Experimental Rate Constants for the Catalyzed Hydrolysis of I

No. of runs	Catalyst active species	pK_a	pH range	Concn range, M [a]	k_2, M^{-1} min^{-1} Found	Calcd
2	$CH_3CH_2ONH_2$	4.83	5.7–6.4	0.08–0.10	0.009 ± 0.001	0.009
6	$H_2N(CH_2)_2NH_3^+$	7.20	7.0–7.4	0.03–0.08	0.37 ± 0.04	0.20
5	H_2NNH_2	8.10	7.0–8.5	0.04–0.06	0.81 ± 0.09	0.57
15	$H_2N(CH_2)_3NH_3^+$	8.80	7.5–8.5	0.04–0.15	0.97 ± 0.19	1.31
6	$C_6H_5CH_2NH_2$	9.49	7.9–8.6	0.05–0.09	2.04 ± 0.30	2.05
8	$CH_3OC_6H_4CH_2NH_2$	9.57	7.5–8.6	0.07–0.15	2.46 ± 0.86	2.25
3	$CH_3O(CH_2)_3NH_2$	10.13	8.5–8.8	0.14–0.17	4.28 ± 0.13	4.31
3	$CH_3CH_2OCH_2CH_2O(CH_2)_3NH_2$	10.16	7.9–8.6	0.07–0.22	4.15 ± 0.18	4.46

[a] Total amine concentration.

Table III. Data on the 1,3-Propanediamine-Catalyzed Hydrolysis of I at 25°

Run no.	pH	[Amine] × 10^5 M	[Amine·H$^+$] × 10^3 M	[Amine·2H$^+$] × 10^2 M	k_{obsd} × 10^3,[a] min^{-1}	k_2,[b] M^{-1} min^{-1}
1	7.48	0.56	4.97	10.39	8.22	1.65
2	7.50	0.61	5.19	10.35	5.55	1.07
3	7.55	0.79	5.97	10.62	4.86	0.81
4	7.99	1.99	5.48	3.54	6.34	1.15
5	7.99	2.62	7.20	4.65	6.94	0.96
6	7.99	2.83	7.80	5.04	8.48	1.09
7	7.99	3.64	10.03	6.48	8.85	0.86
8	7.99	4.18	11.50	7.43	9.54	0.83
9	7.99	4.30	11.83	7.64	10.67	0.90
10	7.99	5.05	13.91	8.98	13.11	0.94
11	7.99	3.72	10.24	6.61	13.22	1.29
12	7.99	7.24	19.95	12.88	15.73	0.79
13	8.40	29.6	31.7	7.96	26.12	0.82
14	8.42	31.4	32.2	7.71	18.43	0.57
15	8.49	39.0	33.9	6.93	25.30	0.75

[a] k_{obsd} corrected for hydrolysis due to hydroxide ion. [b] $k_2 = k_{obsd}$/[amine·H$^-$].

Table IV. Data on the 1,2-Ethanediamine-Catalyzed Hydrolysis of I at 25°

Run no.	pH	[Amine] × 10^5 M	[Amine·H$^+$] × 10^2 M	[Amine·2H$^+$] × 10^2 M	k_{obsd} × 10^3,[a] min^{-1}	k_2 × 10,[b] M^{-1} min^{-1}
1	6.96	2.08	2.23	3.88	7.54	3.4
2	6.99	2.48	2.48	4.03	10.70	4.3
3	7.00	1.36	1.33	2.11	5.61	4.2
4	7.07	4.35	3.62	4.88	11.82	3.3
5	7.25	7.14	3.92	3.50	14.01	3.6
6	7.40	13.4	5.22	3.29	16.89	3.2

[a] k_{obsd} corrected for hydroxide-catalyzed hydrolysis. [b] $k_2 = k_{obsd}$/[amine·H$^+$].

Table V. Data on the Hydrazine-Catalyzed Hydrolysis of I at 25°

Run no.	pH	[Amine] × 10^3 M	[Amine·H$^+$] × 10^3 M	[Amine·2H$^+$] M	k_{obsd},[a] min^{-1}	k_2 × 10,[b] M^{-1} min^{-1}
1	6.98	2.8	37.3		2.33	8.3
2	6.98	3.7	48.6		2.30	6.2
3	6.98	4.3	57.0		4.17	9.7
4	7.60	12.4	39.4		9.51	7.7
5	8.50	30.8	12.3		26.19	8.5

[a] k_{obsd} corrected for hydroxide-catalyzed hydrolysis. [b] $k_2 = k_{obsd}$/[amine].

only simple primary amines to conclude that there are no dramatic effects on the rate attributable to "charged" or "α" nucleophiles.

Tables III–V inclusive give the experimental conditions and results for the diamines. The data indicate no dependence on the diprotonated species of the diamines 1,2-ethanediamine (see *e.g.*, runs 4 and 5, Table IV) and 1,3-propanediamine (runs 3 and 4, Table III) or on monoprotonated hydrazine (runs 4 and 5, Table V). The activities of the unprotonated species of 1,2-ethanediamine and 1,3-propanediamine are masked because of their low concentrations relative to the monoprotonated species. Even at pH $\sim$ 8.5, the concentration of the unprotonated species of 1,3-propanediamine is only approximately 1% of that of the monoprotonated species. If the second-order rate constant of the free diamine is taken as approximately 12 M^{-1} min^{-1} (calculated from the equation log k_2 = 0.505pK_a − 4.480, pK_a = 10.43, and statistically corrected), the contribution to the overall rate due to the free amine species is less than 15%. Experiments at higher pH's are not practical due to the high rate of reaction of I with hydroxide ion ($k_{OH} \sim 2000$ M^{-1} min^{-1}).[6] The inclusion of a termolecular term in the rate equation involving two molecules of the reactive species, as in base-assisted catalysis, is not indicated by the data.

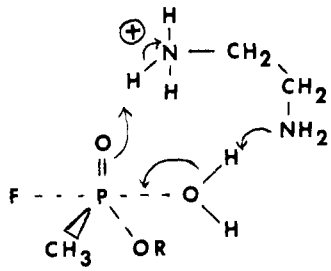
The monoprotonated species of 1,2-ethanediamine is almost twice as reactive as would be expected from its pK_a. The increased reactivity cannot be assigned to a "charge" effect of the nature found in nucleophilic displacements[1] for the following reasons: (a) if there were a "charge" effect by monoprotonated amines, one would have expected to have found it in the monoprotonated hydrazine.[18] The reactivity of the monoprotonated hydrazine should be of the same order as that of hydrazine since, according to the postulate, the basicity of a "charged" nucleophile toward a neutral molecule will be similar to that of the uncharged nucleophile. (b) The monoprotonated species of 1,3-propanediamine has a slightly lower reactivity than predicted from its pK_a. (c) It is to be expected that both charged and uncharged nucleophiles will show basicities in general base catalyzed hydrolyses which are reflected in their pK_a's since these are, as in ionization, proton displacements.

The slightly higher reactivity shown by the monoprotonated species of 1,2-ethanediamine might be due to an intramolecular[19] acid–base catalysis on the bipyramidal transition state of a water coordinated I—a

(18) The lack of reactivity of the monoprotonated hydrazine could also be ascribed to the difficulty in the formation of a transition state which contains two positive charges adjacent to one another.

(19) T. C. Bruice and R. G. Willis [*J. Amer. Chem. Soc.*, 87, 531 (1965)] have postulated such a mechanism to explain the abnormally high reactivity of the protonated form of 2-dimethylaminoethylhydrazine in the catalysis of the aminolysis of phenyl acetate by primary amines. This interpretation has been criticized, however; see W. P. Jencks and M. Gilchrist *ibid.*, 88, 104 (1966).

concerted hydrogen abstraction from the axial water by the unprotonated nitrogen and hydrogen donation to the equatorial phosphoryl oxygen by the protonated portion. The spatial arrangement for such an occurrence is plausible from geometric models (II).



II

In all cases, isopropylmethylphosphonic acid was the product when I and amines were present in aqueous solution. Isopropylmethylphosphonic acid may be formed by nucleophilic attack of amines[20] followed by rapid hydrolysis of the amidate or by general or specific base catalysis of a transition state containing a water molecule. In support of the latter mechanism, *O*-isopropyl *N*-benzylmethylphosphonoamidate, the intermediate expected from the nucleophilic attack of benzylamine on I, was found to be stable under the reaction conditions for several days, showing that it could not have been formed under the experimental conditions. Also, nmr studies of the reaction between I and benzylamine or 3-methoxypropylamine showed no evidence of amidate formation. A Brønsted slope of 0.50 is also consistent with a general base catalyzed hydrolysis mechanism;[17] much higher slopes have been obtained in nucleophilic displacements of fluoride ion from I (see ref 1–4). Furthermore, the linear free-energy equation reported herein is qualitatively similar to that reported for the base-catalyzed hydrolysis of diisopropylphosphorofluoridate (DFP),[9] *viz.*, $\log k_2 = 0.42pK_a - 4.9$. Marked dissimilarities between the rates of reaction of DFP and I are found in their reactions with nucleophiles where displacement on the phosphorus is the mechanistic pathway.

Finally, the "α" amines, ethoxyamine and hydrazine, have reactivities no greater or only slightly greater than that predicted from their pK_a's. If the "α" effect is related to the polarizability of the nucleophile[3d] then its impact would be expected to be of much less importance in proton displacement reactions than in reactions involving attack on an atom which can accommodate a high electron density. For base-catalyzed hydrolyses, both the "charge" (as described in ref 1) and "α" effects appear to be nonoperative. Use can be made of this observation, in conjunction with others, to distinguish between several base and nucleophilic catalytic mechanisms.

(20) Although amines are known to react with phosphoro- and phosphonochloridate esters to produce amidates, it should be pointed out that their reaction with the corresponding fluoridates in aqueous solution does not produce the amidate (see ref 10).

The Hydrolysis of *p*-Nitrophenyl Diphenyl Phosphate Catalyzed by a Nucleophilic Detergent[1]

C. A. Bunton,* L. Robinson, and M. Stam

Contribution from the Department of Chemistry, University of California, Santa Barbara, California 93106.
Received June 20, 1970

Abstract: Micelles of 1,1-phenylhydroxypropyl-2-dimethylalkylammonium bromide (I, alkyl = n-$C_{10}H_{21}$, $C_{12}H_{25}$) are good catalysts of the reaction of *p*-nitrophenyl diphenyl phosphate in aqueous hydroxide ion, relative to micelles of the corresponding trimethylalkylammonium bromide because of nucleophilic participation by an ionized hydroxyl group in the detergent. The variation of rate with increasing hydroxide ion concentration can be explained in terms of ionization of the hydroxyl group at high pH, and $pK_a \approx 12.7$. There is no special catalytic activity of micelles of I for reactions of fluoride ion. Micelles of 1,1-phenylmethoxypropyl-2-dimethyldodecylammonium bromide (II) are not particularly effective catalysts for reactions of hydroxide or fluoride ions with *p*-nitrophenyl diphenyl phosphate. The choline anion is approximately 35 times as reactive as hydroxide ion toward *p*-nitrophenyl diphenyl phosphate.

There are now many examples of micellar catalysis of reactions in solution, and the subject has been extensively reviewed.[2-4] In most of the catalytic systems studied the substrate is incorporated into the micellar phase where it is in a favorable position to be attacked by an external reagent,[2-4] or to decompose spontaneously.[5,6]

In a few systems the detergent contains a nucleophilic group which is the active reagent, and these systems

* To whom correspondence should be addressed.

(1) Support of this work by the Arthritis and Metabolic Diseases Institute of the USPHS is gratefully acknowledged.

(2) E. H. Cordes and R. B. Dunlap, *Accounts Chem. Res.*, **2**, 329 (1969).

(3) H. Morawetz, *Advan. Catal.*, **20**, 341 (1969).

(4) E. J. Fendler and J. H. Fendler, *Advan. Phys. Org. Chem.*, **8**, 271 (1970).

(5) C. A. Bunton, E. J. Fendler, L. Sepulveda, and K.-U. Yang, *J. Amer. Chem. Soc.*, **90**, 5512 (1968); G. J. Buist, C. A. Bunton, L. Robinson, L. Sepulveda, and M. Stam, *ibid.*, **92**, 4072 (1970).

(6) E. J. Fendler, J. H. Fendler, and R. R. Liechti, *J. Org. Chem.*, **35**, 1958 (1970).