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HYDROLYSIS OF BIS(CHLOROMETHYL)PHOSPHONIC ACID p-NITROANILIDE IN AQUEOUS MICELLAR SURFACTANT SOLUTIONS

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The hydrolysis of bis(chloromethyl)phosphonic acid p-nitroanilide has been studied in the pH range 6.86-13.0 and the effects of ionic surfactant micelles on this process have also been examined. The nature of the micellar effects of cetyltrimethylammonium bromide (CTAB) and sodium dodecylsulfate (SDS) on this reaction lead us to conclude that both the neutral and anionic forms of the substrate are reactive, and that in the range of pH > pK_a hydrolysis of the ionic form of the anilide predominates, while at pH < pK_b the reaction of the neutral form is predominant. The binding constants for both the neutral and anionic forms of bis(chloromethyl)phosphonic acid p-nitroanilide in micellar CTAB and SDS solutions have been determined using a kinetic method, as well as by measuring the changes in the acid—base properties of the substrate resulting from the influence of micelles.

The hydrolytic stability of phosphonic acid amides in acid media has been widely studied [1-3]. It has been shown that, depending on the structure of the amide, either a dissociative or associative hydrolysis mechanism may be operating. In all cases, however, cleavage of the P--N bond occurs along with formation of phosphonic acid and the corresponding amine. Basic hydrolysis of phosphonic acid amides, on the other hand, has been much less studied. This process takes place only under harsh conditions, namely, at high temperatures and in strongly basic media. For example, the bimolecular rate constant for basic hydrolysis of diphenylphosphonic acid amide at 90°C is equal to $1.42 \cdot 10^{-5}$ liter/mole·sec [2]. In a series of papers [4-6] the hydrolysis of phosphoric acid amide ester derivatives containing several different groups susceptible to cleavage was examined in detail; included was the hydrolysis of amides accompanied by N-H bond dissociation [4]. Phosphonic acid amides which do not contain an ionizable hydrogen atom attached to the nitrogen atom, or which cannot undergo N-H bond cleavage via a bimolecular addition-elimination mechanism involving a pentacoordinate transition state [2].



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TABLE 1. Arrhenius Equation Parameters for the Hydrolysis Reaction of Bis(chloromethyl)phosphonic Acid p-Nitroanilide in 0.01 N NaOH

т, °С	k·104, sec ⁻¹	E _{act} , kJ/mole	lg A
25 35 44 55	0,331 0,753 1,37 3,93	66,1	7,10



Fig. 1. pH Rate profile for the hydrolysis reaction of bis(chloromethyl)phosphonic acid p-nitroanilide at 25°C. Curve, experimental values; points, theoretical values calculated using the equation $k_{\rm H} = k_2[\text{OH}^-](1 - \alpha)$, $k_2 = 1.6$ liter/mole-sec (1) or the equation $k_{\rm H} = k_1 \alpha$, $k_1 = 5.6 \cdot 10^{-5}$ sec⁻¹ (2).

Fig. 2. Rate constants for hydrolysis of bis(chloromethyl)phosphonic acid p-nitroanilide as a function of surfactant concentration at 25°C: 1) 0.05 M phosphate buffer, CTAB; 2) 0.05 M borate rubber, SDS; 3) 0.01 N NaOH, CTAB; 4) 0.05 M borate buffer, CTAB; 5) 0.01 N NaOH, SDS.

Our goal in the present paper was to investigate the behavior of bis(chloromethyl)phosphonic acid pnitroanilide at various pH values in the presence of cetyltrimethylammonium bromide (CTAB) and sodium dodecylsulfate (SDS) micelles. Phosphoric acid amides containing an active hydrogen atom attached to the amide nitrogen undergo dissociation in basic media; the substrate in question, with a pK_a value of 9.55, can therefore exist in basic solution in both a neutral and anionic form. We have studied the hydrolysis of this substrate in the pH range 6.86-13.0. In the case of both borate and phosphate buffer solutions, it was found that neither borate nor phosphate anions react with the substrate. The following overall reaction scheme for the hydrolysis process can therefore be proposed:



TABLE 2. Binding Constants (liter/mole) for the Neutral (K_b) and Anionic (K_b) Forms of (Bis)chloromethylphosphonic Acid p-Nitroanilide with Different Surfactant Micelles (at 25°C)

SAA	Solution composition	^к ́ъ	к _ь	k ^{eff} b
CTAB CTAB CTAB SDS	0.01 N NaOH 0.01 mole/liter borate buffer (pH 9.2) 0.01 N phosphate buffer (pH 6.86) 0.01 mole/liter borate buffer (pH 9.2)	$300 \\ 540 \\ 64$	40 000 48 000 1	3300 665 41

Notes. K_b and K_b' were determined based on the changes in the acid-base properties of the substrate; K_b^{eff} was determined using the kinetic method.

TABLE 3. Acid—Base Properties of Bis(chloromethyl)phosphonic Acid p-Nitroanilide in Aqueous Micellar Solutions as a Function of Surfactant Concentration (25°C)

	0,05 M bor	0,05 M phosphate buffer			
C _{CTAB} , mole/liter	pK _a	C _{SDS} , mole/liter	pK _a	C _{CTAB} , mole/liter	pK _a
0 0,0002 0,0004 0,0006 0,0008 0,0010 0,0030 0,0050	9.55 9.46 9.07 8.73 8.43 8.26 7.71 7.64	0 0,005 0,010 0,020 0,030 0,050	9,55 9,60 9,69 9,86 9,98 10,15	0 0,0005 0,0010 0,0020 0,0030 0,0050 0,0100	9,55 8,48 8,16 7,89 7,80 7,72 7,70

The pH rate profile or dependence of the observed pseudo-first order rate constant (for hydrolysis) is shown in Fig. 1; the rate constants were measured spectrophotometrically based on the increase in the absorption band of one of the products, p-nitroaniline (λ_{max} 418 nm). It should be noted in this regard that reaction pathways (1a) and (1b) are kinetically indistinguishable. It is clear from the curve in Fig. 1 that the observed pH rate profile for this reaction can be expressed in terms of a kinetic equation for the basic hydrolysis reaction (pathway 1a) as follows [7]:

$$k_{a} = k_{2} [OH^{-}] (1 - \alpha)$$
 (2)

where $\alpha = K_a/(K_a + [H^+])$, namely, the fraction of ionized form of the substrate, given a value for the bimolecular rate constant for basic hydrolysis of the neutral form of the anilide equal to $k_2 = 1.6$ liter/mole-sec; the pH profile, however, can also be described in terms of the following kinetic equation relating to spontaneous hydrolysis of the anionic form of the substrate (pathway 1b) [7]:

$$k_{\rm H} = k_1 \alpha \tag{3}$$

where k_1 is the pseudo-first order rate constant equal to 5.6.10⁻⁵ sec⁻¹. It is also possible that both processes are occurring simultaneously, as represented by the following equation (4)

$$k_{\rm H} = k_2' \, [\rm OH^-] \, (1 - \alpha) + k_1' \alpha \tag{4}$$

with different contributions by reactions (1a) and (1b). The pH rate profile for all three kinetic equations (2)-(4) would look the same, with a characteristic rate plateau at high pH values.

We have also determined the activation parameters for this hydrolysis process in 0.01 N NaOH solution (Table 1). The observed values for the activation enthalpy (ΔH^{\ddagger} 69.0 kJ/mole) and activation entropy (ΔS^{\ddagger} = 238 J/K·mole)

would seem to indicate a bimolecular mechanism for hydrolysis of this substrate [8]. The kinetic results do not make it possible therefore to say which reaction pathway predominates in the overall process.

For this reason, we examined hydrolysis of the anilide in micellar solutions of ionic surfactants (SAA), which provided qualitative information concerning the contributions of reactions (1a) and (1b) at various pH values for the medium. The curves relating the observed rate constants for hydrolysis of the substrate as a function of SAA concentration are shown in Fig. 2. The experimental data thus obtained was analyzed within the framework of the pseudophase theory model for micellar catalysis, using Eq. (5) [9]:

$$k_{\rm H} = \frac{k_{\rm o} + k_{\rm m}/V K_{\rm b}^{\rm eff} C_{\rm SAA}}{1 + K_{\rm b} C_{\rm SAA}}$$
(5)

where k_o and k_m are the pseudo-first order rate constants in the aqueous and micellar pseudophases, respectively; V is the molar volume of SAA; K_b^{eff} is the effective binding constant reflecting the degree of solubilization of both reactive substrate forms by SAA micelles; and C_{SAA} is the concentration of surfactant corrected for the value of the critical concentration for micelle formation (CCM).

In 0.01 N NaOH in the presence of CTAB the reaction rate is retarded by a factor of six. It is well known that basic hydrolysis reactions are accelerated in micellar cationic SAA solutions due to electrostatic attraction between hydroxide ions and the positively charged micellar surface [10]. The absence of rate acceleration due to the effect of CTAB micelles in this case leads us to conclude that reaction pathway (1b) predominates in the region of high pH values. This is consistent with the fact that in 0.01 N NaOH solution the anilide occurs primarily in its ionized form ($\alpha = 0.9996$). The conclusion that under these reaction conditions the process proceeds via the anionic form of the substrate is also supported by the observed value of $K_b^{eff} = 3300$ liters/mole, which is substantially greater than the value of the binding constant for the neutral form (Table 2). It is reasonable to expect that in the case of reaction (1b) for the substrate the rate should be reduced in the transition from an aqueous to micellar medium since the concentration of water in the Stern layer, and even more in the hydrocarbon core of the micelles, is significantly lower than in the bulk solution [11].

In phosphate buffer solution (pH 6.86) a 40-fold rate acceleration for the reaction is observed in the presence of CTAB. Of the two parallel reaction pathways, this type of micellar effect is characteristic of basic hydrolysis of the neutral form of the anilide, which is the principal form of the substrate at this pH value. In borate buffer solution (pH 9.2), on the other hand, CTAB micelles do not affect the reaction rate for the process. Under these conditions the two substrate forms are present in solution in roughly equal amounts. As a result, the inhibitory effect of CTAB micelles on spontaneous hydrolysis of the anionic form of the compound is completely compensated for by the catalytic micellar effect on basic hydrolysis of the neutral form.

The absence of a micellar effect due to SDS in 0.01 N NaOH (Fig. 2) is strong evidence in favor of the predominance of substrate reaction via pathway (1b). Due to electrostatic repulsion between the anionic form of the anilide and the negatively charged micellar surface hydrolysis occurs preferentially in the bulk solution and thus does not depend on the presence of micellar SDS.

In borate buffer solution, in contrast, inhibition of the hydrolysis reaction takes place due to SDS micelles. This is apparently due to several factors. First of all, because of more efficient binding of the neutral form of the substrate by the anionic micelles (Table 2) the contribution of reaction pathway (1a) increases upon transfer from the aqueous to the micellar phase; this reaction pathway is inhibited by anionic micelles due to reagent separation, which in turn occurs since the substrate is bound to SDS micelles via hydrophobic interactions, while the nucleophile remains in the bulk solution because of electrostatic repulsion by the micellar surface. Secondly, this process of substrate solubilization leads to a decrease in the contribution of the reaction involving the anionic form of the substrate in the solution volume.

EXPERIMENTAL

Bis(chloromethyl)phosphonic acid p-nitroanilide was prepared by reaction of bis(chloromethyl)phosphonyl chloride with p-nitroaniline in the presence of triethylamine in benzene at 80°C. The sample was recrystallized twice from a mixture of ethanol with acetone, mp 206°C. Found: C 33.7; H 3.2; N 10.1; P 10.7%. C₇H₉Cl₂O₃N₂P. Calculated: C 33.92; H 3.18; N 9.89; P 10.85%. SDS was obtained from "Sigma," CTAB from "Chemapol," which was redeposited

from ethanol with ethyl ether.

Reaction kinetics were measured spectrophotometrically on a Specord UV-VIS instrument based on the change in absorption of the solution at 417 and 385 nm, corresponding to the ionic form of the substrate and p-nitroaniline, respectively. Substrate concentration in these experiments was maintained at $2.5 \cdot 10^{-5}$ mole/liter. Values of the observed rate constants were calculated on an Élektronika DZ-28 computer using least squares regression analysis. The observed rate constants for substrate hydrolysis in the absence of SAA were as follows, in sec⁻¹ (Fig. 1): pH 6.86 (phosphate buffer). $1.1 \cdot 10^{-7}$; 8.8 (borate buffer), $1.0 \cdot 10^{-5}$; 9.2 (borate buffer), $2.0 \cdot 10^{-5}$; 9.6 (carbonate buffer), $3.1 \cdot 10^{-5}$; 10.0 (carbonate rubber), $4.3 \cdot 10^{-5}$; 10.8 (carbonate buffer), $5.5 \cdot 10^{-5}$; 12.0 (NaOH solution), $5.6 \cdot 10^{-5}$; 13.0 (NaOH solution), $5.6 \cdot 10^{-5}$. The experimental data for the micellar-catalyzed reactions were analyzed using Eq. (5). The binding constant values, which were determined by graphical solution of this equation transformed into linear coordinates, are given in Table 2. Binding constants for the neutral and anionic forms of the substrate were also determined independently based on the changes in acid—base properties of the anilide in the presence of SAA micelles, using the following equation [12]:

$$K_{a, n} = \frac{1 + K_b C_{SAA}}{1 + K_b C_{SAA}} K_a$$
(6)

where $K_{a,H}$ is the observed dissociation constant for the substrate in the presence of SAA micelles, determined spectrophotometrically in the absorption region for the anionic form of the anilide at λ 418 nm at 25°C, according to a literature procedure [13] (Table 3); K_a is the substrate dissociation constant in water at 25°C, equal to 2.8·10⁻¹⁰; C_{SAA} is the concentration of surfactant corrected for its CCM value; K_b and K_b are the binding constants for the neutral and anionic forms of the anilide, respectively, with surfactant micelles. The binding constant values are given in Table 2.

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