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NUCLEOPHILIC SUBSTITUTION REACTION OF *p*–NITROPHENYL BENZOATE WITH SALICYLIC HYDOXAMATE ION IN PRESENCE OF CATIONIC MICELLES

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ABSTRACT

Pseudo first order rate constant have been determined for the nucleophilic substitution reaction of *p*–nitrophenyl benzoate with salicylhydoxamate ion ($HO-C_6H_5CONHO^-$) in buffer (pH-7.9) at 27^{0}C. The k_{obs} value increases upon addition of cationic surfactant (CTAB, CPB) to the reaction medium which is typical behavior of micelle- assisted bimolecular reactions.

Keywords: Nucleophilic substitution, Corboxylic ester, Hydroxamic acid,α-effect, pseudo first order, cationic micelles

INTRODUCTION

Hydroxamate ions are α–effect nucleophiles, whose reactivity is higher than that predicted by Bronsted relations between nucleophilicity and basicity[1-3]. These are effective deacylating, debenzoylating and dephosphorylating agents. This enhanced reactivity in comparison to a normal nucleophile is due to presence of an unshared electron pair adjacent to the nucleophilic center i.e., the α-effect. Numerous studies[4-14] have been performed to account for the origin of the α-effect, solvent effect and nucleophilic substitution reaction of carboxylic and phosphate esters using peroxyanions oximate and hypochlorite etc. Carboxylate and phosphoric ester with nitrophenoxy groups are often used in simulating detoxification of phosphoro fluoridates e.g. Sarin, GB by nucleophilic attack [5] because formation of nitrophenoxide ion is readily followed spectrophotometrically. Surprisingly nucleophile aided hydrolysis of simple and ecotoxic esters using hydroxamate ions[15-17] have not been studied extensively. Hydroxamic acid are weak acids and very important reagents with biological activity and medical and analytical application.

In transferring the reaction from water to micelles an increase in reaction rate have been observed. The structure and properties of surfactant play an important role in determining chemical reactivity. In view of accelerating the hydrolysis of these esters, the effect of micellar catalysis, on one hand, and of specific nucleophiles, on the other hand, have been explored. The effect of surfactant on the α-effect is not completely understood yet.

Therefore we have initiated a systematic study to obtain more conclusive information of the role of micelles on the α-effect of hydroxamate ions. The *p*–nitrophenyl benzoate was already used as a substrate in miceller media[8-9]. But in our knowledge, there is no report describing the miceller reaction kinetics of *p*–nitrophenyl benzoate catalyzed by hydroxamate ions.

In present investigation, a series of reactions of *p*–nitrophenyl benzoate with salicylhydoxamate ion i.e α-nucleophile have been carried out in aqueous solution of cetyltrymethylammonum bromide and cetyl pyridinium bromide.

EXPERIMENTAL

Materials:

Salicylhydroxamic acid and *p*–nitrophenyl benzoate was obtained from sigma /Aldrich. Cetyltrimethylammonium bromide and Cetylpyridinium bromide were obtained from SD fine chemicals. Other chemical used are of analytical grades.

Method:

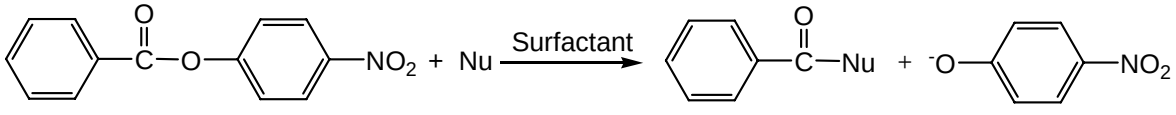
All the kinetic measurement was carried out spectrophotometrically by following the appearance of *p*–nitrophenoxide ion at 400 nm using a systronic UV–vis. spectrophotometer (type-169). All the kinetic experiments were performed at ionic strength of 0.1M (with KCl) and at 27^0 C. Phosphate buffer was employed for all the kinetic runs the absorbance time result fit very well to the following first order rate equation.

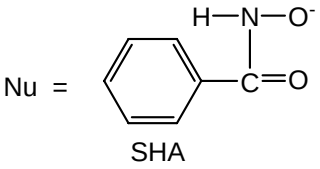
$$\ln (A_\infty - A_t) = \ln (A_\infty - A_0) - kt \qquad (1)$$

Pseudo first order rate constants, K_{obs} were derived from the plots of $\ln (A_\infty - A_0) / (A_\infty - A_t)$ versus time. All the rate constant were reproducible to within 2%. A progressive reaction profile is in figure 4. The spectrum exhibits an increase in absorbance at 400nm with the formation of *p*-nitrophenoxide ion during the course of reaction. The pka value (± 0.03) of hydroxamic acid was determined by potentiometric method using a systronic pH meter.

RESULT AND DISCUSSION

Pseudo first order rate constant have been determined at different pH values in the presence and absence of salicyl hydroxamic acid (SHA). The ionic strength is maintained by 0.1 M KCl. The observed rate constant for the hydrolysis in the presence of SHA^-, k_{obs}^{HA} and in buffer alone k_{obs}^{o} are presented in Table 1.





Surfactant = $C_{16}H_{33}N(Me)_3Br$, $C_{16}H_{33}(Py)Br$

Scheme-1

Table-1: pH dependent rate constant for the reaction of PNPB with SHA

pH	k_{obs}^{o} **x** 10^3 s^{-1}	k_{obs}^{HA} **x** 10^3 s^{-1}
6.9	a	0.33
7.2	a	0.36
7.9	0.01	1.08
10.0	0.09	5.56

[PNPB] = 1.0 x 10^{-4} M [SHA] = 1.0 x 10^{-3} M, [KCl] = 0.1M; a = no reaction

By comparison of k_{obs}^{HA} and k_{obs}^{o} it is apparent that the addition of hydroxamic acid under this condition increases the rate of reaction from 100 fold at pH 7.9, upto 62 fold at pH 10.02. The ionized form of hydroxamic acid (hydroxamate) is responsible for the increase in the rate constant. The actual concentration of hydroxamate ion in the reaction mixture increases with increasing pH.

The catalysis by SHA is dependent upon the ionization state of hydroxamic acid. The following equation may be written as

$$k_{obs}^{HA} = k_{obs}^{o} + k_{HA}\,[HA]_T\ \alpha_{HA} \qquad (2)$$

The k_{obs}^{o} rate constant probably have contributions from lyate species, OH^- and H_2O , and buffer catalysis

$$k_{obs}^{o} = k_{OH^-}\,[OH^-] + k_{H_2O}[H_2O] + k_B[\text{buffer}] \qquad (3)$$

In Eq. 1 k_{HA} is a second order rate constant, $[HA]_T$ is the concentration of Hydroxamic acid, and α_{HA} is the fraction of $(HA)_T$ ionized. Since α_{HA} is equal to $K_a/(K_a + H^+)$, where K_a is the dissociation constant for SHA, rearrangement of Equation (1) given Eq. (2)

$$\log\,(k_{obs}^{HA} - k_{obs}^{o}) = \log\,(k_{HA}\,[HA]_T) + \log\left[\frac{K_a}{K_a + [H^+]}\right] \qquad (4)$$

This equation predicts that a plot of LHS of eq. (2) versus pH should have a slope of one at low pH, $K_a << [H^+]$ and approaches a limiting value of log (k_{HA} $[HA]_T$) at high pH, $K_a >> [H^+]$. Plotting k_{obs}^{HA} vs. $[HA]_T$ gave a linear plot with very low value intercept k_{obs}^{o} at constant pH. This indicates that competition with other nucleophile, i.e. OH^- and H_2O, is not expected and hydroxamate are very strong nucleophiles in this system. pH was routinely measured before and after each reaction to ensure it remained unchanged.

Analysis of rate data indicates that the reaction is bimolecular, and that the rate of reaction of PNPB is proportional to the first power of SHA^- . The magnitude of the influence of the cationic surfactant, cetyltrimethylammonium bromide CTAB and cetylpyridinium bromide CPB on the nucleophilic substitution of PNPB is quite evident from table III & IV. In the absence of SHA surfactants enhance the rate by 1 -1.5 times in the presence of SHA the rate increases 180 times.

SHA is N substituted hydroxamic acid and ionize in a normal way within the ordinary pH range .In view of the N-C=O conjugation, the SHA and its anion would be planar ,with the nitrogen lone pair in a P_Π orbital . Repulsion between lone pairs on oxygen and nitrogen is possible, and this may be the cause of the enhanced reactivity.

$$HO - C_6H_4 - C(=O) - N(H) - OH \rightleftharpoons HO - C_6H_4 - C(=O) - N(\bar{}) - O - H^+ \qquad (5)$$

Scheme-2

Table-2: First order rate constants for the reaction of PNPB with excess hydroxamic acid in phosphate buffer pH 7.9.

SHA x 10^{-3} M	**[PNPB]x 10^{-4} M**	k_{obs}^{HA} **x 10^3 S^{-1}**
0	1.0	0.01
0.5	1.0	0.90
1.0	1.0	1.08
2.0	1.0	1.83
3.0	1.0	2.45

Mechanism:

A simplified and generalized mechanistic pathway for SHA is shown in scheme 2In aqueous solution the salicyl hydroxamate anion can potentially exist in three form (A, B, C) and the position of the equilibrium is solvent dependent. Now it has been established that hydroxamic acid are OH rather than NH^- acids in H_2O[19-20]. The forms B and C would be considered to be less nucleophilic than A toward the carbonyl carbon of PNPB due to the steric factor of B and the non α-effect nucleophile structure of C. This argument can be supported from the fact that the O-benzoylated product can be easily prepared quantitatively from the reaction of salicyl hydroxamic acid with benzoylating agent such a benzoyl chloride. The salicyl hydroxamate ion then react with PNPB and gave intermediate I which decomposes into *p*-nitrophenoxide ions and O-benzyolated product.

Effect of Cationic Surfactant:

Anionic nucleophiles such as oximate[5-7] thiolate, hypochorite, hydroxamate[7-8] and alkoxide[13] are considerably activated in the presence of cationic micelles. The hydroxamate surfactant combination will be useful for decontamination of toxic ester. It has been very well known that the enhanced reactivity observed in reactions performed in cationic surfactant shows a good correlation with hydrophobicity of reactant. The hydrolytic property of SHA was assessed for cleavage of PNPB from the observed first order rate constants versus surfactant concentration profile (Table 3 and Fig. 2)

Table-3: Summary of kinetic rate data for the reaction of PNPB with SHA in phosphate buffer (pH 7.9) containing various concentration of cationic surfactant at 27^0 C. μ = 0.1 M KCl, [PNPB] = 1.0 x 10^{-4} M

[SHA] x 10^{-4} M	**[Surfactant] x 10^{-3} M**	k_{obs}^{HA} **x 10^3 sec^{-1}**	
		CTAB	**CPB**
1.0	0.9	2.80	4.42
1.0	1.8	3.00	5.60
1.0	2.7	4.00	5.83
1.0	3.6	5.26	6.86

It is illustrated in Fig. 2 that the reactivity increases sharply as the surfactant concentration increases as expected for the reaction of anionic nucleophiles in cationic surfactant solutions. The CPB is more reactive than CTAB. The α-effects are also very high. However, the effect of CTAB & CPB on reactivity in buffer alone (pH 7.9) is very small (Table 4 and Fig-3). This indicates that nucleophile aided hydrolysis is the most suitable reaction medium to detoxify ecotoxic esters.

Table-4: Summary of kinetic rate data for the nucleophilic reactivity of PNPB in the presence of cationic surfactant at 27^0C μ = 0.1 KCl

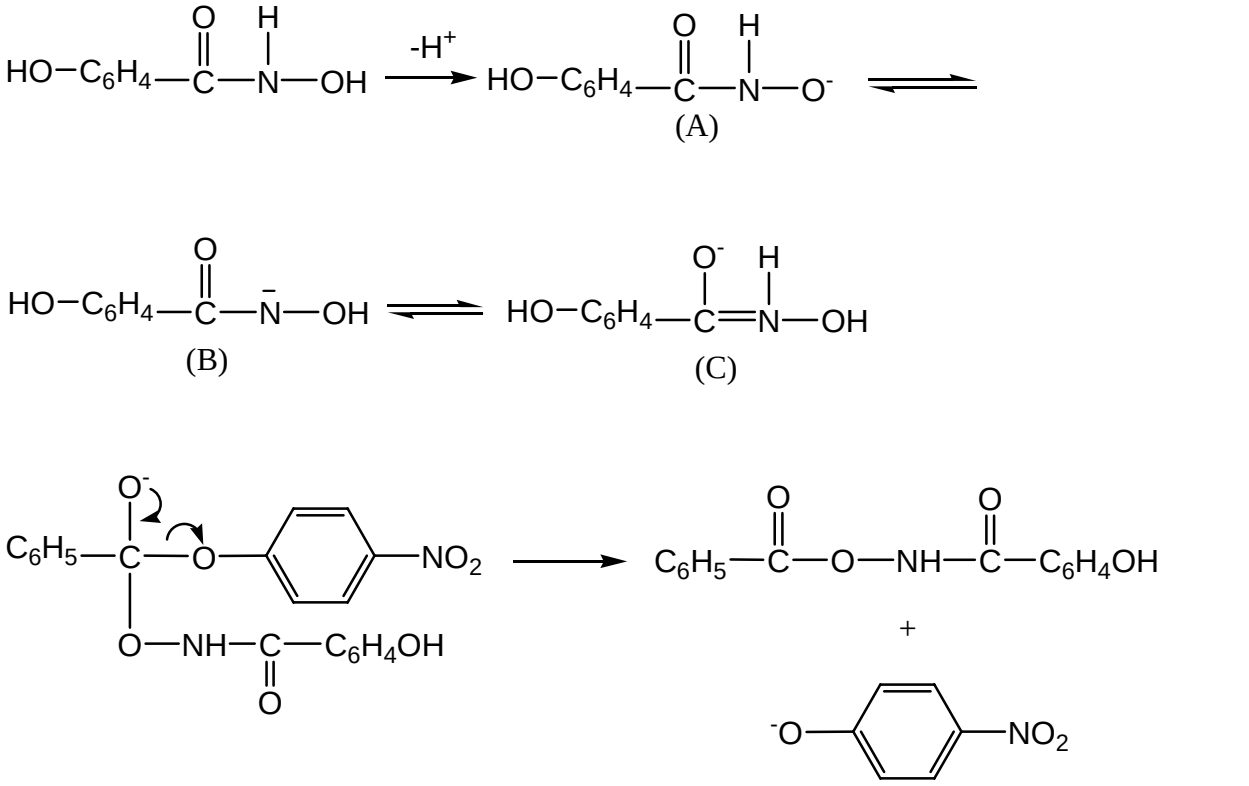
[PNPB]	**[Surfactant]**	k_{obs} **x 10^3 sec^{-1}**	
x 10-^{4} M	**10^{-3} M**	**CTAB**	**CPB**
1.0	0.9	0.015	0.019
1.0	1.8	0.017	0.023
1.0	2.7	0.023	0.026
1.0	3.6	0.026	0.034

The acid dissociation constant pK_a of SHA has been determined pH metrically in 1 M KCl. The Pka alone cannot be measure of nuclephilicity for the present system. The interaction between hydroxamic acid and carbonic surfactant are also important. The nucleophilicty will be governed not only by the pK_a of

nucleophile but also by the strength of interaction between the nucleophile and CTAB aggregate [21-22] as expressed in Eq.

$$\log k = \alpha \log K_s + \beta \log K_a \qquad (6)$$

where k, K_s and K_a represent nucleophilicity, strength of interaction between hydroxamate and surfactant and acid dissociation constant of hydroxamate respectively.



Scheme-3

Similarly α and β represent sensitivity parameter for K_s and K_a respectively. Equation would resemble the Bronsted type of equation when the first term approaches to zero. The present results clearly illustrate that the α-effect is present in aqueans CTAB and CPB solutions as well and the magnitude of the α-effect increases with increasing surfactant concentration cationic micelle bring reactants closer by hydrophobicity binding the PNPB and coulombically attracting the negatively charged hydroxamate ions (nucleophile).

As the number of micelles became large virtually all the substrate gets associated to micellarephase. At higher surfactant concentration the rate acceleration is not very significant, because micelles simply taken up the nucleophile anions in to stern layer. More work is in progress in the view of reaching the role of surfactant on the α-effect of other hydroxamate ions in benzoyl transfer reaction.

CONCLUSION

To examine the α-nucleophilic activity of salicyl hydroxamic acid for the hydrolytic cleavage of PNPB a detailed kinetic study has been made in cationic surfactants. Our results support the enhanced esterolytic properties of hydroxamate ion in the presence of miceller aggregates. Although some very effective α-nucleophiles are available, none is applicable to all classes of compound. It is observed that nucleophile strongly depends on pK_a values. Work is in progress to study the α effect, solvent effect and the kinetic model for toxic ester and pesticides cleavage.

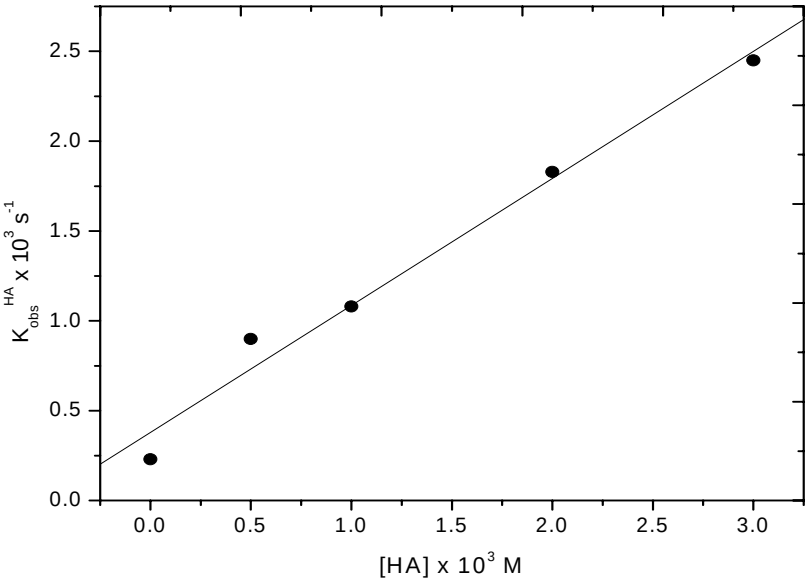


Fig.-1: Plot of k_{obs} vs. [SHA] for the reaction of PNPB.

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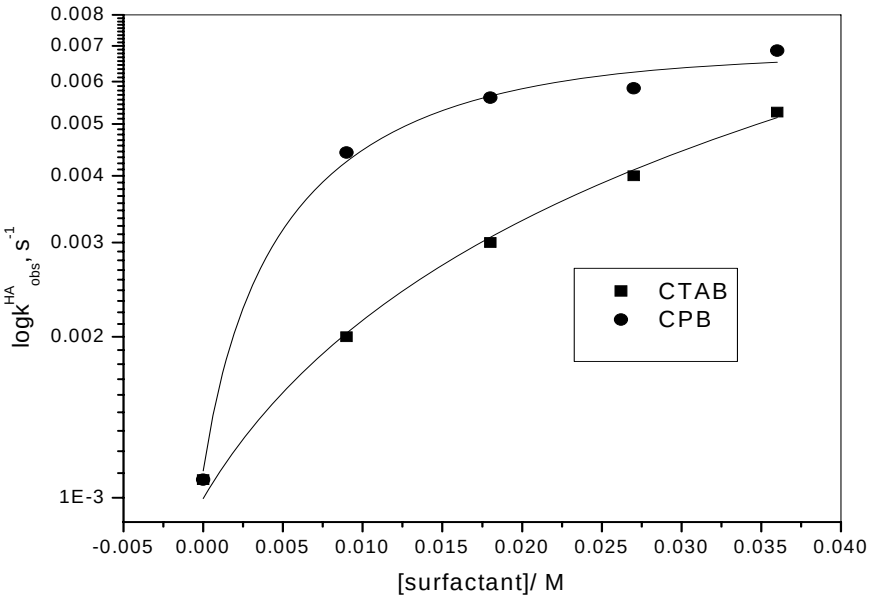

Fig.–2:Rate surfactant profile for the reaction of PNPB with SHA in various concentration of cationic surfactants at pH 7.9 and μ = 0.1 KCl.

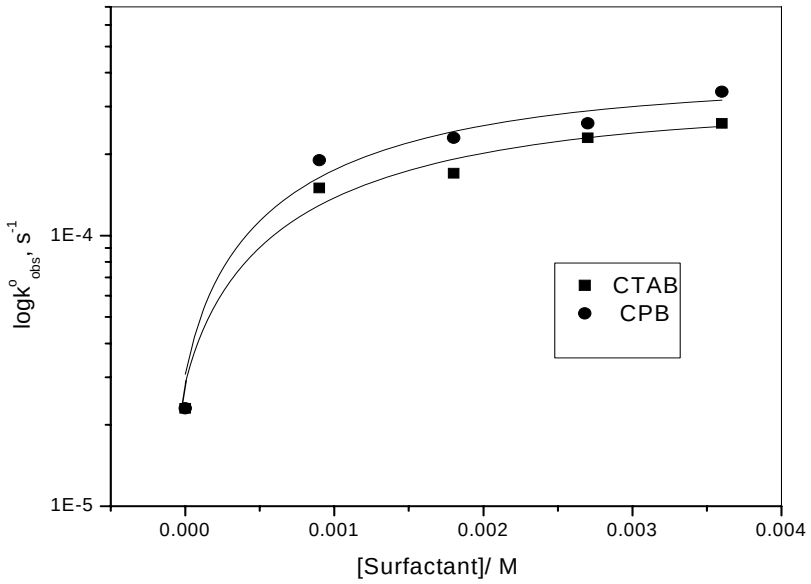

Fig.-3:Rate surfactant profiles for the hydrolysis of PNPB in buffer alone at pH 7.9. μ = 0.1 M KCl

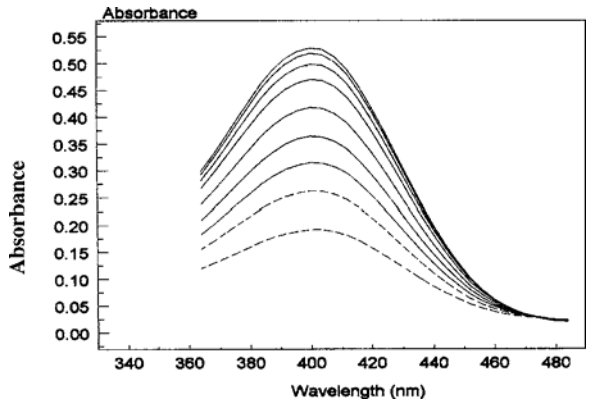

Fig.- 4: Repeat scan (1–9) graphs showing increasing absorbance at 400nm [PNPB] = 1.0×10^{-3} M, pH =7.9.[SHA] = 1.0×10^{-3} M.

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