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KINETIC STUDIES AND MICELLAR EFFECT ON THE AMINOLYSIS OF CERTAIN O-ARYL OXIMES

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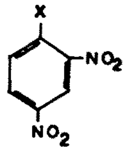
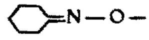
ABSTRACT - Rate constants for the aminolysis of a few O-aryl oximes with several primary alkyl amines, CH_3NH_2 —— $C_6H_{13}NH_2$, in 1:1 water-acetonitrile are reported. Reactions of methylamine with substrates possessing poor nucleofugues are very weakly sensitive to base catalysis while reactions of higher amines are not. Slightly higher rate of long chain amine may be considered as a consequence of hydrophobic interaction. Cationic micelles of cetyltrimethyl ammonium bromide enhance the rate. Magnitude of micellar catalysis increases towards higher amines.

Substitution reactions by amine nucleophiles have been extensively studied for a variety of substrates like esters, thiolesters, lactones, thiolactones and nitroactivated aryl halides as well as aryl ethers. Surprisingly, in spite of their well known pharmacological potency, oxime ethers remain scarcely investigated. Only recently, from this laboratory Malik and Co-workers (1) studied nucleophilic reactivities of certain nucleophiles other than amines and advocated cleavage of N-O bond through a nucleophilic attack at the oxime nitrogen in O – (2, 4 - dinitrophenyl) cyclohexanone oxime. Subsequently we suggested (2) cleavage of C-O bond rather than N-O bond, while reporting kinetic studies on hydrolysis of the same oxime ether. As no information on the aminolysis of oxime ether was available in literature, we took up these investigations and in a recent communication reported (3) on n-propylaminolysis of certain oxime ethers. In continuation of this work (3), a more detailed investigation on the aminolysis of four oxime ethers (**A**,**B**,**C**,**D**) with several primary alkylamines, CH_3NH_2 —— $C_6H_{13}NH_2$, was undertaken to examine their nucleophilic reactivities and existence of base catalysis.



X = A, 

B, $C_6H_5(CH_3)C=N\text{-}O\text{-}$
C, $(C_6H_5)_2C=N\text{-}O\text{-}$
D, $Br(4)\ C_6H_4\ (C_6H_5)\ C = N\text{-}O\text{-}$

Results and Discussion

All reactions of primary amines viz. methylamine (MA), ethylamine (EA), n-propylamine (NPrA), n-butylamine (NBA), n-pentylamine (NPA), and n-hexylamine (NHA) with all substrates proceed to give a coloured product of N - (2, 4 - dinitrophenyl) amine in 1:1 water - acetonitrile. At 35 ± 0.1°C, constant pH, ionic strength, the pseudo-first order rate constant (k_o) for reactions of **A** with methylamine increases slightly more than first power of amine concentration. Plots of k_o vs [amine] for other amines are satisfactorily linear (Fig.1). The apparent second order rate constant obtained by dividing k_o by [amine] mildly increases in case of methylamine (≈ 2 fold increase for 4 fold increase in [MA]) while they remain fairly constant with other amines (Table 1). The reaction of A with methylamine is thus more than first order with respect to amine concentration - a situation which shows evidence of general base catalysis (4) of nucleophilic aromatic substitution, the mechanism of which is depicted as in scheme - 1.

Application of steady state hypothesis gives equation (1),

$$k_r = \frac{k_1(k_2 + k_3[B])}{k_{-1} + k_2 + k_3[B]} \qquad \text{.......(1)}$$

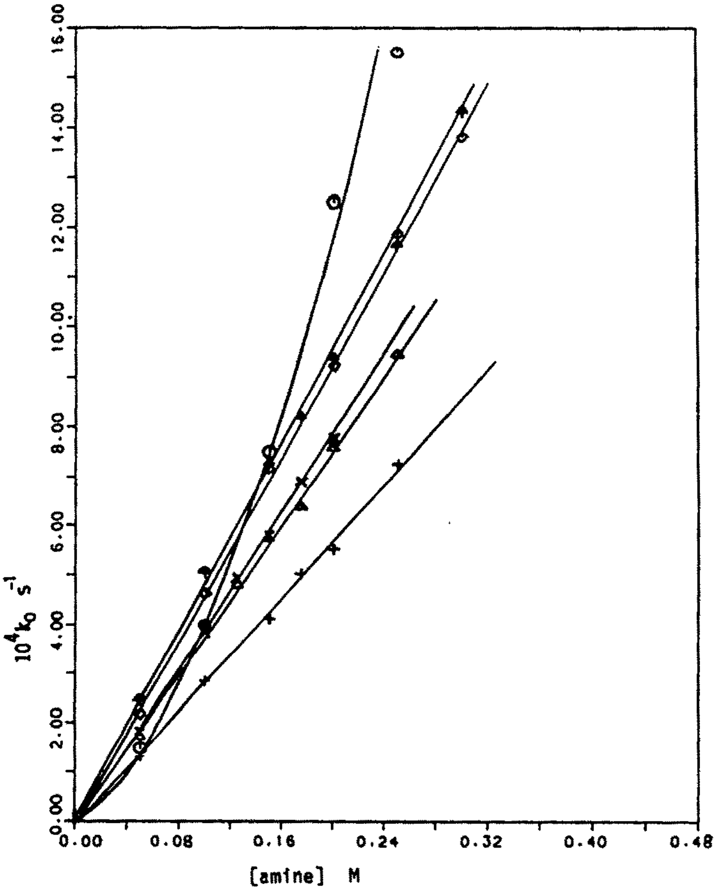


Fig. 1 : Reactions of DNPCHOX with MA(○), EA(△), NPrA(+), NBA(×), NPA(◇) and NHA(✦) in 1:1 water-acetonitrile at 35 ± 0.1°C, pH=11.2, μ=0.2 M

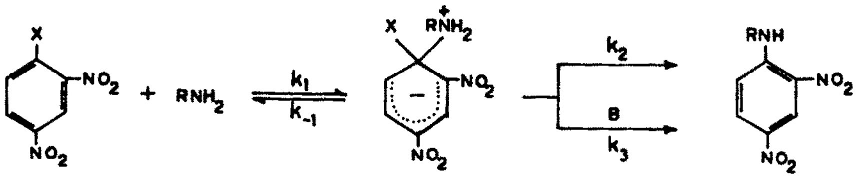
where k_r is the observed second order rate constant and B can be either a second molecule of the nucleophile or an added base. Now if $k_2 >> k_{-1}$, $k_r = k_1$ and the reaction is not base catalysed. When $k_{-1} >> k_2 + k_3[B]$, equation (1) reduces to -

$$k_r = k' + k''[B] \qquad \text{....(2)}$$

where k_r is the observed second order rate constant and k' and k'' are, respectively, second order and catalytic rate co-efficients. The reaction of methylamine mostly conforms to this mathematical form.

The extent of catalysis is expressed as k''/k'. This ratio for reaction of methylamine with A is only 9.5 which indicates mild acceleration. In case of higher amines, the catalysis appears to be insignificant and is difficult to ascertain. The alkyl aminolysis of phenylacetate (4,5) is another example where base catalysis becomes insignificant with higher amines.

The extent of base catalysis in the reaction of methylamine further diminishes with the substrates in the order A > B > C and virtually disappears at D (Fig. 2). This catalytic and the reactivity order of the substrate, D > C > B > A, towards any of the amines can be explained on the basis of leaving group departure ability (6,7,8). Due to



Scheme — 1

Table 1. Observed second order rate constants, (k_r) for the aminolysis of oxime ethers in 1:1 H_2O - MeCN at 35 ± 0.1°C, pH = 11.2, μ = 0.2 M, [sub.] = 4.0×10^{-5} M

[amine] M	10^3 k_r M^{-1} s^{-1}					
	MA	EA	NPrA	NBA	NPA	NHA
			Reactions of A			
0.050	3.0	3.5	2.6	3.6	4.3	4.9
0.100	4.0	3.9	2.8	3.8	4.6	5.0
0.150	5.0	3.8	2.8	3.8	4.8	4.8
0.175	-	3.6	2.9	3.9	-	4.8
0.200	6.25	3.8	2.8	3.9	4.6	4.7
0.250	6.20	3.8	2.9	-	4.7	4.6
			Reactions of B			
0.050	7.0	6.4	5.4	7.5	7.8	10.0
0.075	7.7	-	5.0	-	7.8	-
0.100	8.5	7.0	4.8	7.5	7.7	10.0
0.125	8.5	7.0	5.1	7.4	7.7	-
0.150	9.2	6.5	5.4	7.3	7.1	9.9
0.175	9.75	6.3	5.3	7.8	-	9.5
0.200	10.4	6.5	5.4	7.7	8.0	9.0
0.250	10.3	6.3	-	-	7.3	9.4
			Reactions of C			
0.025	8.8	-	6.6	-	12.4	15.0
0.050	11.0	8.8	6.9	11.0	12.4	15.5
0.075	11.5	-	7.2	11.1	-	-
0.100	12.5	9.0	7.1	11.4	12.4	14.9
0.125	12.6	9.4	7.7	10.4	13.2	14.7
0.150	12.6	8.9	7.6	11.5	12.7	15.2
0.175	13.2	8.9	7.7	11.0	-	-
0.200	13.3	10.4	-	11.8	13.6	13.3
			Reactions of D			
0.025	15.2	8.9	-	12.7	13.0	15.5
0.050	16.0	9.3	8.7	12.7	14.4	18.0
0.075	15.7	-	8.7	12.1	-	-
0.100	16.0	9.9	8.7	12.3	14.4	17.3
0.125	16.2	9.4	8.6	11.9	14.1	17.9
0.150	16.0	9.0	9.2	12.6	15.2	18.5
0.175	16.2	9.8	8.1	12.7	-	-
0.200	15.8	-	8.0	12.3	-	16.2

inductive effect and stabilization through conjugation (9) of the oxime nitrogen to the phenyl ring, the leaving group becomes comparatively better in **D** imparting maximum reactivity and base catalysis by methylamine disappears. To get a semi-quantitative understanding of the leaving group departure ability, we determined the pKa of the conjugate acid of the leaving groups (i.e. pKa of oximes) in 1:1 water-acetonitrile and found values of 13.18, 12.96, 12.82 and 12.66 for oximes of **A**, **B**, **C** and **D** respectively. These pKa values further indicate a better leaving group in **D**.

The reactivity order of the oxime derivatives **A**, **B**, **C**, **D** coupled with appearance of base catalysis in reactions of methylamine with substrates possessing poor nucleofugues is in conformity with the aromatic nucleophilic nature of these reactions. The site of nucleophilic attack in these oxime ethers is, therefore, the nitroactivated aromatic carbon attached to the ether oxygen. Product analysis also confirms this site.

Reactions of all the four substrates with MA,EA,NPrA,NBA were studied at various pH values. pH was kept constant by keeping the RNH_2 : RNH_3^+ ratio fixed and was changed to observe the pH effect by varying this ratio. Free amine concentration and other parameters were kept constant. At a fixed free amine concentration, the rates of all the reactions were found to be insensitive to the variation of pH within the range 10.0-11.2.

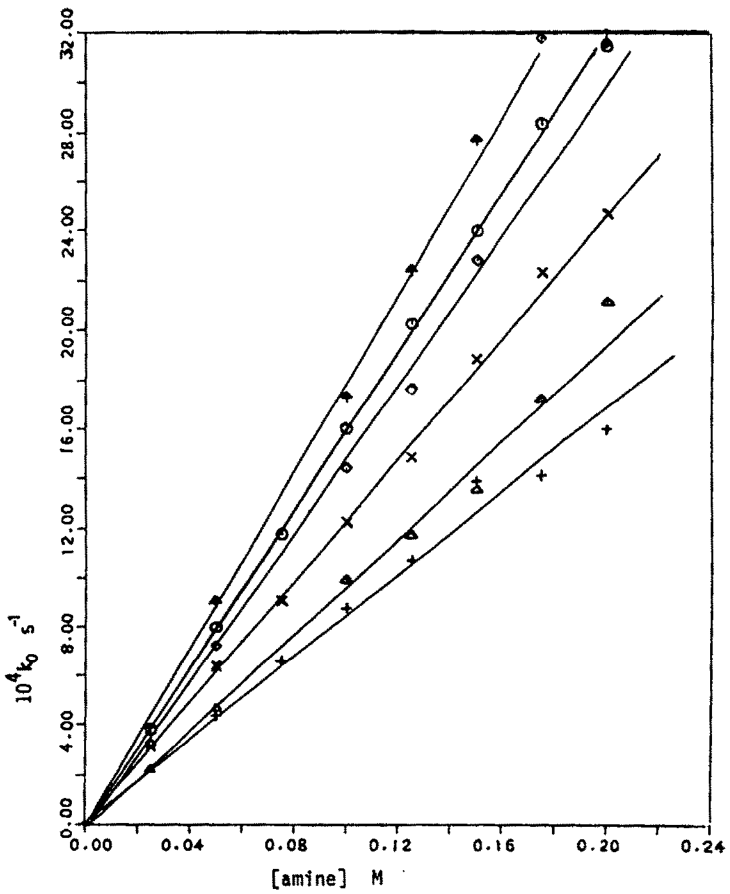


Fig. 2: Effect of amine concentration on the reaction of DNPBrBPOX with MA(⊙), EA(▲), NPrA(+), NBA(×), NPA(◇) and NHA(♦) in 1:1 water-acetonitrile at 35 ± 0.1°C, pH=11.2, μ=0.2 M

Due to involvement of a catalytic term in methylamine, its rate cannot be reasonably compared with those of other amines at least for substrates where there is mild catalysis. In compound D, the catalytic term disappears and apparent reactivity (Table 1) decreases from methylamine to n-propylamine and then gradually increases. As the pKa of these amines are comparable, the reactivity was expected to decrease from methylamine right up to n-hexylamine due to steric hinderance. However, partial reversal of the order and the fact, n-hexylamine has reactivity higher than even methylamine, can be explained on the basis of hydrophobic interaction between the substrate and long chain amine. The effect appears at NBA and increases as we pass on to NHA. Apparently the hydrophobic interactions overcome steric hinderance effect. Similar observations were made by Blyth and Knowles (10) while reporting the aminolysis of p-nitrophenyl decanoate and acetate by n-decylamine and ethylamine. The solvent polarity effect also supports the concept of hydrophobic interaction in the present case. Rate changes linearly but more sharply in case of long chain amine with solvent polarity. The rate ratios in 90:10 and in 50:50 water-acetonitrile (v/v) are 1.11, 1.38 and 2.42 for reactions of EA, NBA and NHA respectively. The higher rate ratio for higher amines may be attributed to hydrophobic action of the long chain amine.

Further, cationic micellar effect of cetyltrimethylammonium bromide (CTAB) on reactions of **A** with EA, NBA and NHA in 10% acetonitrile (CMC = 2.0×10^{-3} M) shows an accelerating effect . The rate enhancement is rapid at low [CTAB] and reaches a maximum at CTAB concentration of ca 0.0075 M (Fig.3). The effect of CTAB on rate enhancement is large with long chain amine, the order being NHA >NBA > EA. Rate enhancement by CTAB like on other reactions (11-13) can be explained in terms of distribution of the reactants between the micellar phase and the bulk phase (14). The substrate being sufficiently hydrophobic in nature, is preferentially taken up by the micelle where it reacts with the amine and the reaction rate enhancement is observed due to increased local concentration of the reactants in the micelles. The

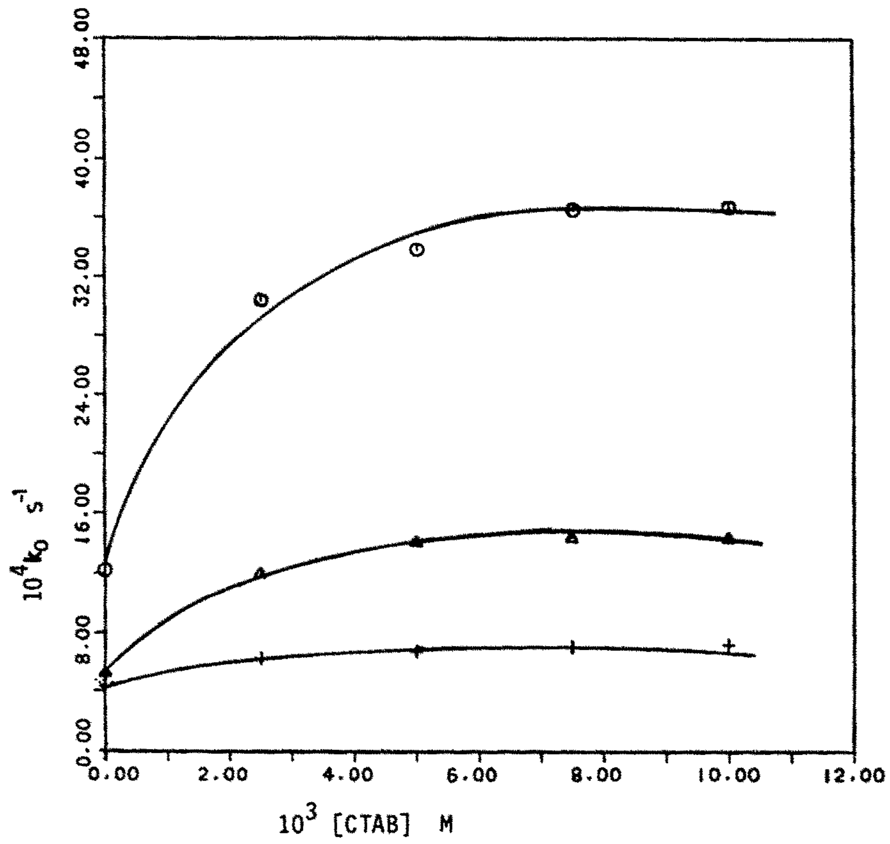


Fig.3 : Effect of [CTAB] on reactions of EA(+), NBA(▲) and NHA(⊙) with DNPCHOX in 10% water-acetonitrile (v/v) at 35±0·1° C [AMINE]=0.1 M

n-hexylamine being more hydrophobic is partitioned more towards micellar phase causing larger rate enhancement.

Experimental

Reagents & solvent :- Substrates were prepared as per method described elsewhere (15, 16). Methylamine (BDH) and ethylamine (Riedel, Germany) were obtained as 50% solution in water and were used as such after standardisation by pH-metric titration. n-Propylamine (E. Merck), n-butylamine (Fluka), n-pentylamine (Fluka) and n-hexylamine (Fluka) were of high purity and were used after checking their boiling points. HCl, $NaClO_4$ and cetyltrimethylammonium bromide were BDH analar grade chemicals. Acetonitrile (E. Merck, G.R. Garde) was used without further purification. Glass still double distilled water was used all throughout.

Kinetic procedure :- Kinetics were studied spectrophotometrically by running the reactions in thermostated cell compartments of UNICAM SP 500 spectrophotometer. A full range uv/vis scan of reaction mixture was occasionally recorded in CARL-ZEIES SPECORD uv/vis spectrophotometer. As the reaction proceeded, absorbance in the visible region increased gradually showing an absorption maximum at a wavelength corresponding to the λ_{max} of the expected aminolysis product. The full range scan also recorded a clear isobestic point to rule out accumulation of substantial concentration of stable intermediate during the reaction.

Kinetics were followed measuring the formation of the product at the λ_{max}. In all runs, amine concentration was kept in large excess over the substrate concentration (4.0×10^{-5} M) in order to obtain pseudo-first order rate constants. Ionic strength was maintained at 0.2 M with calculated amount of $NaClO_4$.

Rate constants were calculated by least square fitted method from a plot of log $(A_\infty - A_o) / (A_\infty - A_t)$ vs time where $A_\infty A_o$ and A_t are absorbance of the reaction mixture at infinite, zero and 't' time respectively. All rate calculations were done with the aid of a DEC-2050 computer. Reproducibility of k_o was found to be within ± 3%.

Product analysis :- The coloured reaction products were characterized to be N-(2, 4-dinitrophenyl)substituted amines from comparison of tlc and spectral properties with those of authentic samples. Authentic samples were prepared by known reactions and identified from m.p. determination and uv/vis absorption records.

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