Aminolysis of Oxime Ethers in Protic and Aprotic Solvents

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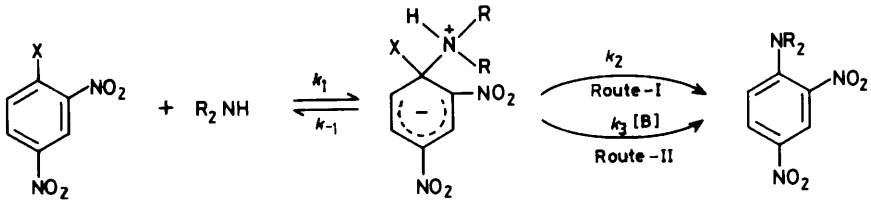
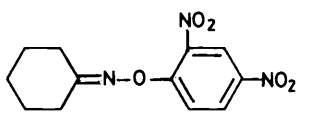
Reactions of oxime ethers with the primary amines, n-propyl-, n-butyl-, n-pentyl-, and n-hexyl-amine in DMSO, DMF, and MeCN are strongly catalysed by general bases. The observed second-order rate constants (k_A) exhibit a curvilinear dependence on amine concentration leaving a positive intercept. The reactions of piperidine in DMSO follow a wholly catalysed pathway. A plot of k_A *versus* [piperidine] is linear and passes through the origin. No base catalysis is observed for the reactions of n-butylamine in methanol and 1:1 (v/v) methanol–acetonitrile. The participation of the hydrogen-bond donor solvent molecule in the intermediate may account for absence of base catalysis in these solvents.

During the last 30 years, extensive work on aromatic substitution reactions by amine nucleophiles has been reported and reviewed. The broad mechanistic features are now fairly well established (Scheme 1), but the mechanism of base catalysis which is frequently encountered in aromatic substitution by amine nucleophiles remains unclear particularly for aprotic solvents.[1] A change of reaction medium has a great effect on the aminolysis mechanism. In addition to the widely accepted SB-GA mechanism for dipolar aprotic solvents, a dimer mechanism[2,3] and a cyclic transition-state mechanism[4,5] have been proposed. Recently Silber *et al.*[6] reported wholly catalysed denitration of 1,2-dinitrobenzene by piperidine in the non-polar aprotic solvents, n-hexane *etc.* The role of electron donor–acceptor complexes prior to the formation of σ-complex has been proposed.[6,7]

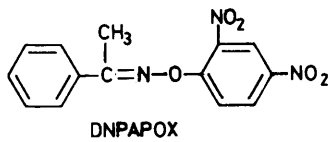
These studies are largely devoted to the reactions of various nitro-activated substrates such as aryl halides as well as aryl ethers. In spite of their well known pharmacological potency, oxime ethers remain little investigated. Malik and his co-workers[8] reported the nucleophilic reactions of *O*-(2,4-dinitrophenyl)cyclohexanone oxime with certain nucleophiles other than amines and advocated N–O cleavage through nucleophilic attack at the oxime nitrogen. We took up these investigations and were able to show[9,10] that substitution occurs at the nitro-activated carbon attached to the oxime oxygen in some *O*-aryl oximes having structural variations in the oxime moiety *viz.* *O*-(2,4-dinitrophenyl)-substituted cyclohexanone oxime (DNPCHOX), acetophenone oxime (DNPAPOX), benzophenone oxime (DNPBPOX), and 4′-bromobenzophenone oxime (DNPBrBPOX). Recently we have reported on the aminolysis of these oxime ethers with several primary alkylamines in 1:1 water–acetonitrile.[11] In continuation of this work we now report on the aminolysis of these oxime ethers in protic and aprotic solvents and show that the reactions are



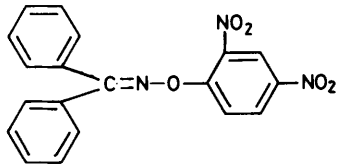
Scheme 1.



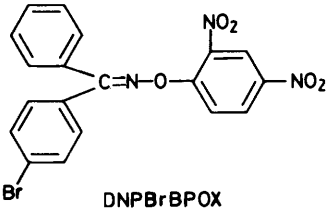
DNPCHOX



DNPAPOX



DNPBPOX



DNPBrBPOX

Table 1. Second-order rate constants (k_A) for primary alkylaminolysis of oxime ethers in DMSO at 35 ± 0.1 °C; [Substrate] 4.0 × 10^{-5} M

	$10^2 k_A$/l mol^{-1} s^{-1}			
10^2[amine]/M	NPrA	NBA	NPA	NHA
A Reactions of DNPCHOX				
0.25	2.8	3.5		5.6
0.50	4.2	5.0	6.1	7.0
0.75	5.3	6.1	6.9	8.1
1.00	5.5	7.0	7.9	8.9
1.25	6.2	7.0	8.1	9.2
1.50	6.7	7.3		9.5
B Reactions of DNPAPOX				
0.25	6.8	9.5	11.1	15.1
0.50	10.5	12.9	15.9	18.5
0.75	13.6	14.7	18.2	20.0
1.00	14.9	16.8	19.0	22.6
1.25	15.8	16.3	20.3	22.7
1.50	16.3	17.3		22.2
C Reactions of DNPBOX				
0.125		13.9	18.8	14.5
0.250	13.4	17.8	22.2	20.6
0.500	19.8	22.2	26.2	29.6
0.750	22.8	24.9	29.6	30.4
1.000	22.2	26.9	32.8	33.0
1.250	28.8	28.1	29.4	33.1
D Reactions of DNPBrBOX				
0.125		17.2	19.3	23.0
0.250	15.9	21.7	26.1	26.5
0.500	23.2	26.2	31.3	35.2
0.750	26.4	29.2	35.7	38.0
1.000	28.2		33.4	41.0
1.250	30.0	38.6	34.4	41.0
1.500	30.5	40.0		

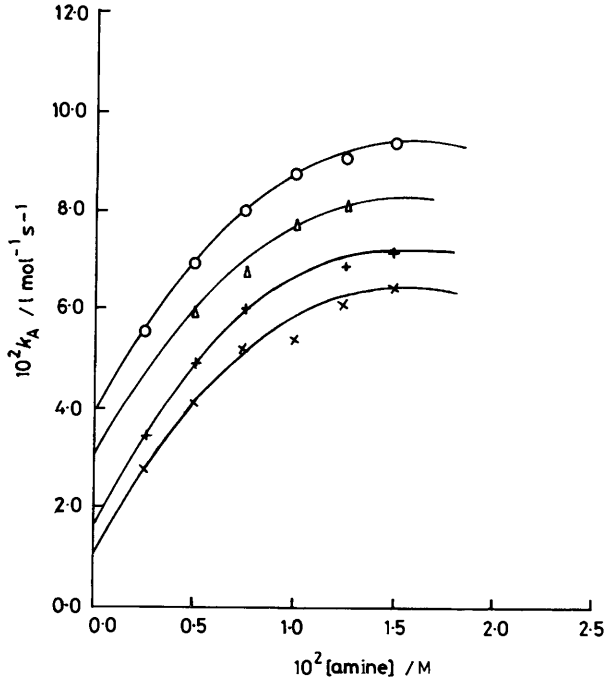


Figure 1. k_A *versus* [amine] for reactions of DNPCHOX in DMSO at 35 ± 0.1 °C; NPrA (×), NBA (+), NPA (△), NHA (○)

Table 2. Reactions of PIP with the oxime ethers in DMSO at 35 ± 0.1 °C; [Substrate] 4.0 × 10^{-5} M

[PIP]/M	$10^4 k_0$/ s^{-1}	$10^2 k_A$ /l mol^{-1} s^{-1}	$10^1 k_{PIP} = k_0/[PIP]^2$/ l^2 mol^{-2} s^{-1}
A Reaction of DNPCHOX			
0.050	1.63	0.33	0.66
0.075	3.51	0.47	0.63
0.100	6.73	0.67	0.67
0.125	10.6	0.85	0.68
0.150	15.0	1.0	0.67
B Reaction of DNPAPOX			
0.025	1.37	0.55	2.2
0.050	5.17	1.1	2.1
0.075	12.7	1.7	2.2
0.100	24.2	2.4	2.4
0.125	38.5	3.1	2.4
0.150	61.7	4.1	2.7
C Reaction of DNPBPOX			
0.0125	0.535	0.43	4.3
0.025	2.20	0.88	3.5
0.035	5.26	1.5	4.3
0.050	10.5	2.1	4.2
0.075	24.4	3.2	4.3
0.100	41.2	4.1	4.1
0.125	67.6	5.4	4.3
D Reaction of DNPBrBPOX			
0.0125	0.773	0.62	5.0
0.025	2.51	1.0	4.0
0.050	11.8	2.4	4.8
0.075	27.2	3.6	4.8
0.100	48.2	4.8	4.8
0.125	81.2	6.5	5.2

wholly catalysed by piperidine even in the dipolar aprotic solvent DMSO.

Results and Discussion

Second-order rate constants (k_A) obtained by dividing the pseudo-first-order rate constants (k_0) by the amine concentration for the aminolysis of oxime ethers by n-propylamine (NPrA), n-butylamine (NBA), n-pentylamine (NPA), and n-hexylamine (NHA) in DMSO are set forth in Table 1. The figure shows plots of k_A *versus* [amine] for the reaction of DNPCHOX in DMSO at 35 ± 0.1 °C. The dependence of k_A on [amine] exhibits a curved response concave downward towards the [amine] concentration axis. This behaviour is similar for all substrates. The curved response indicates strong catalysis by general bases.[12–14] For reactions showing downward curvature in plots of k_A *versus* [amine], k_{-1}, k_2, and k_3[B] are of comparable magnitude[12,13,15,16] and the kinetic expression (1),

$$k_A = \frac{k_1(k_2 + k_3[B])}{k_{-1} + k_2 + k_3[B]} \quad (1)$$

derived by application of the steady-state assumption to Scheme 1 cannot be further simplified. Further, the downward curvature indicates an overall order equal to or smaller than two with respect to these amines.[17]

On the other hand, reactions of the oxime ethers with piperidine (PIP) in DMSO at 35 ± 0.1 °C exhibit linear dependence of k_A on [PIP]. These plots pass through the origin. On further division of k_A by [PIP] or dividing k_0 by [PIP]^2 constant values are obtained (Table 2) which indicates the

Table 3. Reactions of NBA with DNPCHOX and DNPAPOX in DMF and MeCN at 35 ± 0.1 °C; [Substrate] 4.0 × 10^{-5}M

	DNPCHOX		DNPAPOX	
[NBA]/M	10^4k_0/ s^{-1}	10^2k_A/ l mol^{-1} s^{-1}	10^4k_0/ s^{-1}	10^2k_A/ l mol^{-1} s^{-1}
A Reactions in DMF				
0.005	1.23	2.5	2.69	5.4
0.010	3.24	3.2	7.87	7.9
0.015	5.40	3.6	13.2	8.8
0.020	7.67	3.8	16.7	8.3
0.025	9.67	3.9	22.1	8.8
0.030	12.0	4.0	28.0	9.3
0.035	14.6	4.2		
B Reactions in MeCN				
0.01			1.48	1.48
0.02	1.43	0.72	3.88	1.9
0.04	4.16	1.0	10.0	2.5
0.06	6.66	1.1	15.6	2.6
0.08	9.13	1.1	21.8	2.7
0.10	12.5	1.3	28.8	2.9
0.12	14.6	1.2		
0.14	17.9	1.3		

Table 4. Reactions of NBA with DNPCHOX and DNPAPOX in methanol and with DNPCHOX in 1:1 methanol–acetonitrile at 35 ± 0.1 °C

	DNPCHOX		DNPAPOX	
[NBA]/M	10^4k_0/ s^{-1}	10^2k_A/ l mol^{-1} s^{-1}	10^4k_0/ s^{-1}	10^3k_A/ l mol^{-1} s^{-1}
A Reactions in methanol				
0.05			0.64	1.3
0.10	0.80	8.0	1.37	1.4
0.20	1.56	7.8	2.77	1.4
0.25	1.87	7.5	3.86	1.5
0.30	2.30	7.7	4.19	1.4
0.35	2.68	7.6	5.08	1.4
0.40	3.20	8.0	5.90	1.5
B Reaction in 1:1 methanol–acetonitrile				
0.05	1.25	25.0		
0.10	2.82	28.0		
0.15	4.45	29.0		
0.20	5.71	28.0		
0.25	7.50	30.0		
0.30	8.50	28.0		

linearity of the plots and the fact that they pass through the origin. Thus, the order of the reaction with respect to piperidine is two.[17] Whereas k_A–[amine] plots for reactions of primary amines have an intercept, showing the occurrence of a partly uncatalytic pathway (Route I, Scheme 1), plots of k_A *versus* [PIP] pass through the origin, indicating that the reaction is wholly catalysed by piperidine and thus proceeds only through Route II of Scheme 1. Thus for reactions of piperidine, $k_{-1} \gg k_3[B] \gg k_2$ and the kinetic expression (1) takes the form

$$k_A = \frac{k_1k_2}{k_{-1}} + \frac{k_1k_3[PIP]}{k_{-1}} \quad (2)$$

(2). Since the uncatalytic path is undetected (zero intercept in plots of k_A *versus* [PIP]) k_1k_2/k_{-1} is zero and hence equations (3) hold where k_{PIP} is the piperidine-catalysed rate constant which can be calculated from the slope of k_A–[PIP] plots. The values of k_{PIP} for the substrates DNPCHOX, DNPAPOX, DNPBPOX, and DNPBrBPOX are 0.067, 0.253, 0.422, and 0.497 l^2 mol^{-1} s^{-1}, respectively.

$$k_A = k_1k_3[PIP]/k_{-1} = k_{PIP}[PIP] \quad (3)$$

Reactions of n-butylamine with DNPCHOX and DNPAPOX in two other aprotic solvents, dimethylformamide (DMF) and acetonitrile (MeCN), are also strongly general base-catalysed. The experimental second-order rate constant (k_A) at 35 ± 0.1 °C increases curvilinearly as in the case of reactions in DMSO (Table 3). However, when the reactions of n-butylamine with DNPCHOX and DNPAPOX are run in methanol, pseudo-first-order rate constant (k_0) increases linearly and k_A remains constant (Table 4). The linear dependence k_0 on [NBA] and constancy of k_A establishes that the reaction of NBA in methanol is not general base-catalysed.[18] Similarly reaction of NBA with DNPCHOX at 35 ± 0.1 °C shows no catalysis in 1:1 methanol–acetonitrile.

For reactions in dipolar aprotic solvents (DMSO, DMF, MeCN), the generally accepted mechanism for base catalysis is that usually referred to as the SB-GA mechanism.[1,19–22] In this mechanism there is rapid transformation of the first-formed zwitterionic intermediate ($T^{\pm}$) into its conjugate base (T^-) with the help of another base molecule (specific base). This is then followed by slow electrophilically catalysed expulsion of the leaving group from T^- (general acid catalysis by $R_2N^+H_2$).

According to Bernasconi *et al.*,[23] leaving group departure becomes difficult in aprotic solvents and the pK difference between the leaving group and acid catalyst ($R_2N^+H_2$) becomes very large so that proton transfer is possible and SB-GA mechanism in aprotic solvent is an efficient pathway. In view of the pK of oximes (pK_a for K_a of the oximes > 12 in 1:1 water–acetonitrile[10]) being higher than those of amines, the SB-GA mechanism seems operative.

Owing to the unsimplified kinetic form of these reactions in DMSO, DMF, and MeCN the catalytic rate coefficients cannot be accurately calculated in order to compare catalytic efficacy in these solvents. However, the rate of formation of zwitterionic intermediate (k_1) in these solvents may be compared. For reactions in methanol and 1:1 (v/v) methanol–acetonitrile, the observed second-order rate constants (k_A) are equivalent to k_1($k_A = k_1$ when $k_2 \gg k_{-1}$) since in these two solvents reactions are not base catalysed. k_1 Values for reactions of NBA with DNPCHOX in DMSO, DMF, and MeCN may be calculated from the inverse of the intercept of linear plots of $1/k_A$ against 1/[B].[13,17,24] The values of k_1 so obtained in DMSO, DMF, and MeCN when compared with those in 1:1 MeCN–MeOH and MeOH show the following order:

10^4k_1/l mol^{-1} s^{-1}

DMSO > DMF > MeCN > 1:1 MeCN–MeOH > MeOH

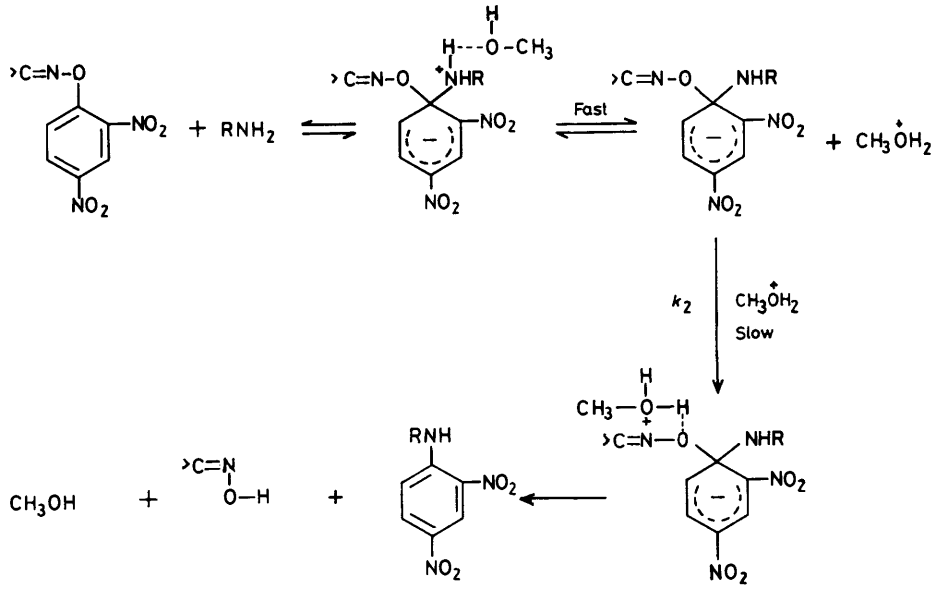
1 000 450 150 29 8

Dielectric constant

DMSO > DMF > MeCN > 1:1 MeCN–MeOH > MeOH

47 42 37 36

The above order is quite rational if the dielectric constants of the solvents are considered. To explain the markedly low reactivity and absence of base catalysis in methanol and also in 1:1 methanol–acetonitrile, the hydrogen-bond donor–acceptor properties of solvents may be worth considering. On the empirically defined α- and β-scales[25] DMSO, DMF, and MeCN are hydrogen-bond acceptor (HBA) solvents. In these solvents the ammonium hydrogen in the intermediate ($T^{\pm}$) has been argued to be strongly hydrogen bonded to the *o*-nitro group.[26] The HBA solvents provide additional stability to the



Scheme 2.

intermediate through solvation,[17] so that detachment of the nucleofugue may be rate-limiting. This warrants base catalysis which has been experimentally observed in DMSO, DMF, and MeCN. On the other hand hydrogen-bond donor (HBD) solvents like methanol[25] assist the departure of the leaving group[1] and thus formation of the intermediate may be the rate-determining step in HBD solvents.[1]

Even for poor leaving groups, various workers[15,27,28] reported absence of base catalysis in methanol. Specific solvation of the nucleophile through hydrogen bonding has been said to be the cause of low reactivity in methanol.[29] Nudelman *et al.*[28] observed very low reactivity in methanol as a specific hydroxylic solvent effect. Hydroxylic solvents are able to act as hydrogen-bond donor as well as acceptors (α 0.93, β 0.62 for methanol).[25] On the other hand, the zwitterionic intermediate formed during nucleophilic substitution with primary and secondary amines as nucleophiles may act as hydrogen-bond donor.[30] Hence an intermolecular hydrogen bond between the intermediate ($T^{\pm}$) and the hydroxylic solvent might be possible. The uncatalysed mechanism in hydroxylic solvents proposed by Orvik and Bunnett[22] may proceed through participation of HBD solvents acting as a base (Scheme 2).

Experimental

Reagents and Solvents.—Substrates were prepared as described elsewhere.[31,32] n-Propylamine (E. Merck), n-butylamine (Fluka), n-pentylamine (Fluka), n-hexylamine (Fluka), and piperidine (Fluka) were of high purity and were used after checking their b.p.s. Dimethyl sulphoxide (E. Merck, pure), dimethylformamide (SISCO), methanol (B.D.H, Analar grade) and acetonitrile (E. Merck, G.R. grade) were used after purification. Linde type 4A molecular sieves were used for drying the solvents.

Stock solutions of substrates and amines were prepared in the respective solvents and were used within 48 h.

Kinetic Procedure.—Kinetics were studied spectrophotometrically by running the reactions in the thermostatted cell compartments of Beckman DU-6 and UNICAM SP 500 spectrophotometers. Reactions were tested for the presence of a stable intermediate during the reaction by scanning with a Carl-Zeiss Specord u.v.-visible spectrophotometer. All reactions gave the expected aminolysis product without the accumulation of intermediate. Reactions were followed at the $\lambda_{max.}$ of the aminolysis product. In all runs amine concentrations were in large excess over the substrate concentration (kept constant at 4.0×10^{-5}M in all runs). Good pseudo-first-order plots were obtained. Amine concentration was varied nearly ten-fold in most reactions. All reactions were carried out at 35 $\pm$ 0.1 °C.

Rate constants were calculated by least-squares fitted method from the plot of $\log (A_\infty - A_0)/(A_\infty - A_t)$ *versus* time, where A_∞, A_0, and A_t are absorbance of the reaction mixture at infinite, zero, and time t, respectively. All rate calculations were done with the aid of a DEC-2050 computer. The reproducibility of k_0 was found to be within $\pm 3\%$.

Acknowledgements

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