Base-catalysed Aromatic Nucleophilic Substitution Reactions of *O*-Aryl Oximes with Pyrrolidine in Non-polar Aprotic, Dipolar Aprotic, and Protic Solvents

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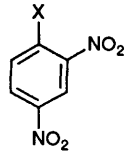
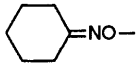
The kinetics of *O*-(2,4-dinitrophenyl) substituted cyclohexanone oxime and benzophenone oxime with pyrrolidine, a secondary alkyl amine have been studied in chlorobenzene, MeCN, DMF, DMSO, and methanol. The reactions are second order in amine in all the solvents except chlorobenzene, in which the order is more than two. Observed rate constants decrease with an increase in temperature in all aprotic solvents except protic methanol, in which an increase in rate constant is observed. The results are explained on the basis of base-catalysed collapse of the tetrahedral intermediate by homo- and hetero-conjugated acids.

The influence of solvent on the course of aminolysis reactions of nitro-activated substrates is well-known, but controversy with regard to the mechanism, especially in non-polar aprotic solvents is still to be resolved. It has been firmly established that in dipolar aprotic solvents in which the order in amine is *ca.* two, the aminolysis proceeds through Bunnett's SB–GA mechanism.[1–5] However, in non-polar aprotic solvents such as benzene,[6,7] toluene,[8] cyclohexane[9,10] most aminolysis reactions show a third-order dependence in amine which implies an alternative mechanism. This third-order dependence has been explained in three main ways: (*i*) attack of amine dimer[8–10] on the substrate leading to formation of an intermediate followed by amine-catalysed decomposition; (*ii*) attack by two amine molecules,[6,7] on the intermediate, in a catalytic step involving a cyclic transition state;[11] (*iii*) electrophilic catalysis by homo-conjugated acids (Hirst *et al.*[12–15]) that is essentially parallel to the SB–GA mechanism. In the process of obtaining further data, in order to resolve this controversy, we have recently reported[16] the aminolysis of four *O*-aryl oximes in benzene and explained the results on the basis of a cyclic-transition-state mechanism. In order to find further evidence to support our earlier views, we investigate in the present paper pyrrolidinolysis of two *O*-aryl oximes *viz.* *O*-(2,4-dinitrophenyl) substituted cyclohexanone oxime (**1**) and benzophenone oxime (**2**) in four aprotic solvents



(1) X = 

(2) X = $(C_6H_5)_2C{=}NO-$

of different hydrogen-bond acceptor ability[17] *viz.* chlorobenzene acetonitrile, dimethyl formamide, and dimethyl sulphoxide; and methanol, a protic solvent of poor hydrogen-bond acceptor and good donor ability.[17] The results obtained indicate that our earlier views ought to be discarded and reactions both in non-polar and dipolar aprotic solvents proceed through an SB–GA mechanism where electrophilic catalysis is due to homo- and hetero-conjugated acids.

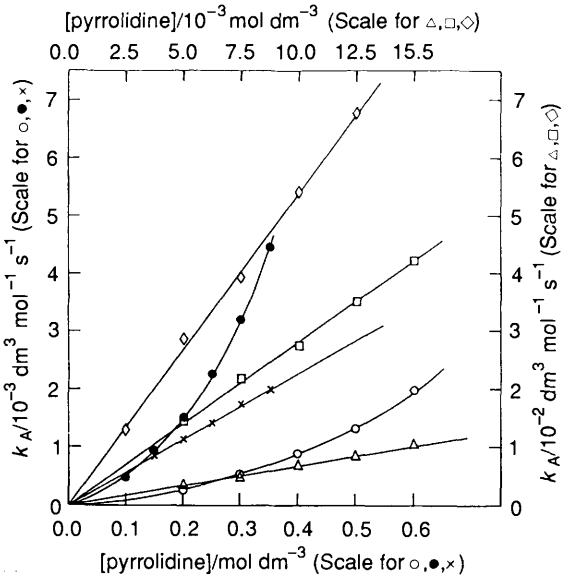


Figure 1. Plots of k_A *versus* [pyrrolidine] for the reaction of (**1**) in benzene (○), chlorobenzene (●), MeCN (△), DMF (□), DMSO (◇), MeOH (×).

Results and Discussion

Pyrrolidine reacts with substrates to give the substituted *N*-(2,4-dinitrophenyl)pyrrolidine as a coloured, substituted product. All reactions have been studied under pseudo-first-order conditions. Reactions were first order in substrate and show a higher-order dependence in pyrrolidine. Second-order rate constants (k_A) obtained by dividing the pseudo-first-order rate constant (k_0) by [pyrrolidine] are given in Tables 1 and 2. The rates for substrate (**1**) are lower than with (**2**) for the reasons previously given.[16,18] The plots of k_A *versus* [pyrrolidine] for substrate (**1**) are given in Figure 1 and they pass through the origin which indicates that reactions are wholly base catalysed in all solvents. Further it is seen that the plot for the pyrrolidinolysis in chlorobenzene shows a curvilinear response concave towards the rate constant axis which indicates that order with respect to amine is more than two whereas the plots for reactions in MeCN, DMF, DMSO, and methanol are linear indicating second-order dependence on pyrrolidine. Similar plots were also obtained with substrate (**2**).

The behaviour in chlorobenzene is similar to that observed in

Table 1. Rate constants for the reaction of pyrrolidine with *O*-aryl oxime (**1**)[a] in non-aqueous solvents.

Solvent	[Pyrrolidine]/ 10^{-2} mol dm^{-3}	$k_0/10^{-4}$ s^{-1}	$k_A/10^{-3}$ dm^3 mol^{-1} s^{-1}
Benzene[b]	20	0.49	0.24
	30	1.60	0.53
	40	3.52	0.88
	50	6.60	1.32
	60	12.13	2.02
Chlorobenzene	10	0.48	0.48
	15	1.39	0.93
	20	3.00	1.50
	25	5.70	2.28
	30	9.57	3.19
	35	15.64	4.47
MeCN	0.50	0.16	3.20
	0.75	0.37	4.93
	1.00	0.68	6.80
	1.25	1.07	8.56
	1.50	1.57	10.46
DMF	0.50	0.74	14.80
	0.75	1.64	21.80
	1.00	2.68	26.80
	1.25	4.41	35.28
	1.50	6.36	42.40
DMSO	0.25	0.32	12.80
	0.50	1.44	28.80
	0.75	2.96	39.46
	1.00	5.40	54.00
	1.25	8.54	68.32
Methanol	15	1.32	0.88
	20	2.28	1.14
	25	3.52	1.41
	30	5.22	1.74
	35	7.07	2.02

[a] At 35 ± 0.1 °C, [Substrate] = 4.0 × 10^{-5} mol dm^{-3}. [b] Data taken from reference 16.

Table 2. Rate constants for the reaction of pyrrolidine with *O*-aryl oxime (**2**)[a] in aprotic solvents.

Solvent	[Pyrrolidine]/ 10^{-3} mol dm^{-3}	$k_0/10^{-4}$ s^{-1}	$k_A/10^{-3}$ dm^3 mol^{-1} s^{-1}
Benzene[b]	50	1.09	2.18
	75	3.15	4.20
	100	6.01	6.01
	125	11.03	8.82
	150	17.95	11.97
Chlorobenzene	15	0.38	2.53
	35	2.51	7.17
	45	4.44	9.87
	55	7.44	13.53
	65	10.90	16.77
MeCN	2	0.49	24.50
	3	1.03	34.33
	4	2.03	50.75
	5	3.00	60.00
	6	4.16	69.33
DMF	2	0.75	37.50
	3	1.83	61.00
	4	3.02	75.50
	5	4.80	96.00
	6	7.04	117.33
DMSO	1.0	0.66	66.00
	1.5	1.46	97.33
	2.0	2.71	135.50
	2.5	4.20	168.00
	3.0	5.59	186.33
	4.0	9.94	248.50

[a] At 35 ± 0.1 °C, [Substrate] = 4.0 × 10^{-5} mol dm^{-3}. [b] Data taken from reference 16.

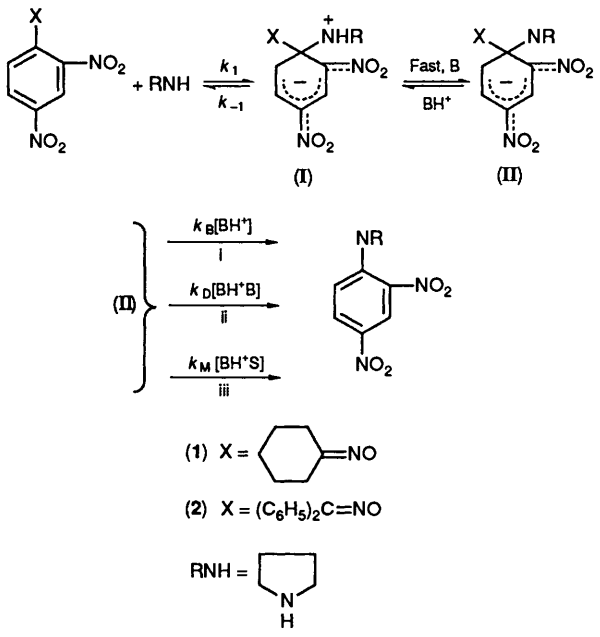
Table 3. Rate constants for pyrrolidinolysis of 1-chloro-2,4-dinitrobenzene[a] in benzene.

[Pyrrolidine]/ 10^{-4} mol dm^{-3}	$k_0/10^{-4}$ s^{-1}	k_A/dm^3 mol^{-1} s^{-1}
5	2.00	0.40
10	3.86	0.38
15	5.62	0.37
20	7.47	0.37
25	9.40	0.38
30	11.29	0.38

[a] At 35 ± 0 °C, [Substrate] = 4.0 × 10^{-5} mol dm^{-3}.

benzene.[16] In order to account for higher-order dependence in amine, we rule out the involvement of the amine dimer in the initial nucleophilic attack leading to intermediate formation as pyrrolidinolysis of 1-chloro-2,4-dinitrobenzene in benzene (Table 3) (a case where Cl^- is a very good leaving group) was not found to be base catalysed and order with respect to pyrrolidine was one. Other reasons for ruling out the dimer attack are previously given.[16] It appears that more than one amine molecule is involved in the catalytic decomposition of the intermediate. In an earlier communication[16] we invoked the participation of two amine molecules through hydrogen bonding leading to the formation of an eight-membered ring (cyclic transition state) to explain third-order dependence on amine in benzene. However, this may not be the case and the reaction might proceed through the mechanism proposed by Hirst *et al.* The reasons for changing our earlier approach are: (*i*) the formation of a cyclic transition state occurs through hydrogen bonding which is favoured due to low polarity of solvent. Thus, it is reasonable to expect that the reaction should proceed to some extent through an uncatalytic path involving a four membered cyclic transition state[19] through intramolecular hydrogen bonding. However, it is seen that most aminolysis reactions are wholly base catalysed[16,18,20,21] in non-polar aprotic solvents and exhibit an uncatalytic path[16,18,20,21] in dipolar aprotic solvents. This shows that hydrogen bonding within the transition state does not play a crucial role in catalytic decomposition. (*ii*) Observation of an inverse temperature effect similar to that observed in benzene and chlorobenzene even for the reactions in MeCN, DMF, and DMSO, which can only be explained by electrophilic catalysis by hetero-conjugates of the conjugated acid of the nucleophile with hydrogen-bond acceptor solvents.

It is possible to explain all results by assuming electrophilic catalysis occurring through conjugate–homo-conjugated–hetero-conjugated acids, Scheme 1. On applying a steady state assumption to Scheme 1, rate equation (1) is obtained and is similar to that obtained by Hirst *et al.*[14] The difference between the two is that Hirst *et al.* considered the formation of hetero-conjugates between the conjugated acid and the additives whereas we consider the formation of hetero-conjugates between BH^+ and the solvent,



Scheme 1.

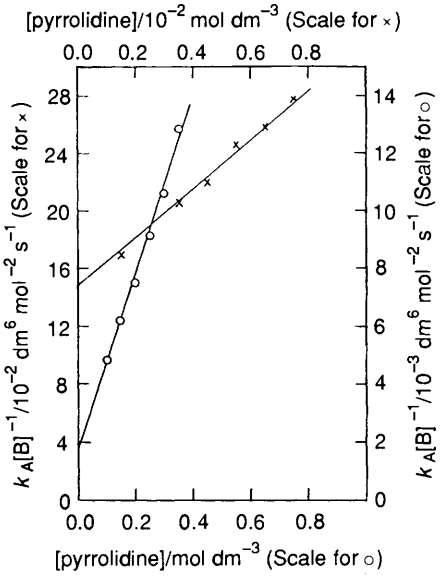


Figure 2. Plots of $k_A[B]^{-1}$ *versus* [pyrrolidine] for the reactions of *O*-aryl oxime (**1**) (○) and (**2**) (×) in chlorobenzene.

$$k_A = \frac{k_1(k_B K_B[B] + k_M K_M K_B[B] + k_D K_D K_B[B]^2)}{k_{-1} + k_B K_B[B] + k_M K_M K_B[B] + k_D K_D K_B[B]^2} \quad (1)$$

where B = nucleophile

$$K_B = \frac{[(II)][BH^+]}{[(I)][B]}, \qquad K_D = \frac{[BH^+B]}{[BH^+][B]}$$

$$K_M = \frac{[BH^+S]}{[BH^+][S]} = \frac{[BH^+S]}{[BH^+]}$$

(omitting [S] term as it represents the concentration of solvent). When $k_{-1} \gg k_B K_B[B] + k_M K_M K_B[B] + k_D K_D K_B[B]^2$ equation (1) reduces to equation (2)

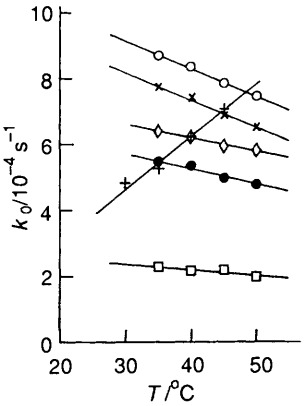


Figure 3. Plots of k_0 *versus* T for pyrrolidinolysis of (**1**) in benzene (○) at [0.55 mol dm^{-3}] PYR, chlorobenzene; (×) at [0.35 mol dm^{-3}] PYR, MeCN; (□) at [0.0175 mol dm^{-3}] PYR, DMF; (◇) at [0.015 mol dm^{-3}] PYR, DMSO; (●) at [0.01 mol dm^{-3}] PYR and MeOH; (+) at [0.3 mol dm^{-3}] PYR. (PYR stands for pyrrolidine.)

$$k_A = \frac{k_1(k_B K_B[B] + k_M K_M K_B[B] + k_D K_D K_B[B]^2)}{k_{-1}} \quad (2)$$

In solvents of low polarity and poor hydrogen-bond acceptor ability like benzene and chlorobenzene, hetero-conjugates BH^+S will not form and the reaction would proceed through routes i and ii only. Thus, by neglecting the term $k_M K_M K_B[B]$, equation (2) reduces to equation (3),

$$k_A[B]^{-1} = \frac{k_1 k_B K_B}{k_{-1}} + \frac{k_1 k_D K_D K_B[B]}{k_{-1}} \quad (3)$$

$$= k' + k''[B]$$

Thus, a plot of $k_A[B]^{-1}$ *versus* [B] for reaction in chlorobenzene should be linear and such plots (Figure 2) have been obtained. From the plots, k' and k'' are computed and given in Table 4 along with data in benzene earlier obtained.[16] The homo-conjugated acid BH^+B appears to be a better electrophile than the conjugate acid BH^+ because after donating a proton, the state B-B is more stabilized as a result of hydrogen bonding. As expected the value of k''/k' (Table 4) is greater for (**1**) than for (**2**) because X of (**1**) is a poorer nucleofuge than (**2**) and so its departure would be facilitated by BH^+B rather than BH^+. Further it is seen that the values of k'' and k' are greater for chlorobenzene than benzene. This is obviously due to the better stabilization of transition state (**I**) in the more polar chlorobenzene which increases the value of k_1 and reduces k_{-1}. However, the ratio k''/k' is in the order benzene > chlorobenzene for both the substrates. This can be explained on the basis of smaller value of K_D in chlorobenzene than benzene as a result of breaking of BH^+B to some extent in more polar chlorobenzene. Thus, the extent of reaction *via* route ii decreases from benzene to chlorobenzene.

The effect of temperature on rate (Figure 3) shows inverse behaviour *i.e.* the rate constant decreased with increase in temperature. This is expected as at higher temperature the hydrogen bond of BH^+B will break down and its concentration decreases. The energy of activation calculated is, therefore, negative and given in Table 5. High negative values of $\Delta S^{\ddagger}$ indicate the degree of crowding in the transition state when transition state (**II**) is electrophilically catalysed by BH^+B rather than BH^+.

The wholly base-catalysed pyrrolidinolysis reactions in MeCN, DMF, and DMSO which are second order in amine, also unexpectedly show an inverse temperature effect (Figure 3). This could be explained on the basis of the reaction proceeding

Table 4. Values of third-order rate coefficient (k' in benzene, chlorobenzene, methanol, k''' in MeCN, DMF, DMSO) and fourth-order rate coefficient (k'') for pyrrolidinolysis of (**1**) and (**2**) at 35 ± 0.1 °C along with α[a] and β[a] values.

Solvent	α	β	k' or $k'''/10^{-4}$ dm^6 mol^{-2} s^{-1}	$k''/10^{-4}$ dm^9 mol^{-3} s^{-1}	k''/k' or k''' dm^3 mol^{-1}
Reactions of (**1**)					
Benzene	0.00	0.10	2.5	50	20.00
Chlorobenzene	0.00	0.07	18	296	16.48
MeCN	0.19	0.31	6 780	—	—
DMF	0.00	0.69	28 600	—	—
DMSO	0.00	0.76	54 500	—	—
Methanol	0.93	0.62	57.6	—	—
Reactions of (**2**)					
Benzene			250	3 700	14.8
Chlorobenzene			1 420	18 000	12.7
MeCN			120 000	—	—
DMF			176 000	—	—
DMSO			640 000	—	—

[a] Values taken from reference 20.

Table 5. Thermodynamic parameters for the pyrrolidinolysis of *O*-aryl oxime.

Solvent	E_a/kJ mol^{-1}	$-\Delta S^{\ddagger}$/JK^{-1} mol^{-1}[a]	$-\Delta H^{\ddagger}$[a]/kJ mol^{-1}
Reactions of (**1**)			
Benzene	−9.1 ± 0.29	338 ± 3.9	11.6 ± 0.29
Chlorobenzene	−9.1 ± 0.32	302 ± 2.8	11.6 ± 0.32
MeCN	−2.7 ± 0.18	257 ± 3.2	5.3 ± 0.18
DMF	−5.1 ± 0.36	253 ± 2.6	7.6 ± 0.36
DMSO	−6.0 ± 0.37	250 ± 3.4	8.6 ± 0.37
Methanol	23.0 ± 0.50	222 ± 2.5	−20.44 ± 0.50
Reactions of (**2**)			
Benzene	−9.8 ± 0.41	280 ± 2.6	12.4 ± 0.41
Chlorobenzene	−7.4 ± 0.38	250 ± 3.1	10.0 ± 0.38
MeCN	0.0 ± 0.21	225 ± 3.8	2.56 ± 0.21
DMF	−12.5 ± 0.29	261 ± 2.9	15.1 ± 0.29
DMSO	−11.5 ± 0.32	248 ± 3.5	14.1 ± 0.32

[a] At 35 °C.

through: (*i*) electrophilic catalysis by conjugate acid BH^+, route i; and (*ii*) electrophilic catalysis by hetero-conjugated acid BH^+S (formed through hydrogen bonding between BH^+ and hydrogen bond acceptor solvents, route iii). In these solvents reaction through route ii is not possible as homo-conjugated acid BH^+B cannot form in view of the high polarity of the solvents. Thus, the equation (2) changes to equation (4), which is consistent with

$$k_A = \frac{k_1 K_B (k_B + k_M K_M)[B]}{k_{-1}} \quad (4)$$

$$= k'''[B]$$

the plots obtained. Third-order rate coefficients k''' obtained are given in Table 4 and are in the order DMSO > DMF > MeCN, parallel to solvent hydrogen-bond acceptor ability.

The decrease in rate constant with increase in temperature can be explained on the basis of a decreasing value of K_M at higher temperature as a result of breakage of hetero-conjugates BH^+S. The energy of activation calculated is negative. Further, energy of activation is minimum in MeCN which being a poor hydrogen-bond acceptor, tends to form hetero-conjugates in lower concentration and, therefore, the inverse temperature effect is lowest in the MeCN and highest in DMF and DMSO which are strong hydrogen-bond acceptor solvents. It is worth mentioning that a similar inverse temperature effect has also been noted recently by Druzian *et al.*[22] for aminolysis of 2,2,2-trichloro-1-arylethanones in MeCN.

In order to find support for the concept of electrophilic catalysis by hetero-conjugates, we have investigated pyrrolidinolysis of (**1**) in methanol. It is seen for α and β values[17]* listed in Table 4 that methanol is a good proton donor. Thus, methanol molecules will associate themselves through hydrogen bonding rather than forming hetero-conjugates with BH^+. It is reasonable to expect pyrrolidinolysis to proceed through route i only and the rate equation (5) for methanol will be

$$k_A = \frac{k_1 k_B K_B[B]}{k_{-1}} = k'[B] \quad (5)$$

The results obtained conform to equation (5). The value of k' calculated from Figure 1 is given in Table 4. The rate coefficients (k_A and k') seen from the Table indicate that the reaction is significantly slower in methanol than in other dipolar aprotic solvents. This considerable decrease in rate is much more than expected on the basis of its low polarity compared with MeCN, DMF, DMSO and this in turn supports the view that in MeCN, DMF, and DMSO the reaction also occurs through route iii, where hetero-conjugates being better electrophiles, enhance the rate. In the absence of hetero-conjugates in methanol, the rates are lower. The main support for catalysis by hetero-conjugates in MeCN, DMF, and DMSO comes from the temperature studies in methanol, in which a normal temperature effect is observed (Figure 3). The energy of activation is found to be positive. Further it is seen from Table 5 that entropy of activation in methanol is least negative, which is accounted for on the basis of a comparatively lower degree of crowding in the transition state as the electrophile is only BH^+. Pyrrolidinolysis with substrate (**2**) in methanol could not be studied due to its poor solubility.

Conclusions

It is reasonable to conclude that: (*i*) homo-conjugated/hetero-conjugated acids are better electrophiles than conjugate acid;

* α = Hydrogen-bond donor ability of solvent, and β = hydrogen-bond acceptor ability of solvent.

(*ii*) in non-polar aprotic solvents homo-conjugates are effective electrophiles and in dipolar aprotic solvents, hetero-conjugates; (*iii*) in protic solvent, the mechanism is different from that in dipolar aprotic solvent of comparable polarity and in such solvents catalysis occurs through conjugate acids alone; (*iv*) hydrogen bonding plays a crucial role in determining the course of the reaction.

Experimental

Solvents were purified by standard methods. Pyrrolidine (Merck) was used after distillation and verification of boiling point. Solvents and pyrrolidine were stored over 4 Å Linde-type molecular sieves. Substrates were prepared following previously published procedures.[23,24] Stock solutions of substrate and amine were used within 24 h. The identification of the product *N*-(2,4-dinitrophenyl)pyrrolidine was carried out by use of TLC and spectral methods. Kinetic runs were carried out on a BECKMAN DU-6 spectrophotometer fitted with thermostatted cell compartments, under pseudo-first-order conditions at 375 nm (λ_{max} of aminolysis product) and 35 ± 0.1 °C. Calculations of k_0 were carried out by use of a least-squares method from a plot of log $(A_\infty - A_0)/(A_\infty - A_t)$ *versus* time, where A_∞, A_t and A_0 are the absorbances at infinity, time t and 0 respectively utilizing a DEC-2050 computer. Rate coefficients were reproducible within ±3%.

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