Aromatic Nucleophilic Substitution Reactions of Oxime Ethers with Aliphatic Primary and Secondary Amines in Benzene

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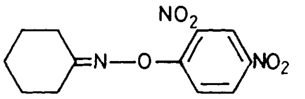
Reactions of various oxime ethers with the primary alkylamines propyl-, butyl-, pentyl-, and hexylamine and with pyrrolidine, a secondary alkyl amine, have been studied in benzene at 35 ± 0.1 °C. These reactions have all been found to be wholly base catalysed. Some reactions, especially those involving strong nucleophiles and substrates with poor leaving groups, exhibit a third-order dependence on amine concentration which has been explained on the basis of a cyclic transition-state mechanism. These reactions also show an inverse-temperature effect. Reactions with substrates which have good leaving groups and with weaker nucleophiles show a second-order dependence on amine concentration. These reactions show normal temperature effects with a low energy of activation. This low energy of activation and high negative entropy of activation support the cyclic transition-state mechanism invoked to explain these data.

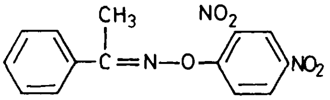
The detailed mechanism of base-catalysed aminolysis reactions of nitro-activated substrates, in both protic[1–3] and dipolar aprotic[4–9] solvents, is firmly established. However, in aprotic solvents of low polarity, such as benzene, the mechanism of aminolysis reactions is believed to be different. There are reports published in which aminolysis reactions in low polarity solvents could be explained[10–13] on the basis of a cyclic transition-state mechanism as proposed by Capon and Rees,[14] or by a modification of the Bunnett mechanism.[15–16] On the other hand, some reactions continue to be explained on the basis of electrophilic catalysis[15,17] in low-polarity solvents. In addition to this complication regarding the mechanism in aprotic solvents of low polarity, it has been observed that aminolysis reactions in some cases show a third-order[10–13,18] dependence while in other cases a second-order[10–13,15,17] dependence on amine concentration is observed. In one case even a first-order[17] dependence has been reported. The reactions in which a third-order dependence has been observed have been explained by two approaches: (i) involving an attack of amine dimer on the substrate leading to intermediate formation;[18] and (ii) attack of two molecules of amine on the intermediate in the catalytic step.[10–13] More information is therefore needed in order to arrive at some broad generalisation. With this aim we have extended our investigations on the aminolysis of oxime ethers, carried out in a range of media from aqueous[19–22] and dipolar aprotic[23] solvents to non-polar aprotic benzene. These investigations have provided results for a number of aminolysis reactions in which both the substrate and the amine have been changed so as to formulate some conclusion with regard to situations in which third- or second-order dependence on base is found. The present communication therefore reports on the aminolysis of four *O*-aryl oximes with structural variations in the oxime moiety [*viz.* the *O*-(2,4-dinitrophenyl)-substituted cyclohexanone oxime (**1**), acetophenone oxime (**2**), benzophenone oxime (**3**) and 4′-bromobenzophenone oxime (**4**)] in benzene with several primary alkyl amines and a secondary alkyl amine.

Results and Discussion

Pyrrolidinolysis of Oxime Ethers.—Pyrrolidine reacts with substrates (**1**)–(**4**) to give the substituted *N*-(2,4-dinitrophenyl)-pyrrolidine as a coloured product. The reactions are first order in substrate and show a higher order dependence on [amine].



(**1**)



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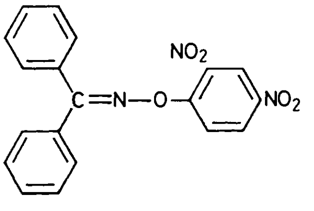
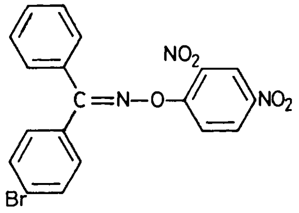


(**3**)



(**4**)

Second-order rate constants (k_A), obtained by dividing the pseudo-first-order rate constants (k_0) by [amine], are gathered in Table 1. The rates for different substrates follow the order (**4**) > (**3**) > (**2**) > (**1**) and are parallel to those found in water–acetonitrile (1:1); this was explained[20] by us by the leaving-group departure ability. The plots (Figure 1) of k_A *versus* [amine] exhibit a curvilinear response which is concave towards the rate constant axis and passes through the origin. This curved response indicates that the order with respect to [amine] is >2. Such behaviour—as observed earlier—has been explained by Banjoko,[10–13] (involving the attack of two amine molecules in the catalytic step) and by Nudelman[18] (on the basis of amine–dimer attack on the substrate). We too tend to agree with Banjoko's approach, as it is then possible to explain all the results. Nudelman's explanation does not appear plausible because: (i) the concentration of amine dimer[18] is too small; (ii) the intermediate with a six-membered ring (as shown in her Scheme)[18] should itself lead to the formation of products without involving another molecule of base in the catalytic step; and (iii) other reasons given by Banjoko.[13] The results obtained by us can be satisfactorily explained by adopting the Scheme shown. In the Scheme the reaction is proposed to proceed through three routes: (*a*) an uncatalytic route involving the formation of a four-membered[11–13] ring (**II**); (*b*) a catalytic

Table 1. Rate constants for the reactions of pyrrolidine with the oxime ethers (1)–(4).

Substrate	T/°C	[Pyrrolidine] /mol dm^{-3}	$k_0/10^{-4}$ s^{-1}	$k_A/10^{-4}$ dm^3 mol^{-1} s^{-1}
(1)	35 ± 0.1	0.20	0.49	2.47
		0.30	1.60	5.34
		0.40	3.52	8.79
		0.50	6.60	13.19
		0.60	12.13	20.22
(2)	35 ± 0.1	0.10	0.81	8.14
		0.15	2.46	16.41
		0.20	5.50	27.49
		0.25	10.24	40.96
		0.30	16.82	56.06
(3)	27 ± 0.1	0.050	1.18	23.6
		0.075	3.25	43.30
		0.100	6.74	67.40
		0.125	12.36	98.88
		0.150	19.39	129.3
	35 ± 0.1	0.050	1.09	21.74
		0.075	3.15	42.04
		0.100	6.01	60.15
		0.125	11.03	88.24
		0.150	17.95	119.66
	40 ± 0.1	0.050	1.01	20.26
		0.075	2.74	36.48
		0.100	5.80	58.00
		0.125	10.07	85.84
		0.150	16.30	108.6
(4)	35 ± 0.1	0.025	0.338	13.52
		0.050	1.78	35.68
		0.075	4.85	64.73
		0.100	9.70	97.00
		0.125	1.84	146.88

route involving the formation of a six-membered[11,13] ring (**III**), due to the participation of one molecule of amine; and (*c*) a catalytic route involving the formation of an eight-membered[10,12,13] ring (**IV**), due to the participation of two amine molecules. For aminolysis reactions in which a curvilinear dependence of k_A on [amine] was observed, Banjoko has not considered route *b* and explained his data on the basis of routes *a* and *c* only. We believe that the attack of one molecule of amine on the intermediate cannot be totally ruled out when compared with the involvement of two amine molecules. Application of the steady-state hypothesis leads to rate equation (1).

$$k_A = \frac{k_1k_2 + k_1k_3[B] + k_1k_4[B]^2}{k_{-1} + k_2 + k_3[B] + k_4[B]^2} \qquad (1)$$

Since the plots of k_A *versus* [amine] pass through the origin, $k_A = 0$ when [amine] = 0. On applying this condition to equation (1), we find that $k_1k_2/k_{-1} + k_2$ must be 0. Since k_1 indicates the rate of monomer attack on substrate, it cannot be 0, so obviously k_2 is 0, *i.e.*, the reaction does not proceed through the uncatalytic route *a*. Thus equation (1) takes the following form [equation (2)], and when $k_{-1} \gg k_3[B] + k_4[B]^2$,

$$k_A = \frac{k_1k_3[B] + k_1k_4[B]^2}{k_{-1} + k_3[B] + k_4[B]^2} \qquad (2)$$

equation (2) reduces to equations (3) and (4).

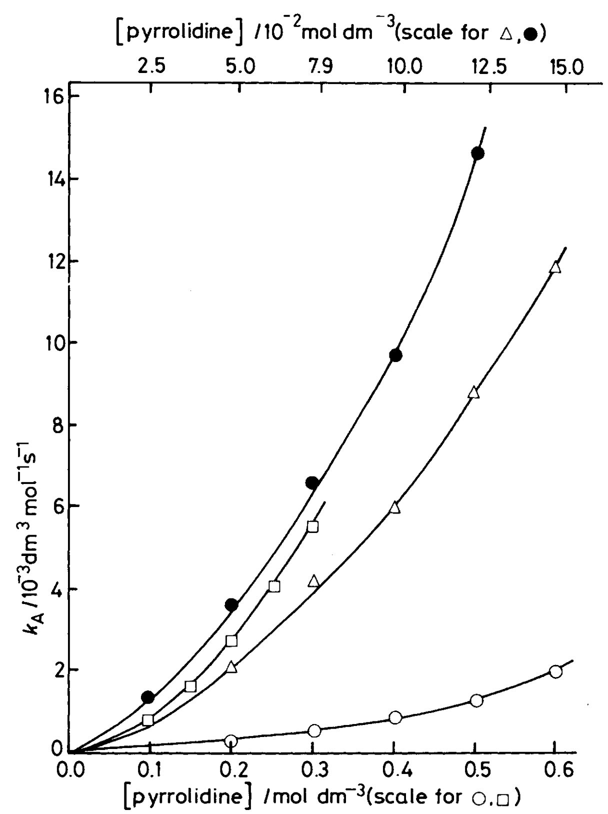
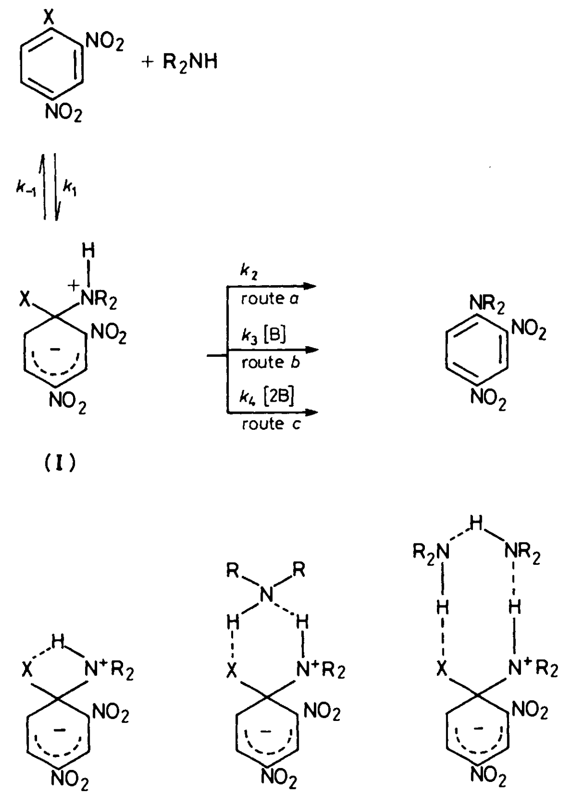


Figure 1. Plots of k_A *versus* [pyrrolidine] for the reactions of oxime ethers: ○, (**1**); □, (**2**); △, (**3**) and ●, (**4**).



(**I**)

(**II**) (**III**) (**IV**)

Scheme 1.

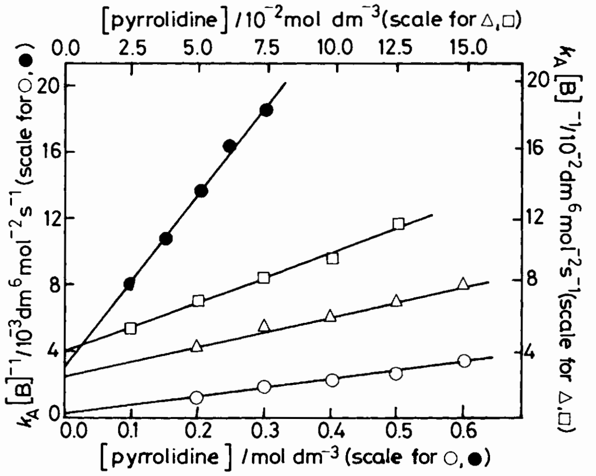


Figure 2. Plots of $k_A[B]^{-1}$ *versus* [pyrrolidine] for the reactions of oxime ethers: ○, (1); ●, (2); △, (3) and □, (4).

Table 2. Values of k' and k'' for the aminolysis of oxime ethers at 35 ± 0.1 °C.

Substrate	Amine	$k'/10^{-3}$ dm^6 mol^{-2} s^{-1}	$k''/10^{-3}$ dm^9 mol^{-3} s^{-1}	k''/k'/ dm^3 mol^{-1}
(1)	Pyrrolidine	0.25	5.0	20.0
(2)	Pyrrolidine	3.19	52.0	16.3
(3)	Pyrrolidine	25.0	370.0	14.8
(4)	Pyrrolidine	40.0	560.0	14.0
(1)	$PrNH_2$	0.60	0.73	1.21
	$BuNH_2$	0.68	0.95	1.39
	$PeNH_2$	0.61	0.80	1.31
	$HexNH_2$	0.52	0.80	1.56
(2)	$PrNH_2$	2.00	—	—
	$BuNH_2$	2.80	—	—
	$PeNH_2$	2.10	1.33	0.63
	$HexNH_2$	1.75	1.38	0.78
(3)	$PrNH_2$	3.60	—	—
	$BuNH_2$	3.80	—	—
	$PeNH_2$	4.30	—	—
	$HexNH_2$	3.80	—	—
(4)	$PrNH_2$	4.2	—	—
	$BuNH_2$	4.9	—	—
	$PeNH_2$	4.4	—	—
	$HexNH_2$	3.9	—	—

$$k_A = \frac{k_1k_3[B]}{k_{-1}} + \frac{k_1k_4[B]^2}{k_{-1}} \qquad (3)$$

$$\frac{k_A}{[B]} = \frac{k_1k_3}{k_{-1}} + \frac{k_1k_4[B]}{k_{-1}} = k' + k''[B] \qquad (4)$$

Thus the plot of $k_A/[B]$ *versus* [amine] should be linear. These plots for the pyrrolidinolysis reactions are found to be linear (Figure 2) and from the intercepts and slopes of these plots, third-order catalytic coefficients k' and fourth-order catalytic coefficients k'' have been calculated and are given in Table 2. It is seen that the ratio $k''/k' = k_4/k_3$ decreases from substrates **(1)**–**(4)** indicating that the extent of the reaction which proceeds through an eight-membered ring decreases and that through a six-membered ring increases as the leaving-group ability improves. This could be explained on the basis of partial negative charge on the oxygen atom. Due to conjugation in the oxime moiety, the partial negative charge on oxygen is in the order **(1)** > **(2)** > **(3)** > **(4)** and this is also the order of the strength of the hydrogen-bond that the oxygen atom can form with the amine hydrogen atom. It is felt that a weak hydrogen bond would facilitate the formation of a six-membered ring. Thus substrate **(4)** which has the best leaving group and forms a relatively weak hydrogen bond, shows the smallest value of k_4/k_3.

The effect of temperature was studied in one case, for pyrrolidinolysis of substrate **(3)**, and the rates were found to decrease (Table 1) with increasing temperature. The thermodynamic parameters calculated for routes *b* and *c* from the temperature variation of the catalytic coefficients k' and k'' are given in Table 3. The negative energy of activation can be explained on the basis of exothermic formation[13] of the six- and eight-membered rings. As expected, route *b* involving six-membered ring formation has a less negative energy of activation than route *c*. Both routes show unusually high negative entropies which are comparable and which point to the formation of ordered ring structures through hydrogen bonding.

Primary Alkylaminolysis of Oxime Ethers.—The oxime ethers react with primary alkyl amines propyl-, butyl-, pentyl- and hexylamine to give the coloured substitution product, *N*-(2,4-dinitrophenyl)alkylamine. The reactions are first order in substrate and exhibit a dependence of higher order on [amine]. The plots of k_0 *versus* [amine] and k_A *versus* [amine] for all the reactions pass through the origin indicating that they are wholly base catalysed. Two types of behaviour have been observed with regard to the rate dependence on [amine]. For the reactions of **(4)** and **(3)**, plots of k_A *versus* [amine] were found to be linear indicating a second-order dependence on amine. Route *c* in the Scheme, which involves two molecules of amine in the catalytic step, does not operate. Thus when the $[B]^2$ term is removed from equation (2), the following kinetic expression [equation (5)] will apply to these reactions:

$$k_A = \frac{k_1k_3[B]}{k_{-1} + k_3[B]} \qquad (5)$$

When $k_{-1} \gg k_3[B]$, equation (5) is simplifed to equation (6).

$$k_A = \frac{k_1k_3[B]}{k_{-1}} = k'[B] \qquad (6)$$

The data fit to equation (6) and the k' values calculated from the slope of k_A *versus* [amine] plots are given in Table 2. In the case of the reaction of substrate **(4)** with all amines, the linear plots of k_A *versus* [amine] adopt a curvature which is concave towards the [amine] axis at higher concentration (Figure 3). At high base concentrations, when k_{-1} and $k_3[B]$ are of comparable magnitude, equation (6) does not hold good and equation (5) applies; this accounts for the curvature.

The primary alkylaminolysis behaviour of substrate **(1)**, which has the poorest leaving group, is different from that of substrates **(3)** and **(4)**. In this case k_A *versus* [amine] plots are curvilinear and similar to those observed for the pyrrolidinolysis. The results can be explained similarly. The values of k' and k'' calculated from the linear part of the $k_A/[B]$ *versus* [amine] plots (Figure 4) are given in Table 2. These plots tend to show curvature which is concave towards the [amine] axis at higher concentrations [when k_{-1} becomes comparable in magnitude with the $k_3[B] + k_4[B]^2$ term in equation (2) at higher concentrations] and the simplified equation (4) is no longer

Table 3. Thermodynamic parameters for the aminolysis of *O*-(2,4-dinitrophenyl)benzophenone oxime.

Amine	E_a/kJ mol^{-1} k'[b]	E_a/kJ mol^{-1} k''[c]	$-\Delta S^{\ddagger}$/J K^{-1} mol^{-1}[a] k'	$-\Delta S^{\ddagger}$/J K^{-1} mol^{-1}[a] k''	$\Delta H^{\ddagger}$/kJ mol^{-1}[a] k'	$\Delta H^{\ddagger}$/kJ mol^{-1}[a] k''
Pyrrolidine	-8.38 ± 0.32	-12.76 ± 0.44	310 ± 2.7	303 ± 3.2	-10.93 ± 0.32	-15.31 ± 0.44
Butylamine	15.32 ± 0.37	—	249 ± 2.6	—	12.76 ± 0.37	—

[a] At 35 °C. [b] dm^6 mol^{-2} s^{-1}. [c] dm^9 mol^{-3} s^{-1}.

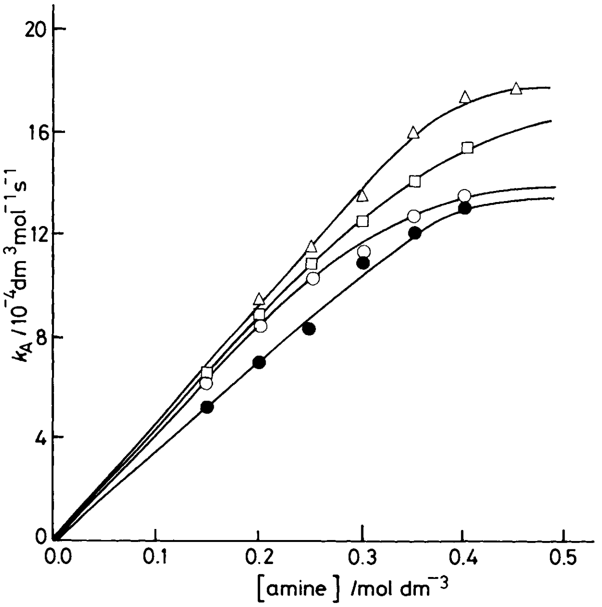


Figure 3. Plots of k_A *versus* [amine] for the reactions of oxime ether (**4**) with: propylamine, ○; butylamine, △; pentylamine, □; and hexylamine, ●.

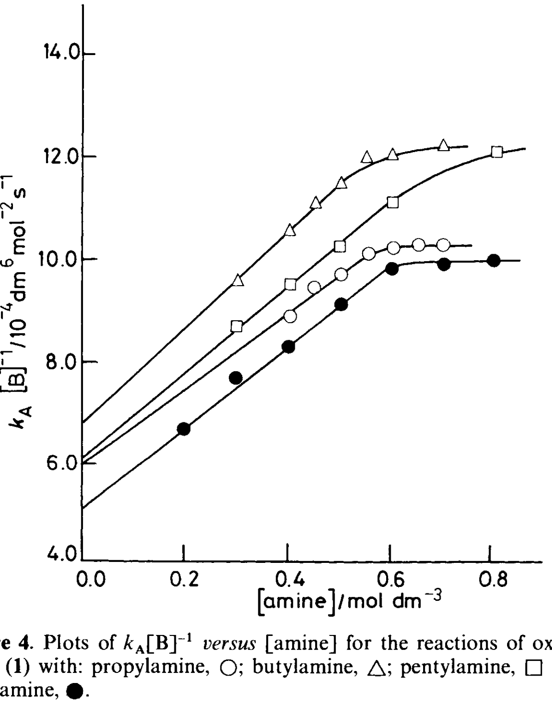


Figure 4. Plots of $k_A[B]^{-1}$ *versus* [amine] for the reactions of oxime ether (**1**) with: propylamine, ○; butylamine, △; pentylamine, □ and hexylamine, ●.

valid. Thus at higher concentrations, kinetic equation (2) applies, which accounts for the curvature.

Table 4. Second-order rate constants k_A for primary alkylaminolysis of oxime ethers.[a]

Substrate	[amine] mol dm^{-3}	k_A/10^{-4} dm^3 mol^{-1} s^{-1} PrNH$_2$	BuNH$_2$	PeNH$_2$	HexNH$_2$
(**1**)	0.20	—	—	—	1.34
	0.30	—	2.85	2.63	2.31
	0.40	3.58	4.22	3.79	3.35
	0.45	4.28	4.98	—	—
	0.50	4.9	5.76	5.1	4.6
	0.55	5.59	6.59	—	—
	0.60	6.14	7.24	6.65	5.96
	0.65	6.71	7.95	—	—
	0.70	7.20	8.65	—	6.94
	0.80	—	—	9.74	8.00
(**2**)	0.12	—	2.90	2.57	—
	0.18	3.74	4.50	3.93	3.33
	0.24	4.97	6.16	5.43	5.04
	0.30	6.24	7.73	7.52	6.55
	0.36	7.77	10.19	8.65	8.28
	0.42	—	—	11.85	10.12
	0.50	10.62	14.30	—	—
(**3**)	0.10	3.72	3.95	—	—
	0.15	5.36	6.12 5.14[b] 6.26[c]	6.5	5.85
	0.20	7.63	7.68 6.66[b] 8.29[c]	8.72	7.22
	0.25	9.23	9.72 8.35[b] 10.20[c]	10.80	9.18
	0.30	10.80	11.83 9.44[b] 12.13[c]	13.15	10.97
	0.35	12.76	—	14.80	12.08
	0.40	—	—	16.79	15.38
(**4**)	0.15	6.43	—	6.60	5.23
	0.20	8.44	9.40	9.08	7.01
	0.25	10.37	11.56	10.95	8.26
	0.30	11.32	13.50	12.56	10.95
	0.35	12.80	16.05	14.14	12.16
	0.40	13.52	17.40	15.50	13.14
	0.45	—	17.76	—	—

[a] At 35 ± 0.1 °C; [substrate] = 4.0 × 10^{-5} mol dm^{-3}. [b] At 27 ± 0.1 °C. [c] At 40 ± 0.1 °C.

The reactions of substrate (**2**) show both types of behaviour. In propyl- and butyl-aminolysis, a second-order dependence on [amine], similar to the reactions of substrates (**3**) and (**4**), is observed. The value of k' calculated from the slope of k_A *versus* [amine] plots for these two reactions are also given in Table 2. However, pentyl- and hexyl-aminolysis exhibits a behaviour similar to pyrrolidinolysis. Thus with substrate (**2**), the eight-membered ring is stabilised in addition to the six-membered ring with long-chain amines. It appears that long hydrocarbon chains tend to promote and stabilize large hydrogen-bonded structures. This is supported by the Frank and Evans[24] 'iceberg concept' of water structure in which they propose that extensive ordering of the water molecules through hydrogen-bonding occurs around the hydrocarbon chains. The values of k' and k'' calculated from $k_A/[B]$ *versus* [amine] plots are also given in Table 2.

As we determined a negative energy of activation for the pyrrolidinolysis of substrate **(3)**, in which eight-membered ring formation **(IV)** was postulated, it was thought important to determine the energy of activation in cases involving only six-membered ring formation **(III)**. Thus the butylaminolysis of **(3)** was also studied at different temperatures. This reaction shows the normal temperature effect. The thermodynamic parameters calculated are summarized in Table 3. It is seen that the energy of activation is unusually low; this indicates the formation of a six-membered ring. As compared with the energy of activation for the six-membered ring route in pyrrolidinolysis, the energy of activation for butylaminolysis is positive. This is due to the low basic character of butylamine which makes the formation of a six-membered ring less exothermic and also increases the positive energy of activation for formation of intermediate **(I)**, thus the overall energy of activation remains positive. On the other hand, pyrrolidine has a more basic character which makes formation of a six-membered ring more exothermic and also decreases the positive energy of activation for formation of intermediate **(I)**, the overall energy of activation becoming negative.

Conclusions

The investigations on aminolysis reactions in aprotic solvents of low polarity have shown that: (*a*) they proceed through routes involving hydrogen-bonded ring formation in the transition state; (*b*) they are wholly base catalysed; (*c*) eight-membered ring formation is facilitated with substrates which have poor leaving groups [substrate **(1)** aminolysis proceeded mainly through route *c* for all the amines investigated]; and (*d*) eight-membered ring formation is also facilitated with stronger nucleophiles, since pyrrolidine even reacted with substrates **(3)** and **(4)** (which have good leaving groups) mainly through route *c* whereas all the other primary amines reacted through route *b* only.

Experimental

Reagent and Solvents.—Substrates were prepared by standard procedures.[25,26] The amines propylamine (E. Merck), butylamine (Fluka), pentylamine (Fluka), hexylamine (Fluka) and pyrrolidine (BDH) were of high purity and were used after distillation and verification of b.p. Benzene (BDH) was dried over calcium chloride and sodium wire and then distilled. The amines and benzene were stored over 4 A Linde-type molecular sieves. Stock solutions of substrate and amines were prepared in benzene and used within 24 h.

Kinetic Procedure.—The reactions were studied spectrophotometrically on a UNICAM SP-500 spectrophotometer under pseudo-first-order conditions at $\lambda_{max.}$ (375 and 350 nm for pyrrolidinolysis and primary alkylaminolysis, respectively) of the aminolysis product at 35 ± 0.1 °C. Pseudo-first-order coefficients, k_0, were obtained by 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. All rate calculations were performed on a DEC-2050 computer. Rate coefficients were reproducible to within ±2%.

References

1 J. F. Bunnett and R. H. Garst, *J. Am. Chem. Soc.*, 1965, **87**, 3879.
2 C. F. Bernasconi and P. Schmid, *J. Org. Chem.*, 1967, **32**, 2953.
3 J. F. Bunnett and C. F. Bernasconi, *J. Org. Chem.*, 1970, **35**, 70.
4 M. R. Crampton, P. J. Routledge, and P. Golding, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1785.
5 J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, 1960, **82**, 665.
6 J. F. Bunnett and A. Orvik, *J. Am. Chem. Soc.*, 1970, **92**, 2417.
7 F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, 1972, **94**, 3824.
8 J. F. Bunnett, S. Sekiguchi, and L. A. Smith, *J. Am. Chem. Soc.*, 1981, **103**, 4865.
9 J. Hirst, G. Hussain, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1986, 397.
10 O. Banjoko and P. Otiono, *J. Chem. Soc., Perkin Trans. 2*, 1981, 399.
11 O. Banjoko and K. U. Rahman, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1105.
12 O. Banjoko and C. Ezeani, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1357.
13 O. Banjoko and C. Ezeani, *J. Chem. Soc., Perkin Trans. 2*, 1986, 531.
14 B. Capon and C. W. Rees, *Annu. Rep. Prog. Chem.*, 1963, **60**, 279.
15 E. T. Akinyele, I. Onyido, and J. Hirst, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1859.
16 D. Ayediran, T. D. Bamkole, J. Hirst, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1977, 597.
17 G. N. Onuoha and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1988, 971.
18 N. S. Nudelman and D. Palleros, *J. Org. Chem.*, 1983, **48**, 1607, 1613.
19 A. K. Jain, V. K. Velu, and K. N. Sarma, *React. Kinst. Catal. Lett.*, 1987, **34**, 155.
20 A. K. Jain, V. K. Velu, and K. N. Sarma, *Tetrahedron*, 1988, **44**, 2569.
21 A. K. Jain, G. Bhattacharjee, V. K. Velu, and Anurag Kumar, *Ind. J. Chem.*, in the press.
22 A. K. Jain, V. K. Gupta, and Anurag Kumar, *React. Kinet. Catal. Lett.*, in the press.
23 A. K. Jain, Anurag Kumar, and K. N. Sarma, *J. Chem. Soc., Perkin Trans. 2*, 153, 1989.
24 H. S. Frank and M. W. Evans, *J. Chem. Phys.*, 1945, **13**, 507.
25 A. I. Vogel, 'Practical Organic Chemistry,' Longman, London, 1975.
26 CIBA Ltd., Swiss Pat., 1965 (*Chem. Abstr.*, 1965, **66**, 28.501a).

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