Catalysis in Aromatic Nucleophilic Substitution. Part 1. Reactions of Piperidine with 2,4-Dinitrophenyl 4-Nitrophenyl Ether and 2,4-Dinitrophenyl Phenyl Sulphone

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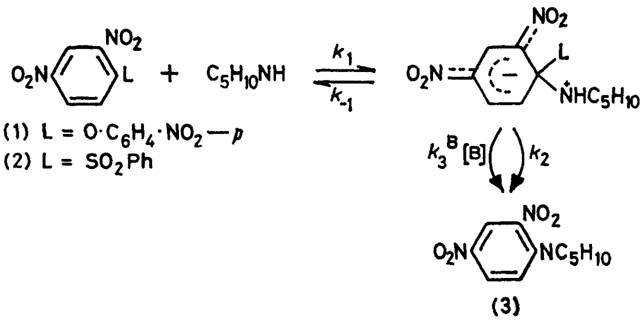
The rates of piperidino-substitution of 2,4-dinitrophenyl 4-nitrophenyl ether (1) and of 2,4-dinitrophenyl phenyl sulphone (2) in benzene at various piperidine concentrations and in the presence of some additives (dioxan, tetrahydrofuran, pyridine, acetonitrile, α-pyridone, methanol, and diazabicyclo[2.2.2]octane) indicate the possibility of catalytic decomposition of the reaction intermediate; *e.g.* clear evidence of catalysis has been obtained in the cases of piperidine and of α-pyridone. In other cases the additives seem to influence the reaction rates by affecting the nature of the solvent (tetrahydrofuran, pyridine, and acetonitrile) or giving rise to opposite, balancing effects (methanol). Dioxan does not affect the reactivity.

THE subject of nucleophilic aromatic substitution continues to attract attention.[1] Recent studies have been aimed at elucidating the catalysis mechanism in S_NAr reactions with amines of substrates containing leaving groups of low nucleofugicity,[1a] *e.g.* fluoro-,[2] alkoxy-,[3] phenoxy-,[3a,4] and cycloalkoxy- [2a] groups.

We have now extended our research [5] on S_NAr to a study of the piperidino-substitution of 2,4-dinitrophenyl 4-nitrophenyl ether (1) and 2,4-dinitrophenyl phenyl sulphone (2) in benzene (hydrophobic solvent unable to assist the decomposition of the S_NAr intermediate) in the presence of additives. The results give additional information about the relationship between the nature of the leaving group and the occurrence of basic catalysis.



SCHEME

RESULTS AND DISCUSSION

Products.—Both substrates (1) and (2) gave 2,4-dinitro-1-piperidinobenzene (3) on treatment with piperidine (PIP) in benzene, in almost quantitative yields as shown by t.l.c. and u.v.–visible (200—450 nm) spectral analysis of the reaction mixtures.

Kinetics.—Kinetic runs of piperidino-substitution of (1) and (2) at various piperidine concentrations show that the apparent second-order rate coefficients (k_A) depend

TABLE 1

Apparent second-order rate constants (k_A) for the piperidino-substitution of compounds (1) and (2) in benzene at 25 °C

(1)	10^2[PIP]/mol l^{-1}	1.02	2.03	3.25	4.07	5.12	5.69
		8.13					
	10^3k_A/l mol^{-1} s^{-1}	4.84	6.44	7.93	9.45	11.5	11.8
		15.2					
(2)	10^2[PIP]/mol l^{-1}	1.03	1.71	2.07	2.73	3.42	4.10
		5.12	5.79	6.83			
	10^2k_A/l mol^{-1} s^{-1}	1.01	1.10	1.09	1.22	1.30	1.27
		1.41	1.40	1.59			

TABLE 2

Apparent second-order rate constants (k_A) for the piperidino-substitution of compound (1) in benzene at 25 °C in the presence of additives

$\frac{10^2[\mathrm{PIP}]}{\mathrm{mol\,l^{-1}}}$	$\frac{[\mathrm{Additive}]}{\mathrm{mol\,l^{-1}}}$	$\frac{10^3k_A}{\mathrm{l\,mol^{-1}\,s^{-1}}}$	$\frac{10^3k_0{}^a}{\mathrm{l\,mol^{-1}\,s^{-1}}}$
2.08	[DIOX] 0.39	6.73	6.48
2.00	[DIOX] 1.2	6.69	6.36
2.08	[THF] 0.41	7.80	6.48
2.00	[THF] 1.2	11.1	6.36
2.00	[PYR] 1.2	16.4	6.36
2.00	[MeCN] 1.0	26.9	6.36
4.08	[DABCO] 0.025	9.83	9.44
4.08	[DABCO] 0.050	10.0	9.44

[a] Values calculated from the equation $k_A = k_0 + k_{PIP}[PIP]$ (Table 5, first line).

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[1] For recent reviews see (*a*) C. F. Bernasconi, 'MTP International Reviews of Science: Organic Chemistry, Series 1,' Butterworths, London, 1973, vol. 3, p. 33; (*b*) F. Pietra, *Quart. Rev.*, 1969, **23**, 504; J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968.

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linearly (in the situation $k_{-1} \gg k_2 + k_3^{\mathrm{PIP}}[\mathrm{PIP}]$)[1a] on the concentration of piperidine (Tables 1—5). According to Bunnett,[6] the k_3^{PIP}/k_2 values obtained (Table 5) allow the inference that there is genuine basic catalysis with (1) ($\mathrm{L} = \mathrm{O{\cdot}C_6H_4{\cdot}NO_2}$-$p$) but not definitely in the case of (2) ($\mathrm{L} = \mathrm{SO_2Ph}$).

TABLE 3

Apparent second-order rate constants (k_A) for the piperidino-substitution of compound (1) in benzene at 25 °C in presence of pyridine or of methanol

(a) [PIP] 0.020 3M								
$10[\mathrm{PYR}]/\mathrm{mol\ l^{-1}}$	1.03	2.07	3.10	4.14	6.20			
$10^3k_A/\mathrm{l\ mol^{-1}\ s^{-1}}$	7.11	7.85	8.55	9.47	10.9			
(b) [PYR] 0.207M								
$10^2[\mathrm{PIP}]/\mathrm{mol\ l^{-1}}$	2.03	3.03	4.25	6.07	9.10			
$10^3k_A/\mathrm{l\ mol^{-1}\ s^{-1}}$	7.85	9.46	11.6	14.7	20.6			
(c) [PYR] 0.414M								
$10^2[\mathrm{PIP}]/\mathrm{mol\ l^{-1}}$	2.03	3.62	4.83	6.04	8.46			
$10^3k_A/\mathrm{l\ mol^{-1}\ s^{-1}}$	9.47	12.9	15.0	17.5	22.9			
(d) [PYR] 0.620M								
$10^2[\mathrm{PIP}]/\mathrm{mol\ l^{-1}}$	2.03	3.03	4.25	6.07	9.10			
$10^3k_A/\mathrm{l\ mol^{-1}\ s^{-1}}$	10.9	13.1	16.0	20.2	28.3			
(e) [PIP] 0.051 2M								
$10[\mathrm{MeOH}]/\mathrm{mol\ l^{-1}}$	0.824	1.65	2.47	3.29	4.12	5.77	6.59	8.24
$10^3k_A/\mathrm{l\ mol^{-1}\ s^{-1}}$	8.61	6.67	5.49	4.57	3.87	3.19	2.95	2.68

TABLE 4

Apparent second-order rate constants (k_A) for the piperidino-substitution of compounds (1) and (2) in benzene at 25 °C in the presence of α-pyridone

(1)	(a) [PIP] 0.010 2M						
	$10^2[\mathrm{PONE}]$[a]$/\mathrm{mol\ l^{-1}}$	0.545	1.96	4.26	7.44	11.5	16.4
	$10^3k_A/\mathrm{l\ mol^{-1}\ s^{-1}}$	5.66	6.38	7.01	7.75	8.81	9.71
	(b) [PONE][a] 0.02M						
	$10^2[\mathrm{PIP}]/\mathrm{mol\ l^{-1}}$	2.04	3.06	4.08	5.72	8.17	
	$10^3k_A/\mathrm{l\ mol^{-1}\ s^{-1}}$	7.97	9.46	10.9	13.5	17.1	
(2)	[PIP] 0.010 1M						
	$10^2[\mathrm{PONE}]$[a]$/\mathrm{mol\ l^{-1}}$	0.542	1.96	4.25	7.43	11.5	16.4
	$10^2k_A/\mathrm{l\ mol^{-1}\ s^{-1}}$	1.20	1.35	1.53	1.67	1.90	2.03

[a] Stoicheiometric concentration.

In order to obtain information about the catalysis mechanism, we have studied the piperidino-substitution reaction of (1) in benzene at 25 °C in the presence of various additives * (Tables 2—4).

Piperidino-substitution of Compound (1) *in the Presence of Additives.*—The addition of dioxan has almost no effect on the rate constant, whereas THF, pyridine, and acetonitrile show an effect which increases in the order THF < PYR < MeCN. The effect with pyridine, only slightly greater than with THF and smaller than with acetonitrile (Table 2), seems to indicate that the low k_B/k_0 value for pyridine (Table 5) cannot be due to basic catalysis. The effects with THF, pyridine, and acetonitrile parallel the variation in polarity of the three additives.[7] Addition of these polar substances to the hydrophobic solvent (benzene) could affect the reaction rate by changing the properties of the medium, such as micro- or macro-dielectric constant, or solvation of the reagents and/or the rate-determining transition state. However, the effect exerted by pyridine confirms indirectly that the less polar but more efficient piperidine acts mainly as a basic catalyst.

TABLE 5

Linear regression analysis of apparent second-order rate constants (k_A) for the piperidino-substitution of compounds (1) and (2) in benzene at 25 °C by the equation: $k_A = k_o + k_B[\mathrm{B}]$ [a]

	Additive	$\dfrac{10^2(k_0 \pm s_0)}{\mathrm{l\ mol^{-1}\ s^{-1}}}$	$\dfrac{10^2(k_B \pm s_B)}{\mathrm{l^2\ mol^{-2}\ s^{-1}}}$	r	n	$\dfrac{k_B/k_0}{\mathrm{l\ mol^{-1}}}$
(1)	PIP	0.340 ±0.024	14.8 ±0.5	0.997 3	8	44
	PYR[b]	0.633 ±0.006	0.740 ±0.015	0.999 3	6	2.2
	PIP[c]	0.401 ±0.019	18.0 ±0.4	0.999 3	6	
	PIP[d]	0.522 ±0.029	20.7 ±0.5	0.999 2	6	
	PIP[e]	0.566 ±0.031	24.6 ±0.6	0.999 2	6	
	PONE[f,g]	0.472 ±0.015	81.0 ±3.8	0.995 6	7	240
	PIP[h]	0.488 ±0.010	15.0 ±0.2	0.999 9	6	
(2)	PIP	0.933 ±0.031	9.12 ±0.75	0.977 1	10	9.8
	PONE[g,i]	1.02 ±0.02	170 ±6	0.997 9	7	182

[a] The confidence levels for significance of k_0 and k_B are all better than 99.9%; s_0 = standard deviation of k_0; s_B standard deviation of k_B; r = correlation coefficient; k_B/k_0 referred to $k_0 = k_1k_2/k_{-1}$ for (1) 0.340×10^{-2} and for (2) $0.933 \times 10^{-2}\ \mathrm{l\ mol^{-1}\ s^{-1}}$; n = number of points. [b] At [PIP] 0.020 3M. [c] At [PYR] 0.207M. [d] At [PYR] 0.414M. [e] At [PYR] 0.620M. [f] At [PIP] 0.010 2M. [g] Values obtained by plotting k_A *versus* monomeric concentration of PONE (see ref. 2c). [h] At PONE 0.02M. [i] At [PIP] 0.010 1M.

In order to eliminate doubt about the possibility of basic catalysis by pyridine we have further investigated the behaviour of this additive. The kinetic results obtained at various pyridine concentrations, keeping the piperidine concentration constant, and *vice versa* (Table 3), show a linear dependence of k_0 and k_{PIP} (Table 5) on pyridine concentration. A least-squares treatment of k_0 and k_{PIP} as a function of pyridine concentration gives: †

$$10^3\,k_0 = 3.37 \pm 0.19 + (3.87 \pm 0.48)\,[\mathrm{PYR}] \qquad r = 0.985 \quad n = 4$$

$$10^3\,k_{\mathrm{PIP}} = 147 \pm 3 + (155 \pm 8)\,[\mathrm{PYR}] \qquad r = 0.997 \quad n = 4$$

and then

$$10^3\,k_0 \simeq 3.40\,(1 + 1.1\,[\mathrm{PYR}])$$

$$10^3\,k_{\mathrm{PIP}} \simeq 148\,(1 + 1.1\,[\mathrm{PYR}]).$$

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* Dioxan (DIOX) and tetrahydrofuran (THF) as two feeble oxygen-bases, the first apolar and the latter polar; acetonitrile (MeCN) as a dipolar aprotic solvent of low basicity; pyridine (PYR) as a nitrogen base stronger than the previous additives which might give an $E2$-like mechanism of catalytic decomposition of the intermediate;[1a] methanol (MeOH) as a protic solvent which could affect the rate of reaction by monofunctional or bifunctional catalysis; α-pyridone (PONE) as a typical bifunctional catalyst; and diazabicyclo[2.2.2]octane (DABCO) as a strong apolar nitrogen base.

† The confidence levels for significance of regression parameters are all better than 98%.

[6] J. F. Bunnett and R. H. Garst, *J. Amer. Chem. Soc.*, 1965, **87**, 3875.

[7] Solvent polarity measured by E_T values; see C. Reichardt, *Angew. Chem. Internat. Edn.*, 1965, **4**, 29; M. H. Abraham, *Progr. Phys. Org. Chem.*, 1974, **11**, 81.

Since at [PYR] = 0

$$k_0 = k_1k_2/k_{-1} \text{ and } k_{\mathrm{PIP}} = k_1k_{3\mathrm{PIP}}/k_{-1}$$

the function (1 + 1.1 [PYR]) has to be related to the k_1/k_{-1} term contained in both k_0 and k_3^{PIP}. These results indicate that perhaps pyridine affects only the first step of the reaction, presumably through specific solvation, and rule out, in this case, the possibility of an $E2$-like catalysis mechanism [1a] for this additive.

A large kinetic effect is observed with α-pyridone. In fact the apparent second-order rate constant shows a linear dependence on the concentration of monomeric pyridone [2c] and the catalytic coefficient is higher than with piperidine ($k_{\mathrm{PONE}}/k_{\mathrm{PIP}}$ *ca.* 5): this result is strongly diagnostic of a bifunctional catalysis exerted by α-pyridone taking into account the low basicity of this additive as compared with piperidine.

The results obtained in the presence of methanol are of particular interest. It is currently believed that methanol can behave in $S_{\mathrm{N}}\mathrm{Ar}$ as monofunctional [8] (electrophilic) or a bifunctional [9] catalyst; moreover, it might be expected to affect the solvent polarity by the same mechanism as observed with THF, pyridine, or acetonitrile (see above).

On the contrary, at constant piperidine concentration, the addition of increasing amounts of methanol causes a reduction of reactivity (Table 3). This result can be understood by considering the various effects that methanol can exert. These include catalysis, acceleration by a ' polarity ' effect, and interaction with the reagents. The magnitudes of all these effects obviously depend on the nature of the leaving group. It is well known [10] that for piperidino-substitution in protic solvents an important part of the activation energy is related to the desolvation of reagents. Thus, because of the solvation by methanol of the molecules of piperidine and the substrate (1) (almost unsolvated in pure benzene) being more important than the favourable effects, the reaction rate is strongly reduced.

Phenylsulphonyl as Leaving Group.—The low k_3^{PIP}/k_2 value observed for the substrate (2) (see above) does not permit a definitive decision about the catalytic effect of piperidine. The reaction of (2) with piperidine was therefore studied in the presence of α-pyridone. The large acceleration observed (Tables 4 and 5) indicates that the piperidino-substitution of the phenylsulphonyl group needs assistance, and allows us to attribute the effect caused by piperidine to genuine basic catalysis.

Conclusions.—The results as a whole allow the following conclusions to be drawn.

(i) The nucleofugicity cannot be evaluated simply in terms of k_{PIP}/k_0, because this depends markedly not only on the leaving group's ' efficient ' [5a] electronegativity but also on its bulk. We consider that the nucleofugicity is a property of the entire reacting system.

(ii) The kinetic influence of some additives such as pyridine and methanol has to be examined carefully in order to interpret unambiguously the character of these catalysts. Moreover, it is sometimes difficult to observe the catalytic effect of a base when the extent of addition is limited by its solubility and when it affects the kinetic constant within the experimental error. Thus, DABCO catalyses piperidino-substitution in benzene of 1-fluoro-2,4-dinitrobenzene, but we cannot safely say that it behaves analogously in the piperidino-substitution of (1) (see Table 2).

(iii) For the catalysis mechanism of the decomposition of the intermediate, two principal routes have been proposed: (*a*) rapid equilibrium deprotonation followed by slow leaving group expulsion, catalysed by the conjugate acid of the catalyst (SB–GA mechanism),[2e] and (*b*) concerted proton transfer and leaving group expulsion with a cyclic transition state, where the protic base acts as a bifunctional catalyst.[2b–d]

We think that also the rate-determining proton transfer and the $E2$-like mechanisms constitute different aspects of a unique general mechanism. The occurrence of one or the other depends on the position on the reaction co-ordinate of the transition state for the decomposition of the intermediate, which in turn is determined by several interlocking factors: degree of activation of the substrate, nature of the leaving group, competition between the nucleophile and the additive, geometry of the catalyst, and solvating ability of the solvent.

In the light of the results obtained with pyridine we think that the $E2$-like mechanism can be excluded. On the other hand, rate-determining proton transfer seems to be favoured in polar solvents and for less activated systems.[11] When the catalyst is a protic base, the two remaining mechanisms (SB–GA and bifunctional catalysis) differ only in relation to the timing of B–H bond formation and fission and H–L bond formation.

In the SB–GA mechanism B–H bond formation is followed by synchronous B–H bond cleavage and L–H bond formation ($\mathrm{B}\cdots\mathrm{H}\cdots\mathrm{L}$) involving the same hydrogen atom; thus the reaction proceeds through the formation of two ions of opposite charge (ion-pairs or free ions) and strongly solvated.

In the bifunctional catalysis mechanism bond fission and formation are concerted and occur in a cyclic transition state.

The latter reaction pathway, in which charge separation is avoided, should be highly favoured in a poorly solvating solvent such as benzene.

EXPERIMENTAL

Synthesis and Purification of Compounds.—2,4-Dinitrophenyl 4-nitrophenyl ether (1),[12] 2,4-dinitrophenyl phenyl sulphone (2),[13] 2,4-dinitro-1-piperidinobenzene (3),[14] piper-

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[8] F. Pietra and A. Fava, *Tetrahedron Letters*, 1963, 1535.

[9] Ref. 1*a*, p. 52.

[10] J. F. Bunnett and R. J. Morath, *J. Amer. Chem. Soc.*, 1955, **77**, 5051.

[11] C. F. Bernasconi and C. L. Gehriger, *J. Amer. Chem. Soc.*, 1974, **96**, 1092.

[12] J. F. Bunnett, E. W. Garbisch, jun., and K. M. Pruitt, *J. Amer. Chem. Soc.*, 1957, **79**, 385.

[13] R. W. Bost, J. O. Turner, and R. Norton, *J. Amer. Chem. Soc.*, 1932, **54**, 1985.

[14] E. Lellmann and W. Geller, *Ber.*, 1888, **21**, 2281.

idine,[5c] benzene,[5c] dioxan,[5c] THF,[15] acetonitrile,[16] and methanol [5c] were prepared and/or purified according to reported methods. Pyridine (Carlo Erba) was left over potassium hydroxide for several days and fractionally distilled. DABCO (Fluka) and α-pyridone (Merck) were recrystallized from benzene.

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described; [5] $\lambda_{max.}$ and log $\varepsilon_{max.}$ of (3) were, respectively, 376 nm and 4.17. The concentration of substrates was 10^{-4}M; those of piperidine and of additive are reported in the Tables. The rate constants are accurate within ±3%.

[6/1957 *Received*, 20*th October*, 1976]

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[15] W. Bunge, in Houben–Weyl–Müller, 'Methoden der Organischen Chemie,' 4th edn., ed. G. Thieme, Stuttgart, 1959, **1/2**, 765.

[16] A. Weissberger, 'Technique of Organic Chemistry,' Interscience Publ., 2nd edn., 1955, 7, 435.