Base Catalysis in the Reactions between 2-Fluoro-6-nitrobenzothiazole and Aliphatic Amines in Benzene

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The kinetic features of the title reactions have been studied. The experimental second-order rate constants increase on increasing the initial concentration of amine used. In some cases an overall third order is observed. The catalytic power of α-pyridone emphasizes the presence of bifunctional catalysis. The data are discussed in terms of steric requirements. Temperature effects on base-catalysed and uncatalysed reactions are discussed.

THE reactivity of 2-halogenobenzothiazoles with nucleophilic reagents has been studied [1] and it is widely accepted that these heteroaromatic 'aza-activated' substrates may react *via* a pathway similar to that usually accepted for nitro-activated nucleophilic aromatic substitution.

Many workers [2-5] have studied S_NAr dehalogenation substitution reactions with aromatic and aliphatic amines. In contrast to the situation where the nucleophile is an anion, in the reactions of halogenonitrobenzenes with aliphatic amines in aprotic solvents it is possible to have complex rate equations in which the concentration of nucleophile appears with an exponent varying from 1 to 2. This is an indication of the presence of further base attack in a rate-determining step. More evidence of a base-catalysed process is also obtained by adding non-nucleophilic bases, *e.g.* α-pyridone,[6,7] 1,4-diaza[2.2.2]bicyclo-octane,[8-11] pyridine,[9-11] *etc.*, to the reaction mixture. These usually enhance the nucleophilic substitution reaction rates.

Evidence for this mechanism is given by varying the leaving group and it is observed that the higher reaction orders in amine are obtained for the 'poorer' leaving groups and for reactions carried out in aprotic, weakly polar solvents. However, when the substrates are nitro-activated halogenobenzenes some complications are present, *e.g.* for an *o*-nitro-group, steric inhibition of resonance,[12] internal catalysis of ammonium proton abstraction,[5,13] *etc.* have to be discussed. Our interest in this problem prompted us to use an aza-activated substrate and we have studied the reactions between 2-fluoro-6-nitrobenzothiazole and some aliphatic amines in benzene.

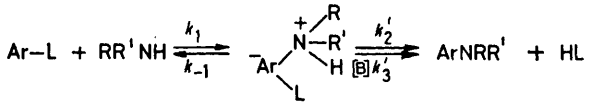
RESULTS

All reactions quantitatively yield the corresponding 2-amino-derivatives as shown by elemental and u.v. spectral analysis (see Experimental section). From kinetic runs (spectrophotometrically performed) the first-order kinetic constants k' were calculated and from these values the second-order kinetic constants ($k_A = k'/[\text{amine}]$) were obtained.

Table 1 reports the results for reactions between 2-fluoro-6-nitrobenzothiazole and piperidine, 2-methylpiperidine, n-butylamine, s-butylamine, and t-butylamine. It is observed for every amine that the experimental second-order constant (k_A) increases on increasing the initial concentration of amine with a constant initial concentration of benzothiazole derivative. The variations observed are higher than the experimental error (±3%). Large changes in k_A are observed (Table 2) for reactions between the benzothiazole derivative and s-butylamine when various amounts of α-pyridone are added initially to the reaction mixture.

DISCUSSION

The treatment of the kinetic results is based on the Scheme [5] where L is the leaving group and R′ = or



SCHEME

≠H. The k_A values reported in Table 1 increase linearly with the amine concentration, following equation (1) where [B] refers to the nucleophilic reagent.

$$k_A = k_2 + k_3[B] \quad (1)$$

Following Bernasconi's treatment the linear relationship of k_A and the base concentration can be rationalized by assuming that $k_3'[B] \ll k_{-1} + k'_2$ and $k'_2 \ll k_{-1}$ and it is possible to write equation (2) which gives the ratio

$$\frac{\text{rate}}{[ArL][RR'NH]} = k_A = k_1k_2'/k_{-1} + k_1k_3'[B]/k_{-1} \quad (2)$$

$k_3' : k_2'$ from experimental k_2 and k_3 values (uncatalysed, 1 mol^{-1} s^{-1}, and catalysed constant, l^2 mol^{-2} s^{-1}, respectively). These were obtained by least square calculations and are collected in Table 3 along with the correlation coefficients.

Bunnett [14] favours the ratio $k_3' : k_2'$ as a test for the presence and importance of the base catalysed process ($k_3' : k_2' \geqslant 50$) to avoid confusion with variations owing to medium changes ($k_3' : k_2' \leqslant 5$). Although this separation between base catalysis and medium effect can be discussed, for the data here reported the values of the ratio $k_3' : k_2'$ are always higher than 50 and base catalysis seems to be present.

It is interesting to note the temperature dependence of k_2 and k_3. Very low values for activation energies are calculated from Table 3 for reactions between 2-fluoro-6-nitrobenzothiazole and t-butylamine (ΔE^* 7.2 ± 0.2 kJ mol^{-1}) and s-butylamine (ΔE^* 14.5 ± 0.8 kJ mol^{-1}) on the basis of k_3 values; $\Delta E^* = 24.4 \pm 0.8$ kJ mol^{-1} on the basis of k_2 values for the reaction with s-butylamine. From Table 3 large negative values of ΔS^* are also calculated: $-\Delta S^*$ 218.9 ± 3 (k_2 for s-

butylamine), 218.9 ± 2 (k_3 for s-butylamine), and 254.1 ± 0.4 J K^{-1} mol^{-1} (k_3 for t-butylamine). These activation parameters are quite unusual for S_NAr reactions and some association pre-equilibria between the reactants should also be discussed, but we have not direct evidences of their presence, at least in our experimental conditions.

However k_2 and k_3 are influenced differently by enhancement of temperature, so that it is possible to minimize the catalysed or uncatalysed process by simple temperature variations. In fact the reactions with t-butylamine is overall third order at lower temperatures only (Table 1): at 80 °C the third order is not reached for low [t-butylamine] values. At this temperature the plot of k_A *versus* [t-butylamine] shows typical curvature. In the literature the temperature is often chosen to avoid experimental difficulties and so full comparisons are not possible.

When α-pyridone is added to the reaction mixture (Table 2) the rates of s-butylamine substitutions are enhanced in proportion to the initial amount of α-pyridone, regarded as monomeric.[7,15] In these cases equation (2) becomes (3) where k_3'' covers both catalysed

$$k_A = k_3'' + k_3^{Py}[\text{Pyridone}] \quad (3)$$

and uncatalysed substitution processes and k_3^{Py} refers to the rate of product formation from a zwitterionic intermediate by α-pyridone catalysis. A graphical evaluation (by least squares method) of k_3^{Py} leads to a value 15.8 ± 0.8 (in l^2 mol^{-2} s^{-1}) (r 0.997 0). The catalytic power of α-pyridone is higher than that of the amine used ($k_3^{Py} : k_3^{B}$ 82), and $k_3^{Py} : k_2$ ratio is 4,630. For

TABLE 1

Rates of reactions between 2-fluoro-6-nitrobenzothiazole (5×10^{-5}M) and amines in benzene

Temp. 25 °C:							
10^2[piperidine]/M		2.04	4.21	10.5	14.0		
k'/s^{-1}		0.126	0.467	2.56	4.70		
k_A/l mol^{-1} s^{-1}		6.17	11.1	24.4	33.6		
Temp. 25 °C:							
10^2[2-methylpiperidine]/M		0.365	2.28	9.13	13.7		
k'/s^{-1}		5.84×10^{-5}	1.34×10^{-3}	1.92×10^{-2}	4.22×10^{-2}		
k_A/l mol^{-1} s^{-1}		1.60×10^{-2}	5.88×10^{-2}	2.10×10^{-1}	3.08×10^{-1}		
Temp. 25 °C							
10^2[2-methylpiperidine]/M		38.7	74.9	147			
k'/s^{-1}		3.45×10^{-1}	1.18	4.28			
k_A/l mol^{-1} s^{-1}		8.92×10^{-1}	1.58	2.91			
Temp. 25 °C							
10^2[n-butylamine]/M	1.74	3.49	5.97	8.63	11.9		
$10^2k'/s^{-1}$	0.108	0.405	1.14	2.37	4.34		
$10k_A$/l mol^{-1} s^{-1}	0.622	1.16	1.91	2.74	3.65		
Temp. 25 °C:							
10^2[s-butylamine]/M		3.87	9.33	13.4	17.06		
$10^3k'/s^{-1}$		0.414	1.97	3.94	6.07		
10^2k_A/l mol^{-1} s^{-1}		1.07	2.11	2.94	3.56		
Temp. 35 °C:							
10^2[s-butylamine]/M		5.39	6.23	8.77	15.3		
$10^3k'/s^{-1}$		0.93	1.18	2.26	6.24		
10^2k_A/l mol^{-1} s^{-1}		1.73	1.90	2.58	4.08		
Temp. 50 °C:							
10^2[s-butylamine]/M		0.604	0.852	1.25	1.41		
$10^3k'/s^{-1}$		1.52	2.80	5.65	6.92		
10^2k_A/l mol^{-1} s^{-1}		2.52	3.29	4.52	4.91		
Temp. 20 °C:							
10[t-butylamine]/M		0.812	1.74	3.48	6.76		
$10^3k'/s^{-1}$		0.281	1.53	3.92	24.0		
10^3k_A/l mol^{-1} s^{-1}		3.46	8.79	17.0	35.5		
Temp. 25 °C:							
10[t-butylamine]/M		0.946	2.04	2.99	4.19		
$10^3k'/s^{-1}$		0.437	2.08	4.66	8.88		
10^3k_A/l mol^{-1} s^{-1}		4.62	10.2	15.6	21.2		
Temp. 35 °C:							
10[t-butylamine]/M		0.515	0.780	1.96	3.35	4.60	7.35
$10^3k'/s^{-1}$		0.143	0.329	2.08	6.40	11.9	30.9
10^2k_A/l mol^{-1} s^{-1}		0.278	0.422	1.06	1.91	2.59	4.20
Temp. 50 °C:							
10[t-butylamine]/M			1.93	3.30	4.52		
$10^3k'/s^{-1}$			2.35	7.03	13.0		
10^2k_A/l mol^{-1} s^{-1}			1.22	2.13	2.87		
Temp. 80 °C:							
10^2[t-butylamine]/M			0.139	0.535	2.29	3.54	
$10^5k'/s^{-1}$			0.0698	0.605	4.47	8.11	
10^3k_A/l mol^{-1} s^{-1}			0.502	1.13	1.95	2.29	

reactions between 1-fluoro-2,4-dinitrobenzene and piperidine in benzene at 25 °C Pietra [7] found k_3^{Pip} 600 and k_3^{Py} 3,600 l^2 mol^{-2} s^{-1} (rate constants for processes

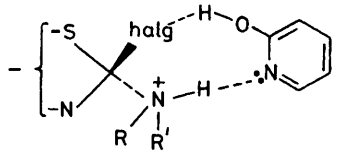
TABLE 2

Reactions (at 25 °C) between 2-fluoro-6-nitrobenzothiazole and s-butylamine in C_6H_6 and in the presence of α-pyridone: [2-fluoro-6-nitrobenzothiazole] 5.0 × 10^{-5}M, [s-butylamine] = 1.11 × 10^{-2}M

10^3[α-pyridone]/M [a]		2.26	3.53	5.17	6.82
$10^3k'$/s^{-1}	0.0380	0.398	0.603	0.958	1.30
$10k_A$/l mol^{-1} s^{-1}	0.0342	0.359	0.543	0.863	1.17

[a] Assumed to be monomeric.[15]

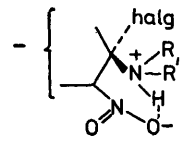
catalysed by piperidine and by α-pyridone, respectively) and the ratio $k_3^{Py} : k_3^{Pip}$ is 6.0. The high value of k_3^{Py} emphasizes the catalytic ability, in our system, of α-pyridone in removing hydrogen halide from the zwitterionic intermediate, probably by bifunctional catalysis [species (A)]. This fact is in agreement with the well known ability of the fluoride ion as a leaving group in S_NAr reactions carried out in protic solvents which makes the behaviour of fluoride very different from that of other leaving halides.



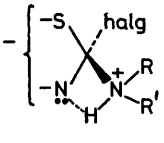
(A)

The presence of an *o*-nitro group in benzene decreases the possibility of observing a base-catalysed process because of intramolecular catalysis [5] (or more probably by genuine steric hindrance). When an ' aza-group ' is present some similar phenomena are also possible but they are more difficult because in halogeno-*o*-nitrobenzenes it is possible to have a six-atom ring (B) but in 2-halogenobenzothiazoles the ring [of four atoms (C)] is strained.

The benzothiazole system is certainly a simpler model for consideration of the steric requirements than the benzene system in which an *o*-nitro group is present. In our case support for this concept is the very similar power (see $k_3 : k_2$ ratios) of catalysis of secondary (piperidine) and primary (n-butylamine) amines. When an *o*-nitro group is present the secondary amine is more susceptible to base catalysis than the primary amine.[16] If α-branching in the amine is considered, the ratios $k_{2(piperidine)} : k_{2(2\text{-methylpiperidine})}$ and $k_{2(n\text{-butylamine})} : k_{2(s\text{-butylamine})}$ are 42 and 3.5, respectively, in agreement



(B)



(C)

with the increased size of the entering groups; retardation is observed despite the electronic effect of the methyl group. At 80 °C the extrapolated value of k_2 for s-butylamine is 1.74 × 10^{-2} and the ratio $k_{2(s\text{-butylamine})} : k_{2(t\text{-butylamine})}$ of 51 is in agreement with

TABLE 3

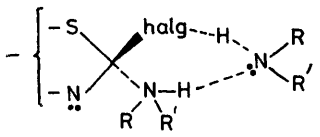
k_2 and k_3 values (see text) for reactions between 2-fluoro-6-nitrobenzothiazole and amines in C_6H_6

Amine	k_2 */l mol^{-1} s^{-1}	k_3 */l^2 mol^{-2} s^{-1}	r	Temp. (°C)	k_3/k_2
Piperidine	1.45 ± 0.7	226 ± 7.6	0.9990	25	207 ± 105
2-Methylpiperidine	(0.44 ± 0.3) × 10^{-1}	1.98 ± 0.04	0.9990	25	85 ± 59
n-Butylamine	(1.20 ± 0.2) × 10^{-2}	2.98 ± 0.03	0.9998	25	256 ± 45
s-Butylamine	(3.41 ± 0.4) × 10^{-3}	(1.90 ± 0.03) × 10^{-1}	0.9995	25	57 ± 8
s-Butylamine	(4.46 ± 0.5) × 10^{-3}	(2.38 ± 0.05) × 10^{-1}	0.9996	35	54 ± 7
s-Butylamine	(7.27 ± 0.8) × 10^{-3}	(3.00 ± 0.07) × 10^{-1}	0.9994	50	42 ± 6
t-Butylamine	*a*	4.86 × 10^{-2} [b]		20	∞
t-Butylamine	*a*	5.04 × 10^{-2} [b]		25	∞
t-Butylamine	*a*	5.57 × 10^{-2} [b]		35	∞
t-Butylamine	*a*	6.37 × 10^{-2} [b]		50	∞
t-Butylamine	3.4 × 10^{-4} [c]	0.17 [c]		80	500

* Errors are standard deviations. [a] Not evaluated. [b] Mean from Table 1, estimated error ±3%. [c] Graphical evaluation.

that observed for measurements of steric factors using other amines.

The usually accepted mechanism for the base catalysed step for halogenonitrobenzene systems, involves an acid–base equilibrium and the expulsion of the halide ion from the intermediate (D) in a concerted step as in an elimination reaction.[17] The presence of methyl groups



(D)

in the nucleophile retards the base-catalysed step slightly more than the process measured by the k_2 values. The catalytic power of amines is apparently independent of the basicity (which is enhanced by the presence of a methyl group in the α-position) but is depressed by steric hindrance. The ratios $k_{3(piperidine)} : k_{3(2\text{-methylpiperidine})}$ and $k_{3(n\text{-butylamine})} : k_{3(s\text{-butylamine})}$ are, respectively, 114 and 15.7. Larger differences are present for the more rigid piperidine system than for butylamine. At 80 °C the value for k_3 for s-butylamine is 5.0 × 10^{-1} and the ratio $k_{3(s\text{-butylamine})} : k_{3(t\text{-butylamine})}$ is 2.9.

TABLE 4

Products of reactions between 2-fluoro-6-nitrobenzothiazole and amines in benzene

Amines	M.p. (°C) (solvent)	Yield (%)	Formula	Analysis (%)	$\lambda_{max.}$ [a]	log ε [b]
Piperidine	170—171 (MeOH)	94	$C_{12}H_{13}N_3SO_2$	Required: C, 54.8; H, 4.95; N, 15.95; S, 12.15 Found: C, 54.5; H, 5.0; N, 15.9; S, 12.0	370	4.291
α-Methylpiperidine	101—102 (MeOH)	87	$C_{13}N_{15}N_3SO_2$	Required: C, 56.3; H, 5.45; N, 15.15; S, 11.55 Found: C, 56.0; H, 5.4; N, 15.2; S, 11.6	370	4.305
n-Butylamine	138 (MeOH)	88	$C_{11}H_{13}N_3SO_2$	Required: C, 52.55; H, 5.2; N, 16.7; S, 12.75 Found: C, 52.8; H, 5.4; N, 16.6; S, 12.6	355	4.240
s-Butylamine	134 (MeOH)	85	$C_{11}H_{13}N_3SO_2$	Required: C, 52.55; H, 5.2; N, 16.7; S, 12.75 Found: C, 52.3; H, 5.2; N, 16.9; S, 12.9	355	4.228
t-Butylamine	70—71 (light petroleum)	90	$C_{11}H_{13}N_3SO_2$	Required: C, 52.55; H, 5.2; N, 16.7; S, 12.75 Found: C, 52.3; H, 5.1; N, 16.8; S, 12.6	355	4.212

[a] nm in benzene. [b] l mol^{-1} cm^{-1}.

EXPERIMENTAL

Materials.—6-Nitro-2-fluorobenzothiazole was prepared and purified by literature procedures.[18] Benzene, amines, and α-pyridone were commercial products purified by the usual methods.

Kinetics.—The reaction between 2-fluoro-6-nitrobenzothiazole and piperidine were estimated by following the appearance of 6-nitro2-piperidylbenzothiazole by a spectrophotometric stopped-flow method using a Gibson–Durrum apparatus. In other reactions the appearance of products was followed using Zeiss DMR 21 or Perkin-Elmer 504 u.v. spectrophotometers. For each run spectrophotometric analysis often with long reaction times showed absorption spectra identical with those of authentic solutions of products (see Table 4).

Products.—The 2-aminobenzothiazole derivatives were obtained in almost quantitative yield in separate preparative experiments under the same conditions as the kinetic runs. Physical properties and elemental analyses are reported in Table 4. N.m.r. spectral data are as expected. M.p.s are uncorrected.

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