Catalysis in Aromatic Nucleophilic Substitution. Part 6.† Reactions of 2-Methoxy-3-nitrothiophen with Cyclic Secondary Amines in Methanol and Benzene

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The kinetics of the reactions of 2-methoxy-3-nitrothiophen (I) with pyrrolidine in methanol and benzene and with perhydroazepine in benzene have been studied as a function of amine concentration. The pyrrolidino-substitution of (I) in methanol is second-order overall whereas the corresponding piperidino-substitution is base-catalysed. The reactions of (I) with pyrrolidine, piperidine, and perhydroazepine in benzene are all catalysed by the nucleophile and by diazabicyclo[2.2.2]octane but the pattern of catalysis depends on the ring size of the cyclic amine. The data are most consistent with the specific base–general acid mechanism for base catalysis. The remarkable difference in behaviour between pyrrolidine and piperidine is suggested to stem from conformational effects concerning the amino-moieties in the transition state for the general acid-catalysed departure of methoxy-group.

WE have recently shown that the piperidino-substitution of 2-methoxy-3-nitrothiophen (I) is catalysed by methoxide ion in methanol [1] and by piperidine in benzene,[2] respectively. These observations can be rationalised on grounds of equation (1) which is appropriate to the mechanism indicated in Scheme 1.[3]

$$k_A = \frac{k_1k_2 + k_1\Sigma_i k_3^{Bi}[B^i]}{k_{-1} + k_2 + \Sigma_i k_3^{Bi}[B_i]} \qquad (1)$$

Base catalysis has been observed in methanol [1] because the product-forming steps designated by k_2 and $k_3^{Bi}[B_i]$ are slower than or as slow as the reversion of the intermediate (XH) to reactants. According to equation (1) this implies a curvilinear dependence of the second-order kinetic constant, k_A, on base concentration. On going from methanol to benzene the k_2/k_{-1} ratio is strongly reduced and the reaction responds linearly to catalysis by piperidine.[2]

The ring size of a secondary cyclic amine such as piperidine could, in principle, influence the steric interactions in the reaction area and if the rate coefficients pertaining to the specific steps of mechanism are significantly changed, a different pattern of catalysis is observed.

In order to give information on these effects we now report a kinetic study of the reactions of (I) with pyrrolidine in methanol and benzene and with perhydroazepine in benzene. We also report kinetic data for the corresponding reactions of 2-bromo-3-nitrothiophen (III). Some aminodemethoxylation reactions have been carried out in the presence of 1,4-diazabicyclo[2.2.2]-octane (DABCO).

RESULTS AND DISCUSSION

Products.—Compounds (I) and (III) gave the substitution products (II) on treatment with pyrrolidine in methanol and benzene and with perhydroazepine in benzene, respectively, in high yields (>95%) as indicated by t.l.c. and u.v.–visible (200—450 nm) spectral analysis of the reaction mixtures at infinity.

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Kinetic Data.—The kinetic data for the amino-substitution reactions of (I) and (III) in methanol or benzene at 20 °C as a function of amine concentration are summarized in Tables 1—4. The results of rate-constant measurements for the aminodemethoxylation reaction of (I) in the presence of DABCO are reported in Table 5.

TABLE 1

Kinetic data [a] and activation parameters [b] for the reaction of 2-methoxy-3-nitrothiophen (I) with pyrrolidine in methanol

[PYR]/M	0.204	0.510	1.02	0.204	0.204
10^3k_A /l mol^{-1} s^{-1}	1.73 [c]	1.75 [c]	1.79 [c]	3.72 [d]	7.23 [e]

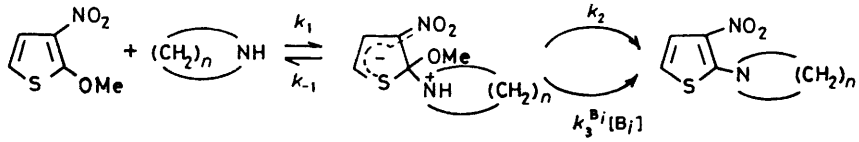
[a] Rate constants are accurate to within ±3%. At λ 408 nm (log ε 3.89). [b] At 20 °C, $\Delta H^{\ddagger}$ 12.5 kcal mol^{-1}, $\Delta S^{\ddagger}$ −34 cal mol^{-1} K^{-1}. [c] At 20.0 °C. [d] At 30.0 °C. [e] At 40.0 °C.

Reaction of (I) *with Pyrrolidine in Methanol.*—The apparent second-order kinetic constant, k_A, for the pyrrolidino-substitution of (I) in methanol at 20 °C (Table 1) is independent of the initial pyrrolidine concentration. Thus the reaction is second-order overall, first-order both in substrate and in nucleophile, and there is no measurable catalysis by the amine acting as a base. This corresponds to the situation where $k_A = k_1$ and the formation of intermediate is rate determining.[3]

The change from piperidine to pyrrolidine therefore causes the spectacular variation from $k_2/k_{-1} \ll 1$ to $k_2/k_{-1} \gg 1$.[3]

Such a curious difference between two amines so similar in structure has precedent [4] but the cause of such behaviour is not well understood.[3] In principle, the smaller k_2/k_{-1} ratio for piperidine could be a consequence of a smaller k_2, or of a larger k_{-1}, or a combination of both. If the k_{-1} values for the two amines are about the same,[5] the cause of the different response to catalysis should be the k_2 parameter.

According to Bernasconi [6] a possible factor of steric nature which has the effect of reducing k_2 is the hindrance, by an *ortho*-substituent, of the developing resonance in the structure (IV), a canonical form of the



(I) (B$_j$) (XH) (II)

n = 4 : B$_j$ = pyrrolidine (PYR)
n = 5 : B$_j$ = piperidine (PIP)
n = 6 : B$_j$ = perhydroazepine (PHA)

SCHEME 1

TABLE 2

Kinetic constants [a] for the reaction of 2-methoxy-3-nitrothiophen (I) with pyrrolidine in benzene at 20 °C

[PYR]/M	0.0282	0.0334	0.0426	0.0470	0.0564	0.0760	0.0940	0.141	0.188	0.248	0.282
$10^3 k_A$/l mol^{-1} s^{-1}	0.916	1.10	1.33	1.54	1.79	2.43	2.99	4.46	5.64	6.91	7.99

[a] Rate constants are accurate to within ±3%. At λ 398 nm (log ε 3.88).

TABLE 3

Kinetic constants [a] for the reaction of 2-methoxy-3-nitrothiophen (I) with perhydroazepine in benzene at 20 °C

[PHA]/M	0.115	0.207	0.297	0.396	0.495	0.594	0.758
$10^5 k_A$/l mol^{-1} s^{-1}	2.32	4.32	6.45	8.99	11.5	14.5	19.5

[a] Rate constants are accurate to within ±3%. At λ 404 nm (log ε 3.85).

product (II). The potential importance of this effect greatly depends on how close the respective transition state is to the intermediate. Since the hyper-*ortho*-relation [7] between 2-methoxy- and 3-nitro-groups in (I) makes the two transition states involved in the addition–elimination mechanism of Scheme 1 closely resemble the reaction intermediate (XH),[1] the observed trend of k_2/k_{-1} ratios could be accounted for on the grounds of a steric effect which concerns specifically the piperidino-moiety in the transition state for the formation of (II).

TABLE 4

Kinetic constants [a] for the reactions of 2-bromo-3-nitrothiophen (III) with amines in methanol or benzene at 20 °C

Solvent	Amine	$10^4 k_A$/l mol^{-1} s^{-1}
Methanol	PYR	3.08 [b]
	PIP	1.14 [c]
Benzene	PYR	16.4 [d]
	PIP	3.78 [e]
	PHA	2.96 [f]

[a] Rate constants are accurate to within ±3%. [b] Value calculated from activation parameters (at 20 °C $\Delta H^{\ddagger}$ 13.2 kcal mol^{-1} and $\Delta S^{\ddagger}$ −29 cal mol^{-1} K^{-1}). [c] D. Spinelli, G. Consiglio, and A. Corrao, *J. Chem. Soc., Perkin Trans. 2*, 1972, 1866. [d] Value calculated at [PYR] = 0. Due to a medium effect (*cf.* ref. 16) k_A increases linearly with increasing amine concentration. A least-squares treatment of the experimental data according to the equation $k_A = k_0 + k_{PYR}$[PYR], gives $10^3 k_0 = 1.64 \pm 0.01$ and $10^3 k_{PYR} = 2.25 \pm 0.07$ (n 4, r 0.999). [e] *Cf.* ref. 16. [f] Average value of measurements at low amine concentrations (0.02—0.1M) where k_A does not change significantly with increasing [PHA].

Aminodemethoxylation Reactions of (I) *in Benzene.*—The reaction of (I) with pyrrolidine in benzene at 20 °C gives a curvilinear plot of k_A *versus* [PYR] and, by standard methods,[8] from the kinetic data of Table 2 one can obtain k_1 0.048 l mol^{-1} s^{-1}, $k_2/k_{-1} = 0$, and $k_3/k_{-1} = 0.70$ l mol^{-1}.

The reaction pathway from the intermediate (XH) to either transition state leads to charge neutralization and both k_{-1} and k_2 are expected to increase strongly on going from methanol to benzene.

TABLE 5

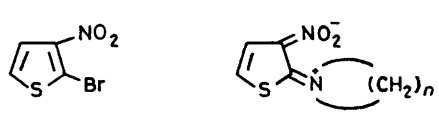
Kinetic constants [a] for the reactions of 2-methoxy-3-nitrothiophen (I) with amines in benzene, at 20 °C, in the presence of DABCO

[DABCO]/M [b]	0.06	0.1	0.2	0.28
$10^3 k_A$/l mol^{-1} s^{-1}	1.37	1.52	2.02	2.40
[DABCO]/M [c]	0.1	0.2	0.3	0.4
$10^4 k_A$/l mol^{-1} s^{-1}	1.80	2.59	3.31	4.13
[DABCO]/M [d]	0.05	0.1	0.15	0.2
$10^5 k_A$/l mol^{-1} s^{-1}	6.07	7.66	9.27	11.1

[a] The rate constants are accurate to within ±3%. [b] [PYR] 0.0334M. [c] [PIP] 0.106M. [d] [PHA] 0.198M.

Apparently the increase in k_{-1} is comparatively greater than that in k_2 and the relation $k_2 \gg k_{-1}$ is reversed on changing from the first to the second solvent.

The reaction of (I) with perhydroazepine in benzene is catalysed by the amine (Table 3). A plot (not shown) of k_A *versus* [PHA] closely resembles that observed in the corresponding piperidino-substitution,[2] where a slight upward curvature was interpreted as a medium effect superimposed on a genuine catalytic effect. Treating

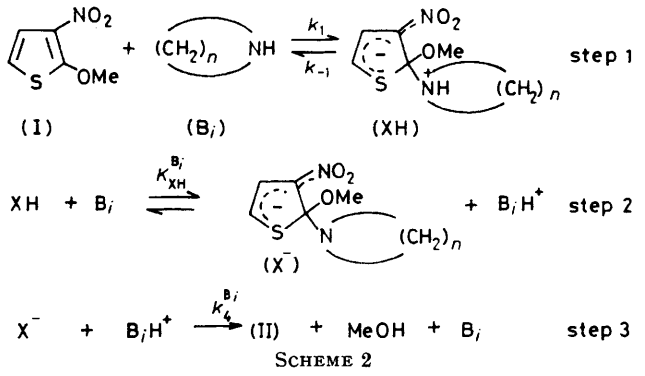


(III) (IV)

the kinetic data of Table 3 as previously [2,*] gives $k_1k_3^{PHA}/k_{-1} = 1.92 \times 10^{-4}$ l^2 mol^{-2} s^{-1} at 20 °C. The corresponding value for the piperidino-substitution is [2] 8.48×10^{-4} l^2 mol^{-2} s^{-1}.

As described in the Experimental section it is possible to estimate the reactivity ratios in nucleophilic attack, expressed as k_1, for each pair of cyclic amines. Thus in benzene we obtain $k_1^{PYR}/k_1^{PIP} = 3.4$ and $k_1^{PIP}/k_1^{PHA} = 1.3$. Assuming $k_{-1}^{PYR} = k_{-1}^{PIP} = k_{-1}^{PHA}$ † one calculates $k_3^{PYR}/k_3^{PIP} = 12$ and $k_3^{PIP}/k_3^{PHA} = 3.4$, or $k_3^{PYR} : k_3^{PIP} : k_3^{PHA} = 40 : 3.4 : 1$.

These results suggest that the base-catalysed product-forming step ($k_3^{B_i}$) is controlled by the ring size of the cyclic amine, in accord with the above interpretation concerning k_2.



SCHEME 2

The Mechanism of the Base-catalysed Step ($k_3^{B_i}$).—The mechanism of the $k_3^{B_i}$ step involves the removal of the ammonium proton from the intermediate (XH): this could happen in different ways, *e.g.* (a) rate-limiting proton abstraction by the base to form deprotonated intermediate, followed by rapid leaving-group expulsion, (b) rapid equilibrium deprotonation followed by rate-limiting general acid-catalysed detachment of the nucleofuge (SB–GA mechanism), or (c) concerted proton transfer and leaving-group detachment with bifunctional catalysis by the amine.

In mechanisms (a) and (c) the deprotonation of the intermediate is completely or in part rate-limiting. Since the process is essentially diffusion controlled,[5] it is not understandable why $k_3^{B_i}$ should depend on the size of cyclic amine. In particular, the above ratios indicate that $k_3^{B_i}$ for perhydroazepine would be from one to two orders of magnitude lower than the diffusion limit, and there is no evident reason for this.‡

In the SB–GA mechanism shown in Scheme 2, $k_3^{B_i}$ represents the product of the acid dissociation constant of zwitterionic intermediate ($K_{XH}^{B_i}$) and the specific rate constant for the general acid-catalysed nucleofuge expulsion ($k_4^{B_i}$). Assuming about the same acidity for the intermediates (XH) derived from the various amines (see below), the difference in the $k_3^{B_i}$ parameter must stem from a difference in $k_4^{B_i}$ values. This would imply such a transition state for the separation of the methoxy-group from (X$^-$) (step 3) that the ring size of the cyclic amine must play a critical role.§

The reactions of (I) with the three cyclic amines in benzene are also catalysed by DABCO. The *homogeneous* reactivity ratio $k_3^{B_i}/k_3^{DABCO}$ (see Experimental section), which represents the relative catalytic efficiency of B$_i$ and DABCO in step 3 of Scheme 2, is respectively, 13 for pyrrolidine, 2.2 for piperidine, and 1.1 for perhydroazepine.

In principle, the source of the remarkable difference between the three cyclic amines might involve *only* the amino-moiety of the σ-adduct (X$^-$) in that the developing resonance in the transition state leading to (II) is sterically hindered to an extent which depends on how 'large' is the amine ring. However, the results obtained in the presence of DABCO show that the observed pattern of catalysis must also involve the amine conjugate acid B$_i$H$^+$. In fact if the $K_{XH}^{B_i}/K_{XH}^{DABCO}$ ratio does not depend on the cyclic amine, as it is reasonable to suppose, the relative catalytic efficiency as measured by $k_4^{B_i}/k_4^{DABCO}$ is determined by the different extent in which, for example, PYR,H$^+$ and DABCO,H$^+$ general acid-catalyse the leaving group detachment from the *same* intermediate (X$^-$). Since the three cyclic amines have very similar pK_a values [11] the reason why this ratio should vary with changing amine size could be the different steric hindrance by the carbon-bound amino-moiety to the approach of DABCO,H$^+$.

This effect can be generalized to include the homogeneous couples B$_i$–B$_i$H$^+$ (for example, PYR–PYR,H$^+$), being the more severe the bulkier the cyclic amine.

We have so far referred to the source of the different behaviour of the three cyclic amines as to an undefined steric effect depending on the ring size of amine. As shown by an examination of molecular models, this effect can only stem from conformational differences which apparently produce additional steric compressions in the reaction area.¶ As also suggested by the above

* A least-squares treatment of kinetic data by the equation $k_A/[PHA] = k_0 + k^{PHA}[PHA]$ gives $k_0 = k_1k_3^{PHA}/k_{-1}$ and $k^{PHA} = 8.62 \times 10^{-5}$ l^3 mol^{-3} s^{-1}.

† This assumption is suggested by the results of measurements of k_{-1} values on analogous systems [5] (see above).

‡ We have recently shown that the piperidino-substitutions of (I),[1] of methyl 2-methoxy-3-nitrothiophen-5-carboxylate,[9] and of 5-acetyl-2-methoxy-3-nitrothiophen [9] are base-catalysed *in methanol* through the SB–GA mechanism.

§ A similar remarkable difference between pyrrolidine and piperidine has been noted by Bunnett and his co-workers.[10] For reactions of these two amines with 2,4-dinitro-1-naphthyl ethyl ether in dimethyl sulphoxide solution, they were able to observe step 3 as a separate process and to measure the $k_4^{B_i}$ values. They found $k_4^{B_i}$ to be *ca.* 10^4 times greater for pyrrolidine than for piperidine.[10b]

¶ As suggested by Bunnett *et. al.*[10b] the unshared electron pair on the amino-nitrogen of (X$^-$) must be antiperiplanar with respect to the rupturing C–O bond in the transition state. In this situation the most likely conformation of the carbon-bound amino-moiety, which in the transition state approaches the largely coplanar geometry of structure (IV), has the *N*-thienyl substituent equatorial with respect to the piperidine ring. Examination of molecular models of (X$^-$) and (IV) reveals that the equatorial hydrogens at the 2′- and 6′-positions of the piperidine moiety protrude laterally toward the 3-nitro-group and the sulphur, more than do the 2′- and 5′-hydrogens of the pyrrolidine moiety in the corresponding structures. An analogous difference involves the axial hydrogens protruding toward the methoxy-moiety in (X$^-$).

$k_3^{B_i}$ values the conformational difference is more crucial for pyrrolidine and piperidine than for piperidine and perhydroazepine.

EXPERIMENTAL

Synthesis and Purification of Compounds.—Compounds (I),[12] (II),[13] ($n = 5$), (III),[14] piperidine,[13] methanol,[15] and benzene [15] were prepared and/or purified according to the methods reported. Pyrrolidine and perhydroazepine were purified by the same procedure used for piperidine.[13] Compounds (II) ($n = 4$), m.p. 86—87 °C, and $n = 6$, m.p. 51—52 °C (from ligroin–benzene), were prepared according to the general method of ref. 13 and gave correct elemental analyses.

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described.[16] The concentrations used were 10^{-3}M for substrates and those indicated in the Tables for cyclic amines.

Evaluation of Kinetic Parameters.—We have assumed that the variation in relative nucleophilicity of pyrrolidine and piperidine, k_1^{PYR}/k_1^{PIP}, as the leaving group is changed from bromine to methoxy, is independent of the solvent. Thus, using $k_1 = 8.15 \times 10^{-4}$ l mol^{-1} s^{-1} for piperidino-substitution of (I) in methanol [1] and the kinetic constants of Tables 1 and 4 we obtain $(k_1^{PYR}/k_1^{PIP})_I/(k_1^{PYR}/k_1^{PIP})_{III} = 0.79$ in methanol and $(k_1^{PYR}/k_1^{PIP})_I = 0.79 \times (k_1^{PYR}/k_1^{PIP})_{III} = 3.4$ in benzene.

On account of the minor variation (see text) from piperidine to perhydroazepine, we have assumed $(k_1^{PIP}/k_1^{PHA})_I = (k_1^{PIP}/k_1^{PHA})_{III} = 1.3$ (Table 4) in benzene.

Rearrangement of equation (1) for the case where B_i = PYR or DABCO affords equation (2). A least-squares

$$\frac{k_A}{k_1 - k_A} = \frac{k_3^{PYR}}{k_{-1}}[PYR] + \frac{k_3^{DABCO}}{k_{-1}}[DABCO] \quad (2)$$

treatment of the kinetic data in Table 5 (line 2) according to equation (2) where $k_1 = 4.8 \times 10^{-2}$ l mol^{-1} s^{-1} (see text) gives $k_3^{DABCO}/k_{-1} = 0.055$ (statistically corrected).

The other two amino-substitutions respond linearly to catalysis by DABCO and the kinetic data obey equation (3) where B_i = PIP or PHA. A least-squares treatment of

$$k_A = \frac{k_1 k_3^{B_i}}{k_{-1}}[B_i] + \frac{k_1 k_3^{DABCO}}{k_{-1}}[DABCO] \quad (3)$$

data in Table 5 (line 4 or 6) gives $k_1 k_3^{DABCO}/k_{-1}$ 3.85×10^{-4} and 1.67×10^{-4} l^2 mol^{-2} s^{-1} for piperidine and perhydroazepine, respectively.

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