Secondary Steric Effects in Piperidinodebromination of Some 2-Bromo-4-R-5-nitrothiophene-3-carboxamides in Methanol

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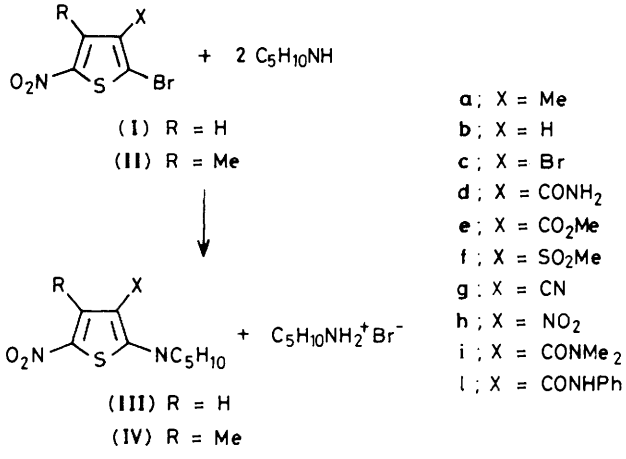
The rates of piperidinodebromination of some *N*-substituted 2-bromo-4-R-5-nitrothiophene-3-carboxamides (R = H and Me) have been measured in methanol. The kinetic data obtained, as well as the investigation of the restricted rotation about the C–N bond of the amino group of some of the above carboxamides by dynamic n.m.r. spectroscopy, have shown the occurrence of steric interactions which force the 3-carboxamido group to rotate about its bond with the aromatic ring. This causes a reduced activation and a kinetic secondary steric effect.

It has been shown [1] that when the logarithmic kinetic constants for the piperidino-substitutions in methanol of some 2-bromo-3-X-5-nitrothiophenes (**Ia—h**) are plotted against the corresponding values for the reactions of 2-bromo-3-X-4-methyl-5-nitrothiophenes (**IIa—h**), an excellent linear correlation is observed, except for X = $CONH_2$. In fact, the point relative to this substituent strongly deviates from the straight line and must be excluded from the correlation.

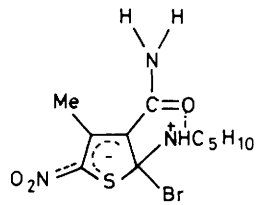
The geometry of the carboxamido group in the transition state and in the reaction intermediate (**V**) involves a steric interaction between the 4-methyl group and one of the two hydrogen atoms of the amino group.[1]

In this situation, the $CONH_2$ substituent, to which the 'internal' conjugation confers some rigidity, is probably forced to rotate about the CO–C(3) bond and thus to be no longer coplanar with the aromatic ring. This gives rise to both reduced conjugation and activation and determines a retarding secondary steric effect.

In order to confirm this interpretation we have studied the reactions of some *N*-substituted 2-bromo-5-nitro-4-R-thiophene-3-carboxamides (**Ii,l**) and (**IIi,l**) with piperidine in methanol and determined the ^1H n.m.r. spectra in [$^2H_6$]DMSO of the carboxamides (**Id**) and (**IId**) and of the corresponding *NN*-dimethyl derivatives (**Ii**) and (**IIi**).



Scheme.



(V)

Results and Discussion

Reaction Products.—2-Bromo-3-X-4-R-5-nitrothiophenes (**Ii,l**) and (**IIi,l**) on treatment with piperidine in methanol gave the corresponding piperidino derivatives (**IIIi,l**) and (**IVi,l**) in high yield, as shown by t.l.c. and u.v.-visible spectral analysis (200—450 nm) of the reaction mixtures. The relevant physical data are shown in Table 1.

Kinetic Data.—Rate constants and activation parameters for the piperidino-substitution reactions of compounds (**Id,i,l**) and (**IId,i,l**) in methanol are reported in Table 2. All the reactions were first-order both in substrate and piperidine, and thus the formation of the intermediate (S_NAr mechanism) is the rate-limiting step.

The kinetic data (Table 3) show that when the two hydrogen atoms of the amido group of (**Id**) are substituted by two methyl groups as in (**Ii**) the reactivity in piperidino-substitution is reduced by a factor of 8. Even if a diminution in reactivity, on changing from (**Id**) to (**Ii**), is expected, on grounds of augmented internal conjugation of the amido group, the decrease in rate observed appears rather large. In fact, the 'analogous' substitution in 5-bromo-4-nitrothiophene-2-carboxamide causes a reduction in reactivity of only 10%.[2]

These findings are easily accounted for on the assumption that the amido group in (**Ii**) is not coplanar with the aromatic ring because of the steric interaction between one of the two methyls of the $CONMe_2$ group and the hydrogen atom at C(4) [(**VI**)], analogously to what has been previously suggested for the case of (**Id**).

In spite of the greater 'absolute' bulkiness of CONHPh compared with $CONH_2$, compound (**Il**) is a little more reactive than (**Id**) (Table 3) as expected on the basis of the reduced

Table 1. Physical and spectroscopic data[a] for piperidino-derivatives (**IIIi,l**) and (**IVi,l**)

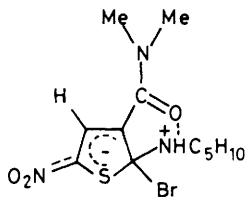
Compound	Crystallization solvent	Colour	M.p. (°C)	$\lambda_{max.}$/nm[b]	log ε[b]
(**IIIi**)	Methanol	Orange	124—125	436	4.31
(**IIIl**)	Light petroleum–benzene	Orange	163—164	435	4.24
(**IVi**)	Ligroin–benzene	Orange	105	435	4.38
(**IVl**)	Methanol–dioxane	Yellow	225—226	436	4.38

[a] All the compounds gave correct analyses. [b] In methanol.

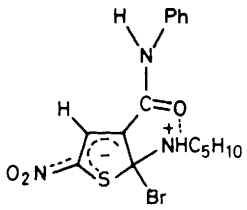
Table 2. Kinetic data and activation parameters for the reactions of compounds (**Ii,l**) and (**IIi,l**) with piperidine in methanol, at various temperatures[a]

Compound	10^4k/l mol^{-1}s^{-1} (T/K in parentheses)			$\Delta H^{\neq}$/kJ mol^{-1}[b]	$\Delta S^{\neq}$/J K^{-1} mol^{-1}[c]
(**Ii**)	3.41 (293.2)	7.79 (303.2)	16.3 (313.1)	57.3	115
(**Il**)	34.5 (293.1)	72.0 (303.1)	140 (313.1)	51.0	118
(**IIi**)	1.25 (293.2)	2.87 (303.1)	6.22 (313.1)	59.0	118
(**IIl**)	3.65 (293.2)	8.26 (303.1)	16.6 (312.9)	55.6	119

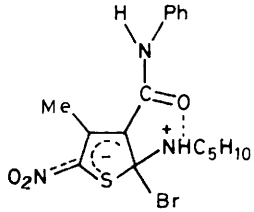
[a] The rate constants are accurate to within ±3%. [b] At 293.2 K; the maximum error is 2.1 kJ mol^{-1}. [c] At 293.2 K; the maximum error is 7 J mol^{-1} K^{-1}.



(**VI**)



(**VII**)

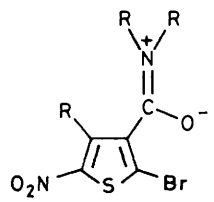


(**VIII**)

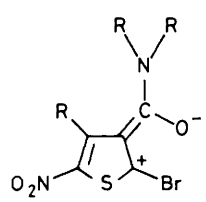
Table 3. Kinetic constants and reactivity ratios for the reactions of compounds (**Id,i,l**) and (**IId,i,l**) with piperidine in methanol

X	10^4k_I[a]	10^4k_{II}[a]	k_{II}/k_I[a]
$CONH_2$[b]	27.8	2.57	0.092
$CONMe_2$	3.42	1.25	0.37
CONHPh	34.8	3.68	0.11

[a] Calculated at 293.2 K from activation parameters. [b] Values from ref. 1.



(**IX**)



(**X**)

R = H or Me

internal conjugation of the *N*-substituted amino group. In this case, the transition state for the piperidino-substitution reaction would be exemplified by (**VII**) where the phenyl group is far away from both the reaction centre and the hydrogen atom at C(4).

The substitution of a hydrogen atom with a methyl group at C(4) gives rise for (**III**) to an effect similar to that observed for (**IId**) because of the steric interaction between the hydrogen atom of the amino group and the methyl group at C(4) [(**VIII**)].

Since the *NN*-dimethylcarboxamido group is not coplanar with the aromatic ring in (**Ii**), the introduction of a methyl group at C(4) does not involve a significant enhancement of the steric inhibition of the resonance of the 3-X substituent: therefore, a k_{II}/k_I ratio of only 0.37 is observed.

This interpretation is supported by the ^{1}H n.m.r. spectra in [$^2H_6$]DMSO (Table 4) of compounds (**Id,i**) and (**IId,i**).

In fact, the spectroscopic data show that the two hydrogen atoms of the amido group in (**Id**) are diastereotopic at room temperature and this suggests some steric hindrance to the coplanarity (and thus of the resonance) of this group with the thiophene ring caused by the hydrogen atom at C(4).

Of course, the two hydrogen atoms of the amido group are diastereotopic at room temperature in the corresponding 4-methyl-substituted compound (**IId**), but in this case the rotational barrier about the C–N bond is expectedly higher. The same phenomenon is observed, *a fortiori*, for *NN*-dimethylcarboxamides (**Ii**) and (**IIi**).

As a matter of fact, the ground state of thiophene-3-carboxamides would be better represented by the contributor (**IX**) than by (**X**).

The above findings, although concerned with the ground state, fit the kinetic data very well. In fact, on going from the initial to the transition state (addition step of the S_NAr mechanism), according to the change in hybridization of the C(2) atom of the thiophene ring, the steric compression of the amido group in (**Id**) is reduced and therefore the coplanarity of this group with the ring is possible. However, when the 4-position is occupied by a methyl group as in (**IId**) the coplanarity is hindered and the resulting steric secondary effect slows down significantly the piperidino-substitution reaction.

The case for (**Ii**) is analogous to that of (**Id**). The steric inhibition of resonance occurs already in the 2,3,5-trisubstituted compound (**Ii**) and therefore it does not significantly increase in the tetrasubstituted compound (**IIi**).

All the data presented in this paper show that, as also suggested by molecular models, the favourite conformation of

Table 4. Chemical shifts δ for N-H and N-Me, coalescence temperatures, and energy of rotation about C–N bond of thiophene-3-carboxamides (**Id,i**) and (**IId,i**) in [$^2H_6$]DMSO

	δ					
Compound	N-H_A[a]	N-H_B	N-Me_A[a]	N-Me_B	T_c/K[b]	$\Delta G^{\neq}$/kJ mol^{-1}[c]
(**Id**)	8.00	7.75			322	68.8
(**Ii**)			3.01	2.91	344	76.2
(**IId**)	7.90	7.77			326	71.6
(**IIi**)			3.04	2.88	398	87.3

[a] H_A is the hydrogen atom pointing toward the oxygen atom of the carbonyl group; Me_A is the methyl group pointing toward the oxygen atom of the carbonyl group. [b] ±1 K. [c] ±0.4 kJ mol^{-1}.

the thiophene-3-carboxamides studied, both in the ground state and in the transition state, is that in which the carbonyl group of $CONH_2$ ($CONMe_2$) points toward the C(2) atom of the thiophene ring (*s-cis* conformation).

Experimental

Synthesis and Purification of Compounds.—Piperidino-derivatives[3] (**III**) and (**IV**), methanol,[4] and piperidine[3] were prepared and /or purified according to the methods reported. The other compounds were prepared as below and gave correct elemental analyses.

2-*Bromo*-5-*nitrothiophene*-3-NN-*dimethylcarboxamide* (**Ii**). Compound (**Ii**) was obtained from 5-nitrothiophene-3-*NN*-dimethylcarboxamide by mercuriation and bromination according to the method used for the synthesis of other thiophene compounds.[5] The crude product was purified by chromatography on a column of silica gel with benzene–ethyl acetate (1:1) as eluant, m.p. 113—114 °C (from light petroleum–benzene).

5-*Nitrothiophene*-3-NN-*dimethylcarboxamide*. 5-Nitrothiophene-3-carboxylic acid[6] (6.2 g) was converted into the acyl chloride (by thionyl chloride) and then dissolved in anhydrous benzene (20 ml). This solution was added dropwise, at 5—10 °C, to a solution of 2M-dimethylamine in anhydrous benzene (100 ml), with stirring. After being kept at 10 °C for 30 min, the mixture was poured into cold water. The organic phase was separated, washed successively with 5M-HCl, 2M-NaOH, and water, and dried ($CaCl_2$). The compound obtained after distillation of the solvent was crystallized from methanol, m.p. 118—119 °C.

2-*Bromo*-5-*nitrothiophene*-3-*carbanilide* (**II**). 2-Bromo-5-nitrothiophene-3-carboxylic acid[7] (4 g) was converted into the acyl chloride as above and dissolved in anhydrous benzene (20 ml). To this solution was added dropwise, at 5—10 °C, a solution of aniline (7.4 g) in anhydrous benzene (15 ml), with stirring. After being kept at 10 °C for 30 min, the precipitated solid was filtered off and the filtrate evaporated. The residue was washed with water and crystallized from methanol, giving the compound, m.p. 153—154 °C.

2-*Bromo*-4-*methyl*-5-*nitrothiophene*-3-NN-*dimethylcarboxamide* (**IIi**). Compound (**IIi**) was obtained from 4-methyl-5-nitrothiophene-3-*NN*-dimethylcarboxamide by mercuriation and bromination as above, m.p. 95—96 °C (from ligroin).

4-*Methyl*-5-*nitrothiophene*-3-NN-*dimethylcarboxamide*. 4-Methyl-5-nitrothiophene-3-carboxylic acid was converted into the acyl chloride and then into the NN-*dimethylamide* as above, m.p. 93 °C (from ligroin).

4-*Methyl*-5-*nitrothiophene*-3-*carboxylic acid*. Methyl 4-methyl-5-nitrothiophene-3-carboxylate[1] (4.5 g) was hydrolysed by boiling for 48 h in the presence of concentrated H_2SO_4 (100 ml) and water (200 ml) to give the acid, m.p. 230 °C (from methanol–dioxane).

2-*Bromo*-4-*methyl*-5-*nitrothiophene*-3-*carbanilide* (**III**). Compound (**III**) was obtained from 2-bromo-4-methyl-5-nitrothiophene-3-carboxylic acid[1] as above, m.p. 195—196 °C (from methanol–dioxane).

Kinetic Measurements.—The kinetic measurements, carried out in the presence of piperidine hydrochloride to avoid competitive methoxydebromination,[5] were taken spectrophotometrically as previously described.[8] The concentrations used were 10^{-3}M-substrate, 3×10^{-2}—3×10^{-1}M-piperidine, and 3×10^{-2}M-piperidine hydrochloride.

^{1}H *N.m.r. Spectra.*—The spectra were recorded at 80 MHz with a Bruker WP-80 spectrometer equipped with variable temperature accessories. All spectra were calibrated against Me_4Si as internal standard.

Acknowledgements

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