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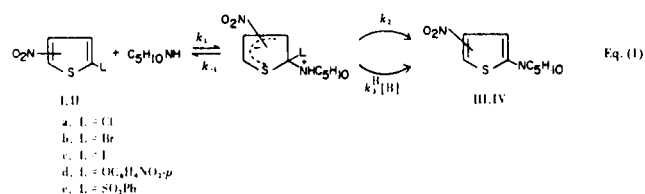
The rates of piperidino substitution of some 2-L-3-nitrothiophenes (I) and 2-L-5-nitrothiophenes (II) (L = Cl, Br, I, OC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>-*p*, and SO<sub>2</sub>Ph) have been measured in methanol and in benzene at various piperidine concentrations. The reactivity of compounds (I) is not affected by the piperidine concentration in both methanol and benzene, except for the case of L = I (Ic). Probably due to association effects, the reactivity of Ic in benzene decreases as the piperidine concentration is increased. The reactions of compounds II follow overall second order kinetics in methanol while in benzene a different behaviour is observed as a function of the nature of the leaving group. In fact, the piperidino substitutions of IIa-c (L = Cl, Br, I) are mildly accelerated at high piperidine concentrations (a moderate solvent effect); on the contrary the reactivity of II d and e shows a strong dependence on the piperidine concentration, pointing out a genuine base catalysis.

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Aromatic nucleophilic substitutions (S<sub>N</sub>Ar) with neutral nucleophiles can be subject to base catalysis (2). The occurrence of this catalysis is an important confirmation of the multi-step nature of the S<sub>N</sub>Ar and can provide interesting information about the rates of formation and decomposition of the intermediate complex and about the factors upon which they are dependent.

Continuing our researches on catalysis in S<sub>N</sub>Ar (1) and with the aim to gain information about the situation in five-membered ring derivatives with particular regard to the role played by leaving groups of different nucleofugicity, we now report a kinetic study on the piperidino substitutions of some 2-L-3-nitrothiophenes (I) and 2-L-5-nitrothiophenes (II) at various temperatures.

The reactions have been carried out in methanol and in benzene, *i.e.* two solvents possessing a very different ability in solvating reagents and intermediates. According to the addition-elimination mechanism (Eq. 1) (2a),



the experimental bimolecular constant  $k_A$  is given by Eq. (2) (2a)

$$k_A = \frac{k_1 k_2 + k_1 \sum_i k_3^B [B_i]}{k_{-1} + k_2 + \sum_i k_3^B [B_i]} \quad \text{Eq. (2)}$$

If  $(k_2 + \sum_i k_3^B [B_i]) \gg k_{-1}$ , then  $k_A = k_1$  Eq. (3)

The reaction is not base catalyzed, and the first step (formation of the intermediate) is rate-determining.

Table I

Kinetic Data and Activation Parameters for the Piperidino Substitution in Methanol of Compounds I and II

Compound	$10^4 k/l \text{ mole}^{-1} \text{ sec}^{-1} (\text{ }^\circ\text{C})$	$\Delta H^\ddagger_{(a,b)}$ kcal mole <sup>-1</sup>	$-\Delta S^\ddagger_{(a)}$ u.e.
Ia (c)	1.71 (20.03), 4.12 (30.05), 9.37 (40.05)	14.9	25
Ib (c)	1.14 (20.00), 2.68 (30.00), 9.58 (46.33)	14.4	27
Ic (c)	0.115 (20.05), 0.321 (30.00), 0.735 (40.10)	16.3	25
Id (c)	69.8 (20.05), 140 (30.02), 268 (40.10)	11.7	28
Ie (c)	0.592 (20.05), 1.48 (30.10), 2.88 (40.10)	13.8	30
IIa (d)	0.255 (19.98), 0.585 (30.05), 1.39 (40.00)	14.8	29
IIb (d)	0.163 (20.01), 0.389 (30.01), 0.937 (40.03)	15.3	28
IIc (d)	0.0245 (19.97), 0.0644 (30.01), 0.160 (39.95)	16.6	28
IId	4.14 (19.98), 8.92 (30.02), 18.1 (39.95)	12.9	30
IIe (d)	0.0655 (19.98), 0.146 (30.30), 0.306 (40.05)	13.4	36

(a) At 20°. (b) The maximum error is 0.5 kcal mole<sup>-1</sup>. (c) Data from reference 4. (d) Data from reference 5.

Table II

Kinetic Data for the Piperidino Substitution in Benzene of Compounds I

Ia							
PIP (mole l <sup>-1</sup> )	0.0505	0.101	0.101	0.101	0.202	0.505	1.01
10 <sup>4</sup> k <sub>A</sub> (l mole <sup>-1</sup> sec <sup>-1</sup> )	5.43 (a)	5.55 (a)	9.87 (b)	16.7 (c)	6.15 (a)	7.63 (a)	10.4 (a)
(a) At 20.00°. (b) At 30.10°. (c) At 40.05°.							
Ib							
PIP (mole l <sup>-1</sup> )	0.0238	0.0238	0.0238	0.0488	0.0970	0.250	0.492
10 <sup>4</sup> k <sub>A</sub> (l mole <sup>-1</sup> sec <sup>-1</sup> )	3.90 (a)	6.90 (b)	12.1 (c)	3.94 (a)	4.14 (a)	4.64 (a)	5.59 (a)
(a) At 20.00°. (b) At 30.05°. (c) At 40.02°.							
Ic							
PIP (mole l <sup>-1</sup> )	0.0204	0.0204	0.0204	0.0408	0.0611	0.120	0.153
10 <sup>5</sup> k <sub>A</sub> (l mole <sup>-1</sup> sec <sup>-1</sup> )	3.37 (a)	6.71 (b)	13.3 (c)	3.14 (a)	2.99 (a)	2.80 (a)	2.56 (a)
PIP (mole l <sup>-1</sup> )	0.202	0.300	0.404	0.505	0.600	0.758	1.01
10 <sup>5</sup> k <sub>A</sub> (l mole <sup>-1</sup> sec <sup>-1</sup> )	2.38 (a)	2.18 (a)	2.06 (a)	2.04 (a)	1.93 (a)	1.85 (a)	1.79 (a)
(a) At 20.00°. (b) At 30.05°. (c) At 40.02°.							
Id							
PIP (mole l <sup>-1</sup> )	0.00500	0.00500	0.00500	0.0250	0.102		
10 <sup>2</sup> k <sub>A</sub> (l mole <sup>-1</sup> sec <sup>-1</sup> )	3.66 (a)	5.89 (b)	8.94 (c)	3.59 (a)	3.86 (a)		
(a) At 20.00°. (b) At 30.06°. (c) At 39.92°.							
Ie							
PIP (mole l <sup>-1</sup> )	0.0200	0.0505	0.100	0.100	0.100	0.202	0.300
10 <sup>4</sup> k <sub>A</sub> (l mole <sup>-1</sup> sec <sup>-1</sup> )	9.05 (a)	9.50 (a)	9.70 (a)	17.0 (b)	27.7 (c)	10.1 (a)	10.8 (a)
(a) At 19.90°. (b) At 30.00°. (c) At 40.02°.							

Table III

Linear Regression Analysis of Apparent Second Order Kinetic Constants (k<sub>A</sub>) for the Piperidino Substitution of Compounds Ia,b,e in Benzene at 20° by the Equation: k<sub>A</sub> = k<sub>0</sub> + k<sub>PIP</sub>[PIP]

Compound	10 <sup>4</sup> k <sub>0</sub> (a)	10 <sup>4</sup> k <sub>PIP</sub> (a)	10 <sup>4</sup> s(k <sub>0</sub> ) (b)	10 <sup>4</sup> s(k <sub>PIP</sub> ) (b)	r (c)	n (d)	k <sub>PIP</sub> /k <sub>0</sub>
Ia	5.08	5.23	0.05	0.10	0.9994	5	1
Ib	3.78	3.63	0.02	0.10	0.9989	5	1
Ie	9.07	5.63	0.10	0.59	0.9837	5	0.6

(a) The confidence levels (6) for significance of k<sub>0</sub> and k<sub>PIP</sub> are all better than 99%. (b) Standard deviations of the regression parameters, k<sub>0</sub> and k<sub>PIP</sub>, respectively. (c) Correlation coefficient. (d) Number of points.When k<sub>-1</sub> ≫ (k<sub>2</sub> + Σ<sub>i</sub>k<sub>3i</sub><sup>B</sup>[B<sub>i</sub>]), then

$$k_A = \frac{k_1 k_2}{k_{-1}} + \frac{k_1 \sum_i k_{3i}^B [B_i]}{k_{-1}} = k_0 + \sum k_{B_i} [B_i] \quad \text{Eq. (4)}$$

In this case, a linear response to base concentration is obtained.

### Results and Discussion.

#### Reaction Products.

Compounds I and II gave the expected piperidino derivatives (III and IV) on treatment with piperidine in methanol as well as in benzene in almost quantitative yield (tle and uv-visible spectral analysis).

#### Kinetic Data.

The leaving groups tested (L = Cl, Br, I, OC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>-p,

SO<sub>2</sub>Ph) are those we have previously used to study element effect in S<sub>N</sub>Ar (3) and leaving group effects on LFER (4). Their different sensitiveness to catalysis has been already emphasized in benzene derivatives (1).

The kinetic data of piperidino substitution and the activation parameters are collected in Tables I-VI.

#### Reactivity of Compounds I and II in Methanol.

Rate constant measurements in methanol at various piperidine concentrations indicate, for the leaving groups considered, absence of catalysis by piperidine. The studied reactions are bimolecular, first order both in substrate and in piperidine and they proceed through a two-step mechanism with fast decomposition of the intermediate complex (Eq. 3). The relevant kinetic data are set forth in Table I.

Table IV

## Kinetic Data for the Piperidino Substitution in Benzene of Compounds II

IIa								
PIP (mole l <sup>-1</sup> )	0.100	0.200	0.400	0.500	0.750	1.00	1.00	1.00
10 <sup>6</sup> k <sub>A</sub> (1 mole <sup>-1</sup> sec <sup>-1</sup> )	1.73 (a)	2.48 (a)	4.04 (a)	4.63 (a)	6.71 (a)	8.39 (a)	13.6 (b)	21.5 (c)
(a) At 19.85°. (b) At 30.05°. (c) At 39.98°.								
IIb								
PIP (mole l <sup>-1</sup> )	0.0200	0.102	0.255	0.510	0.765	1.02		
10 <sup>6</sup> k <sub>A</sub> (1 mole <sup>-1</sup> sec <sup>-1</sup> ) (a)	0.970	1.32	2.05	3.23	4.45	5.49		
PIP (mole l <sup>-1</sup> )	0.0200	0.101	0.252	0.505	0.758	1.01		
10 <sup>6</sup> k <sub>A</sub> (1 mole <sup>-1</sup> sec <sup>-1</sup> ) (b)	1.82	2.52	3.60	5.68	7.55	9.57		
PIP (mole l <sup>-1</sup> )	0.0200	0.102	0.255	0.509	0.764	1.02		
10 <sup>6</sup> k <sub>A</sub> (1 mole <sup>-1</sup> sec <sup>-1</sup> ) (c)	3.63	4.70	6.48	9.39	12.7	15.4		
(a) At 20.00°. (b) At 30.00°. (c) At 40.00°.								
IIc								
PIP (mole l <sup>-1</sup> )	0.202	0.404	0.505	0.758	1.01	1.01	1.01	
10 <sup>7</sup> k <sub>A</sub> (1 mole <sup>-1</sup> sec <sup>-1</sup> )	1.57 (a)	1.79 (a)	1.93 (a)	2.23 (a)	2.47 (a)	5.01 (b)	9.85 (c)	
(a) At 20.05°. (b) At 30.05°. (c) At 40.10°.								
II d								
PIP (mole l <sup>-1</sup> )	0.0495	0.0990	0.198	0.495	0.742	1.02		
10 <sup>5</sup> k <sub>A</sub> (1 mole <sup>-1</sup> sec <sup>-1</sup> ) (a)	1.05	1.97	4.15	10.4	16.1	20.8		
PIP (mole l <sup>-1</sup> )	0.0505	0.101	0.202	0.505	0.758	1.01		
10 <sup>5</sup> k <sub>A</sub> (1 mole <sup>-1</sup> sec <sup>-1</sup> ) (b)	1.43	2.75	5.46	14.2	20.8	29.2		
PIP (mole l <sup>-1</sup> )	0.0505	0.101	0.202	0.505	0.758	1.01		
10 <sup>5</sup> k <sub>A</sub> (1 mole <sup>-1</sup> sec <sup>-1</sup> ) (c)	1.80	3.83	7.49	18.7	28.2	36.5		
(a) At 19.95°. (b) At 30.05°. (c) At 40.10°.								
IIe								
PIP (mole l <sup>-1</sup> )	0.0712	0.142	0.249	0.497	0.994			
10 <sup>7</sup> k <sub>A</sub> (1 mole <sup>-1</sup> sec <sup>-1</sup> ) (a)	1.12	2.11	3.55	6.82	13.3			
PIP (mole l <sup>-1</sup> )	0.142	0.404	0.505	0.758	1.01			
10 <sup>7</sup> k <sub>A</sub> (1 mole <sup>-1</sup> sec <sup>-1</sup> ) (b)	3.44	8.74	11.1	16.0	20.6			
PIP (mole l <sup>-1</sup> )	0.205	0.410	0.512	0.769	1.02			
10 <sup>7</sup> k <sub>A</sub> (1 mole <sup>-1</sup> sec <sup>-1</sup> ) (c)	6.49	12.4	15.8	22.9	30.1			
(a) At 20.05°. (b) At 30.05°. (c) At 39.90°.								

Table V

Linear Regression Analysis of Apparent Second Order Kinetic Constants (k<sub>A</sub>) for the Piperidino Substitution of Compounds II in Benzene by the Equation: k<sub>A</sub> = k<sub>0</sub> + k<sub>PIP</sub>[PIP]

Compound	10 <sup>6</sup> k <sub>0</sub>	10 <sup>6</sup> k <sub>PIP</sub>	10 <sup>6</sup> s(k <sub>0</sub> ) (a)	10 <sup>6</sup> s(k <sub>PIP</sub> ) (a)	t(k <sub>0</sub> ) (b)	C.L. (k <sub>0</sub> ) (b)	r (c)	n (d)	k <sub>PIP</sub> /k <sub>0</sub>
IIa (e)	1.00	7.46	0.07	0.12	14.6	99.9	0.9995	6	7.5
IIb (e)	0.88	4.58	0.03	0.05	28.4	99.9	0.9997	6	5.2
IIb (f)	1.69	7.79	0.03	0.06	50.3	99.9	0.9999	6	4.6
IIb (g)	3.45	11.8	0.09	0.2	40.0	99.9	0.9997	6	3.4
IIc (e)	0.135	0.113	0.002	0.003	61.3	99.9	0.9986	5	0.84
II d (e,h)	0.6	208	2.5	5	0.25	10.0	0.9991	6	∞
II d (f,h)	-2.2	286	2.9	5	0.76	50.0	0.9994	6	∞
II d (g,h)	1.5	364	2.2	4	0.72	40.0	0.9998	6	∞
IIe (e,h)	0.024	1.32	0.003	0.01	7.48	99.0	1.0000	5	55
IIe (f,h)	0.080	1.98	0.025	0.04	3.24	95.0	0.9994	5	25
IIe (g,h)	0.066	2.89	0.022	0.03	3.02	90.0	0.9998	5	44

(a) Standard deviations of the regression parameters, k<sub>0</sub> and k<sub>PIP</sub>, respectively. (b) Student "t" test and confidence level relative to the null hypothesis k<sub>0</sub> = 0. The confidence levels for significance of k<sub>PIP</sub> are all better than 99.9%. (c) Correlation coefficient. (d) Number of points. (e) At 20°. (f) At 30°. (g) At 40°. (h) See text.

Table VI

Activation Parameters for the Piperidino Substitution in Benzene of Compounds I and II

Compound	$\Delta H^\ddagger$ (a)/ kcal mole <sup>-1</sup>	$-\Delta S^\ddagger$ (a)/ u.e.
Ia (b)	9.4	41
Ib (b)	9.7	41
Ic (b)	11.9	38
Id (b)	7.6	39
Ie (b)	8.9	42
IIa (b)	7.9	55
IIb (c)	11.9	46
IIc (b)	12.0	48
IId (d)	4.5	60
IIe (d)	6.6	63

(a) At 20°. (b) Apparent activation parameters calculated from kinetic measurements at the temperatures and at the piperidine concentrations indicated in Tables II and IV. (c) True activation parameters corresponding to [pip] = 0. (d) Activation parameters relative to the catalyzed reaction.

#### Reactivity of Compounds I and II in Benzene.

Rate constant measurements in benzene at various piperidine concentrations (Tables II and IV) indicate a strong difference between *ortho*-like (I) and *para*-like (II) isomers.

The reactivity of *ortho*-like compounds (Ia,b, and e) increases but slightly with increasing piperidine concentration showing  $k_{PIP}/k_O \leq 1$  (Table III). The trend of the rates here is probably due to a solvent effect similar to that observed in benzene derivatives (1,7). The reactivity of Id, in the limited range of piperidine concentrations used by us (8), does not change within the experimental error. The apparent kinetic constant ( $k_A$ ) of Ic decreases as the piperidine concentration is increased (see data in Table II and Figure): this behaviour seems to be linked to

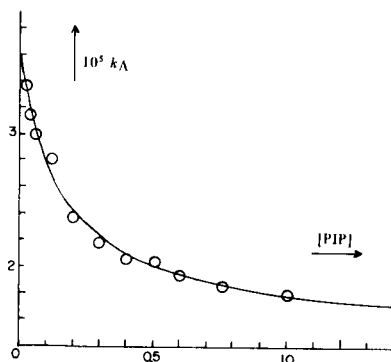


Figure. Plot of apparent second order kinetic constants ( $k_A$ ) for the piperidino substitution of Ic at 20° in benzene versus piperidine concentration.

some effect of complexing between the two reagents (9). The data obtained follow a curvilinear trend and fit an equation of the type

$$k_A = k_O \frac{1 + b[PIP]}{1 + c[PIP]} \quad \text{Eq. (4)}$$

The best values of  $k_O$  [ $0.36 \times 10^{-4}$ , s.e. (10)  $0.01 \times 10^{-4}$ ],  $b$  (2.59, s.e. 0.40), and  $c$  (6.26, s.e. 0.82) have been obtained through a least-square treatment (11) of the experimental data.

The *para*-like isomers (IIa-e) present a range of behaviour (Tables IV-V). The reactivity of the three halogen derivatives increases linearly with increasing piperidine concentration showing low  $k_{PIP}/k_O$  values (1-8), which are not representative of genuine base catalysis according to Bunnett's classification (13). On the other hand, the results obtained for IId and IIe point out high  $k_{PIP}/k_O$  values (12). Thus, due to the low nucleofugicity of the present leaving groups (respectively,  $L = OC_6H_4NO_2-p$  and  $SO_2Ph$ ), base catalysis is needed as observed in benzene derivatives (1).

#### The *o/p* Ratio and the Catalysis by Piperidine.

The decomposition of the reaction intermediates in  $S_NAr$  can be assisted. Thus, the nitrogroup promotes the elimination of the proton and of the leaving group in *ortho*-like derivatives reactions (7a): on the other hand, the reactions of *para*-like isomers are assisted by methanol (14) but certainly not by benzene. These facts can easily explain the values of *o/p* ratios measured and the absence of catalysis by piperidine observed for compounds Ia-e in methanol.

The *ortho*-like isomers are moderately more reactive in benzene than in methanol, the "built-in solvation" (15) levelling the opposite effects on enthalpies and entropies of activation exerted by solvents (Tables I and VI).

The *para*-like isomers are largely more reactive in methanol than in benzene, owing to domination by the entropy factor (Tables I and VI). However, for compounds IIa-c the large absolute activation entropies found in benzene are mainly caused by solvent ordering during the formation of zwitterionic intermediates while those for Id and Ie are also affected by the catalyzed part of the reaction, which involves a transition state much more ordered than the ground state.

As a consequence, irrespective of the nature of the leaving group, the *o/p* ratios in methanol ( $6 \pm 1$ ) are largely lower than in benzene ( $470 \pm 40$ ) (16).

Moreover, in five-membered ring derivatives these ratios are higher than in six-membered ring derivatives because the higher "bond fixation" makes *hyper-ortho* (17) the 2,3-relation and *quasi-para* the 2,5-relation.

The behaviour of compounds IIa-e in benzene requires some more comments. The rates of piperidino substitu-

tions of the studied 2-halogeno-5-nitrothiophenes (IIa-c), as also pointed out by Guanti and coworkers (18), are only slightly affected by the piperidine concentration because the high nucleofugicity of these leaving groups.

The high  $k_{PIP}/k_0$  values observed with compounds IIc and IIe recall the situation observed in the case of the corresponding 1-1,2,4-dinitrobenzenes recently studied by us (1). A similar catalytic effect by piperidine has been observed when studying the piperidino defluorination of 2-fluoro-5-nitrothiophene in benzene (18).

This kind of catalysis has been rationalized in terms of bifunctional catalysis (19), of SB-GA mechanism (20), of rate-determining proton transfer (2a,21), or of  $E_2$ -type mechanism (2a,22), the first two mechanisms being preferred.

Researches are in progress to clarify the nature of the operating mechanism.

#### EXPERIMENTAL

##### Synthesis and Purification of Compounds.

Compounds Ia-c (4), IIa-c,e (5), IIc (23), III (3), IV (3), piperidine (24), methanol (24), and benzene (24) were prepared and/or purified according to the methods reported.

##### Kinetic Measurements.

The kinetics were followed spectrophotometrically as previously described (3). The concentrations used were  $10^{-3}$  M for the substrates and those indicated in the Tables for the piperidine. The runs in benzene were quenched by dilution with acetic acid (1 M) in benzene and those in methanol with hydrochloric acid (0.2 M) in methanol. The rate constants are accurate to within  $\pm 3\%$ .

##### Acknowledgment.

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