Effect of the Nature of the Starting Aromatic Ring on the Cyclization of *o*-Nitroaryl Azides: Kinetic and Thermodynamic Studies of the Conversion of Two Azido(methoxycarbonyl)nitrothiophenes into Methoxycarbonylthienofurazan Oxides

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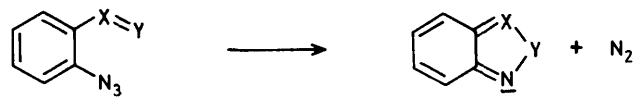
The cyclization of 2-azido-5-methoxycarbonyl-3-nitro- (**8**) and of 3-azido-5-methoxycarbonyl-2-nitro-thiophene (**9**) which give mixtures of 5-methoxycarbonylthieno[3,2-*c*]- and 5-methoxycarbonylthieno[2,3-*c*]-furazan oxides (**10**) and (**11**) has been studied in *NN*-dimethylformamide, dioxane, methanol, and acetonitrile at various temperatures. The equilibrium (**10**) $\rightleftharpoons$ (**11**) has been studied in deuteriochloroform by dynamic ^{1}H n.m.r. spectroscopy. The kinetic and thermodynamic data obtained agree with an electrocyclic mechanism for the conversion characterized by a late transition state, as indicated by the effect on the reactivity of the nature of the starting aromatic ring.

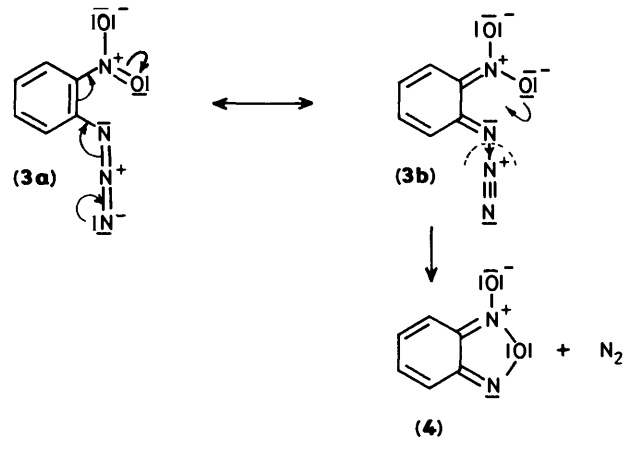
It is known that aryl azides bearing α,β-unsaturated *ortho*-substituents (**1**) readily undergo thermal decomposition to give condensed benzoheterocyclic systems (**2**). The rates of the



(**1**) (**2**)

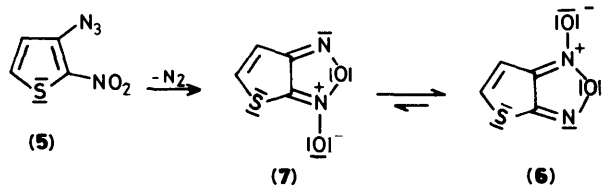
Scheme 1.

cyclization reaction have been related to the stability of the benzoheterocyclic system formed.[1] From 2-azidonitrobenzene (**3a**) benzofurazan oxide (**4**) is formed. The mechanism of this cyclization reaction has been widely studied and the results obtained have allowed the mechanism in Scheme 2 to be proposed.[2]



Scheme 2.

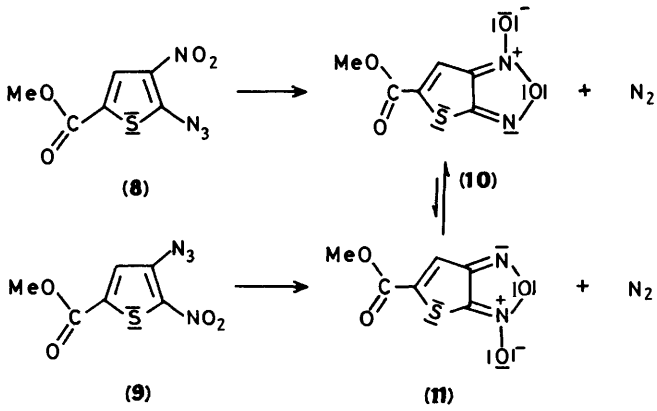
Some furoxans fused with five-membered heterocyclic rings have been prepared, *e.g.* Boulton and Middleton[3] have synthesized thieno[3,2-*c*]- (**6**) and thieno[2,3-*c*]-furazan (**7**) oxides from 3-azido-2-nitrothiophene (**5**), and compared the relevant isomerization reaction (**6**) $\rightleftharpoons$ (**7**) with those of



Scheme 3.

benzofurazan and of furazan oxides. Similar results have been obtained by Paulmier *et al.*[4]

We now report both kinetic (temperature range 25—60 °C) and thermodynamic data on the cyclization of 2-azido-5-methoxycarbonyl-3-nitro- (**8**) and of 3-azido-5-methoxycarbonyl-2-nitro-thiophene (**9**) to the corresponding thieno[3,2-*c*]- and thieno[2,3-*c*]-furazan oxides (**10**) and (**11**), together with some thermodynamic data on their isomerization reactions, in order to gain deeper insight into the mechanism of these reactions. We particularly wished to elucidate the function of the condensed ring present.



Scheme 4.

In order to gain information on the solvent effect, if any, four different solvents [*NN*-dimethylformamide (DMF),

Table. Kinetic data and activation parameters[a] for the cyclization of 2-azido-5-methoxycarbonyl-3-nitro- (**8**) and of 3-azido-5-methoxycarbonyl-2-nitro-thiophene (**9**), in various solvents and in the solid state

Compound	Solvent	$10^5\ k/s^{-1}(T/K)$[b]	$\Delta H^{\ddagger}$[c]	$\Delta S^{\ddagger}$[d]	λ/nm[e]
(**8**)	MeOH[b]	3.97(318.0)	118.7	44	260
(**8**)	MeCN	3.38(318.0)	151.0	145	260
(**8**)	DMF	4.90(318.0)	131.0	85	265
(**8**)	DIOX	2.90(318.0)	106.4	6	265
(**8**)	Solid state	7.40(318.0)	60.2	−134	260
(**9**)	MeOH	0.143(318.0)	87.3	−81	284
(**9**)	MeCN	0.211(318.0)	77.2	−111	284
(**9**)	DMF	0.182(317.6)	79.8	−104	320
(**9**)	DIOX	0.196(319.2)	55.4	−182	320
(**9**)	Solid state	0.294(318.0)	93.7	−56	284

[a] Calculated from kinetic data collected in the temperature range 310—335 K. [b] The rate constants are accurate to within ±5%. [c] kJ mol^{-1}; calculated at 318 K. [d] J K^{-1} mol^{-1}; calculated at 318 K. [e] Wavelengths used for kinetic measurements.

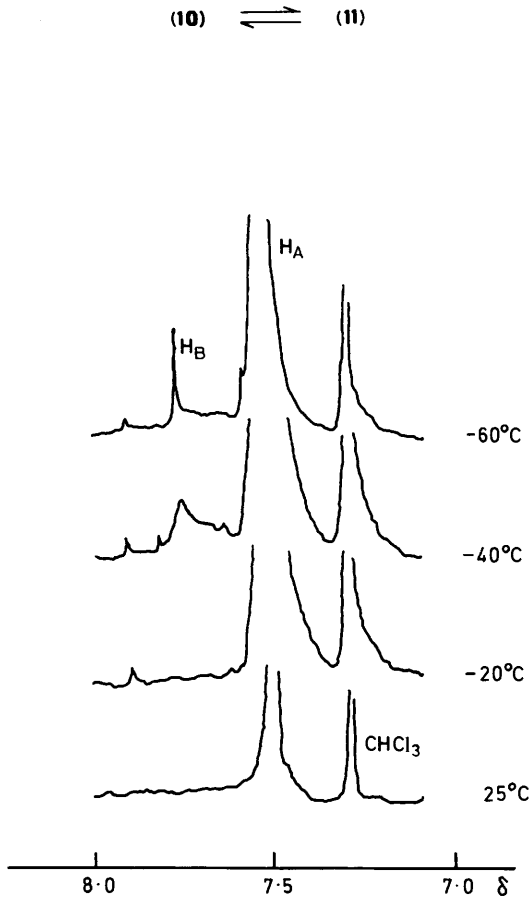


Figure. Temperature-dependent n.m.r. spectra for equilibrium (**10**) ⇌ (**11**)

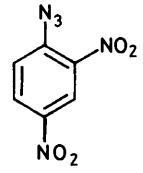
dioxane (DIOX), methanol (MeOH), and acetonitrile (MeCN)] which range from a non-polar solvent with a very low dielectric constant (DIOX, ε 2.21) to some very polar protic (MeOH, ε 32.7) or non-protic (DMF ε 37.0 and MeCN, 37.5) solvents were chosen for the kinetic studies. Moreover, the cyclization has also been studied in the solid state, for comparison.

The isomerization has been studied in deuteriochloroform in the temperature range −60—25 °C.

Results and Discussion

The cyclizations show clean first-order kinetics (taken to 2—3 $t_{\frac{1}{2}}$), and the results obtained (kinetic constants and activation parameters) are in the Table. Both isomeric azido(methoxycarbonyl)nitrothiophenes (**8**) and (**9**) afford the same mixture of thienofurazan oxides, showing that the isomerization rates are very large compared with the cyclization rates. Moreover, the ^{1}H n.m.r. spectra of the two thienofurazan oxide isomers obtained show a unique singlet at room temperature, indicating that the equilibrium (**10**) ⇌ (**11**) is fast on the ^{1}H n.m.r. time scale under these conditions. In fact, the n.m.r. spectrum of the 'product' of cyclization of (**8**) and/or (**9**) showed a single signal for 4-H at room temperature, but at −60 °C two separate signals (Figure) relative to isomers (**10**) and (**11**) were found. By comparison with the thienofurazan oxides (**6**) and (**7**),[3] the shielding effect of the *N*-oxide group on an adjacent proton identifies the major isomer as (**10**). The ratio of the peak areas gave the equilibrium constant (K_e 65, $\Delta G^{\ddagger}$ 7.4 kJ mol^{-1}), whilst from the coalescence temperature (−20 °C) for the fusion of signals, the free energy of activation for the isomerization (**10**) ⇌ (**11**) was 51.3 kJ mol^{-1}.

Under any experimental conditions 2-azido-5-methoxycarbonyl-3-nitrothiophene (**8**) underwent cyclization faster than its isomer (**9**) ($k_{(8)}/k_{(9)}$ *ca.* 15), and is more reactive than the corresponding phenyl azide, as indicated by the fact that (**8**) cyclizes in the solid state at about the same rate as 1-azido-2,4-dinitrobenzene (**12**), notwithstanding the higher electron-withdrawing effect of the nitro with respect to the methoxycarbonyl group.



(**12**)

The cyclization rates of the two azidonitrothiophenes (**8**) and (**9**) are little affected by a change in solvent, as expected for an electrocyclic process[5] [the largest rate ratios, at 61 °C for (**8**) or at 36 °C for (**9**), are *ca.* 2]. In contrast, the thermodynamic parameters show a significant dependence on the nature of the solvent and on the structure of the substrate studied.

Azidothiophenes (**8**) and (**9**) react at 45 °C faster in the solid state than in solution, probably because the solvation of nitro and azido groups retards the electrocyclic process.

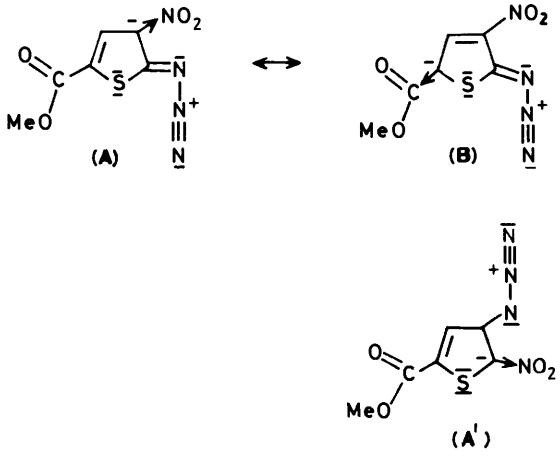
The activation parameters deserve some comment. On comparing the data obtained in solution different trends are observed for the two azides studied. In fact, in the various solvents for isomer (**8**) high activation enthalpies and positive activation entropies are observed; on the other hand, isomer (**9**) shows low activation enthalpies and negative activation entropies. Moreover, the behaviour in solution of (**9**) resembles that observed for (**8**) in the solid state. Probably this resemblance is fortuitous, because solvation and desolvation energies usually have an effect in solution and complicate the direct comparison between data obtained for reactions in solution or in the absence of solvents.

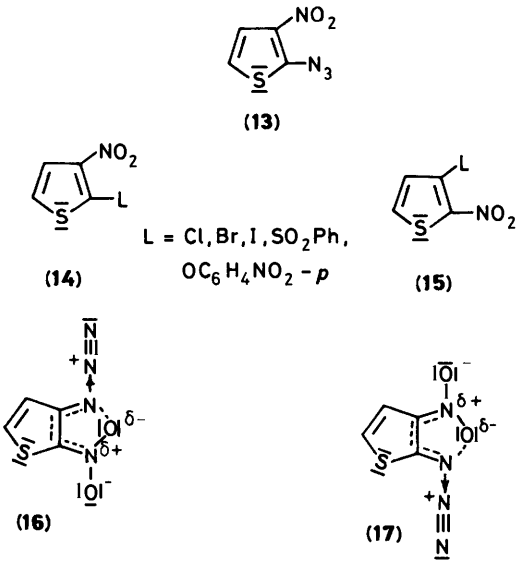
Large negative activation entropies, such as those calculated for the reactions of (**8**) and (**9**) in the solid state, indicate transition states much more ordered than reagents and resembling the final products. Moreover the differences in the values of activation entropies between (**8**) and (**9**) in solution can be accounted for by assuming that the transition state for the reaction of isomer (**9**) is later than that for isomer (**8**) or alternatively by assuming a higher degree of solvation of (**9**) than of (**8**).

In order to explain the higher reactivity of (**8**) compared with (**9**) both steric and electronic effects can be considered, in the light of the results obtained from the cyclization of some substituted 2-nitroaryl azides.[2] In fact, it has been observed that substituents *ortho* to nitro or to azido groups always cause a decrease in reactivity independent of their nature.[6] On the other hand, the electronic effects of substituents *meta* or *para* to nitro or to azido groups can be correlated through a two-parameter equation ($\log k/k_0 = \rho_A\sigma_A^- + \rho_N\sigma_N$, where A and N refer to the effect exerted by substituents on the azido and the nitro group, respectively). This fact confirms the involvement of a cyclic transition-state characteristic of an electrocyclic reaction. The calculated susceptibility constants (*e.g.* at 50 °C: ρ_A 1.353; ρ_N −0.676) show that any substituent influences the electronic distribution on the two reacting sites (azido and nitro group) in opposite ways. This also indicates that the effect of the substituent on the azido group is larger than that of the nitro group.

Accordingly, an examination of canonical structures of azidothiophenes can give some information. In fact, any structure which favours the displacement of a nitrogen molecule from a neutral nitrogen atom favours the cyclization reaction. In the case of (**8**) the structures (**A**) and (**B**) (the carbanion structure can equally be considered as dipole- or resonance-stabilized) agree with the previous requirement. In the case of (**9**) only structure (**A′**) gives the same effect, whereas no structure corresponding to (**B**) is possible.

On the assumption that the substituent effects in thiophene and benzene derivatives are similar, the weight of the electronic effect of a 5-substituent on the azido and nitro groups can be roughly estimated, using the susceptibility constants calculated by Dyall[6] at 50 °C. Thus one observes that the methoxycarbonyl group in (**8**) would increase the reactivity by a factor of *ca.* 4 and in (**9**) would have no effect on the reactivity. The higher difference in reactivity observed between (**8**) and (**9**) ($k_{(8)}/k_{(9)}$ *ca.* 15) would depend on the difference already present in the unsubstituted azidonitrothiophenes (**5**) and (**13**). It probably depends on some stereoelectronic effect exerted by the endocyclic sulphur atom, which obviously also operates in the unsubstituted azidonitrothiophenes.





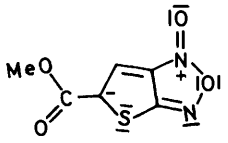
Some results previously obtained for studies of benzenethiolate substitution in some 2-L-3-nitro (**14**) and 3-L-2-nitrothiophenes (**15**) have shown that the $k_{3\text{-L-2-NO}_2}/k_{2\text{-L-3-NO}_2}$ ratios range from 0.5 to 10 depending on the size of the leaving group:[7] the trend observed indicates that the endocyclic sulphur atom behaves as an *ortho*-substituent exerting a small primary steric effect. In the present reaction the lone pair of the sulphur atom probably disfavours the formation of the transition state (**16**) from (**5**), whereas it probably favours the formation of (**17**) from (**13**) (see also later).

The thermodynamic data (K_e calculated at −60 °C, *ca.* 65) have shown that 5-methoxycarbonylthieno[3,2-*c*]furazan oxide (**10**) is more stable than the isomer (**11**), *i.e.* the isomer which is formed faster is the more stable, indicating that similar factors affect the formation of the (late) transition states for both cyclization and isomerization.

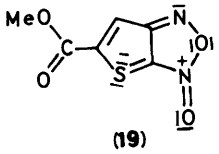
All the observations account well for the higher reactivity of azidonitrothiophenes with respect to azidonitrobenzenes. In fact, a late transition state requires a loss of stabilization energy by resonance of the aromatic systems (thiophene and benzene, respectively), on going from the initial to the transition states: data on electrophilic[8] and nucleophilic[9] substitutions in homocyclic and five-membered-ring heterocyclic systems have shown that this can happen more easily in thiophene than in benzene derivatives. Another factor which would affect the reactivity of azidonitrothiophenes with respect to azidonitrobenzenes is the more favourable geometry of the two interacting azido and nitro groups which characterizes five-membered- with respect to six-membered-ring derivatives.

The thermodynamic data deserve some further comments. As shown by Boulton and Middleton[3] thieno[3,2-*c*]furazan oxide (**6**) is more stable than thieno[2,3-*c*]furazan oxide (**7**). We think that both in the compounds studied by us [(**10**), (**11**)] and in the unsubstituted thienofurazan oxides previously studied

[(**6**), (**7**)][3] an important factor is stereoelectronic repulsion between the lone pair of endocyclic sulphur and the negatively charged oxygen atom in (**7**), which largely disfavours (**7**) with respect to (**6**) (K_e calculated at −45 °C, *ca.* 8), where this destabilizing effect is not present. An electron-withdrawing substituent (the methoxycarbonyl group) further stabilizes the '*O*-outside' form (K_e calculated at −60 °C, *ca.* 65). In fact, in this instance, besides (**10**) a further canonical structure (**18**) stabilizes the thienofurazan oxide; on the other hand, the isomer (**11**) gives only a further structure (**19**), where the electron-withdrawing substituent cannot exert its electronic (stabilizing) effect and the heteroatom is a decet-sulphur atom.



(**18**)



(**19**)

Experimental

Spectral Data, Kinetic, and Thermodynamic Measurements.—U.v. spectra were recorded with a Beckman DU-6 instrument; i.r. frequencies were recorded with a Perkin-Elmer model 1310 instrument; ^{1}H n.m.r. spectra were run on a 60 MHz JEOL PM 60 instrument at 25 °C with Me_4Si as internal standard. Mass spectra were performed on a Kratos MS 25 instrument at an ionization potential of 70 eV.

The kinetics of the cyclization reactions were followed spectrophotometrically over the temperature range 310—335 K by measuring the disappearance of azides (the wavelengths used are reported in the Table); the concentrations employed were *ca.* 10^{-3}M and withdrawn samples were quenched by dilution.

Kinetic experiments with neat materials were followed spectrophotometrically, by determining eight experimental points separately for each run. The reaction was quenched by adding cold methanol to the sample at predetermined reaction times.

The solvents used for kinetic measurements were purified according to literature methods.[10]

For low-temperature ^{1}H n.m.r. spectra a solution of the compound (*ca.* 10 mg) in deuteriated chloroform (0.5 ml) was used with tetramethylsilane as internal standard (some significant spectra are reported in the Figure). The temperatures quoted are accurate to within ±2 °C. Free energies of activation $\Delta G^{\ddagger}$ were obtained from the coalescence temperature and chemical shift values, by using the Gutowsky–Holm equation.[11]

Synthesis of Azidothiophenes.—The azidothiophenes were obtained by reacting the corresponding bromothiophenes with sodium azide.

2-Azido-5-methoxycarbonyl-3-nitrothiophene (**8**). A solution of sodium azide (0.9 g, 3.5 mmol) in methanol (40 ml) was treated with a solution of 2-bromo-5-methoxycarbonyl-3-nitrothiophene[12] (0.4 g, 1.7 mmol) in methanol (40 ml). The mixture was set aside, in the dark, until a t.l.c. test indicated that reaction was complete (*ca.* 2 h). By adding water to the mixture, the azido compound was precipitated and was filtered off (0.2 g, 58%). Compound (**8**) had m.p. 67—70 °C; $\nu(CHBr_3)$ 3 100, 2 190, 2 120, 1 710, 1 525, and 1 310 cm^{-1}; $\delta_H(CDCl_3)$ 8.00 (s, H-4) and 3.86 (s, 3 H, Me); $\lambda_{max.}$(MeOH) 338 (ε 4 500), 282 (7 700), and 260 nm (12 500).

3-Azido-5-methoxycarbonyl-2-nitrothiophene (**9**). A solution of 3-bromo-5-methoxycarbonyl-2-nitrothiophene[12] (0.5 g, 1.9 mmol) in dimethyl sulphoxide (5 ml) was treated with a solution of sodium azide (1.25 g, 19.2 mmol) in dimethyl sulphoxide (30 ml) at room temperature, in the dark. After 10 min reaction was complete (t.l.c.). The solid precipitated by treatment with water was filtered off (0.3 g, 70%). Compound (**9**) had m.p. 83—85 °C; $\nu(CHBr_3)$ 3 080, 2 180, 2 130, 1 725, 1 510, and 1 330 cm^{-1}; $\delta_H(CDCl_3)$ 7.52 (s, H-4) and 3.96 (s, 3 H, Me); $\lambda_{max.}$(MeOH) 350 (ε 8 000), 312 (7 800), and 253 nm (9 200).

5-Methoxycarbonylthieno[3,2-*c*]- *and 5-methoxycarbonylthieno*[2,3-*c*]*-furazan oxides* (**10**), (**11**). Compound (**8**) (0.2 g, 1 mmol) was dissolved in methanol (30 ml) and the solution was set aside for one day, in the dark, and after evaporation under reduced pressure a mixture of (**10**) and (**11**) was obtained. The inseparable mixture was purified by column chromatography (silica gel, eluant light petroleum–ethyl acetate, 20:1; 0.17 g, 97%). The same mixture was obtained from (**9**) using the above procedure or a literature method.[3]

The mixture showed the following physical properties: m.p. 87—91 °C (Found: C, 36.1; H, 2.1; N, 13.6. Calc. for $C_6H_4N_2O_4S$: C, 36.0; H, 2.0; N, 14.0%); $\nu(CHBr_3)$ 3 120, 1 730, 1 630, 1 530, 1 470, and 1 410 cm^{-1}; $\delta_H(CDCl_3)$ 7.50 (s, H-4) and 3.97 (s, 3 H, Me); $\lambda_{max.}$(MeOH) 353 (ε 6 500), 276 (6 700), and 240 nm (9 450); *m/z* 200(54), 184(98), 169(13), 168(13), 141(10), 137(38), 95(34), 94(36), 59(100), 57(15), and 44(23%).

Thienyl azides (**8**) and (**9**) were each dissolved in both methanol or dioxane and the solutions were outgassed with N_2 for 20 min. The solutions obtained by irradiation (λ 254 nm) for 30 min with a 17 W low-pressure mercury lamp (Helios-Italquartz) surrounded by a quartz water-jacket, did not give the mixture of thienofurazan oxides (**10**), (**11**). In order to find out whether thienofurazan oxides were intermediates in photolysis, a mixture of furazan oxides was irradiated under the same experimental conditions. The mixture which resulted was quite stable.

Acknowledgements

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