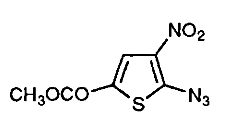
Factors Affecting the Rates of Thermal Decomposition of Azidothiophenes

Leonard K. Dyall,*[a] **Peter M. Suffolk**,[a] **Wim Dehaen**[b] and **Gerrit L'abbé***[b]
[a] *Department of Chemistry, University of Newcastle, Callaghan, NSW 2308, Australia*
[b] *Department of Chemistry, University of Leuven, Celestijnenlaan 200F, 3001 Leuven (Heverlee), Belgium*

The thermolysis rate of 4-methoxy-1-azidobenzene reveals that the methoxy group increases the rate much less than the endocyclic sulfur does in 3-azidothiophene. With 3-azidothiophene, the neighbouring groups 2-acetyl and 2-nitro enhanced the rate in decalin solution only 5- and 17-fold, respectively, whereas in azidobenzene the corresponding enhancements are 413 and 1060. It is argued that the preferred electron distribution in the transition state for decomposition of 3-azidothiophene is not consistent with that required for effective neighbouring group participation. 2-Cyano and 2-methoxycarbonyl substituents, which are not known as effective neighbouring groups in thermal decompositions of azides, have very little effect on the rate for 3-azidothiophene.

Noto *et al.*[1] have reported thermal decomposition rates of methyl 5-azido-4-nitrothiophene-2-carboxylate **1** and methyl 4-azido-5-nitrothiophene-2-carboxylate **2**. The azide **1** decomposed faster than 1-azido-2,4-dinitrobenzene, a compound in which nitro is known to exert a very large neighbouring group effect.[2] The other azidonitrothiophene, **2**, reacted 19 times slower, but this rate is nevertheless high. It was argued[1] that azidonitrothiophenes are more reactive than analogous azidonitrobenzenes because the loss of aromatic delocalization energy inherent in the thermolysis (see Scheme 1) is less serious for thiophene. Moreover, it was asserted that the interacting azido and nitro groups have more favourable geometry. The observed reactivity order, **1** > **2**, was attributed to a small primary steric effect of the endocyclic sulfur.



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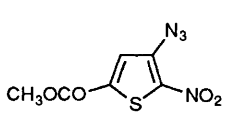

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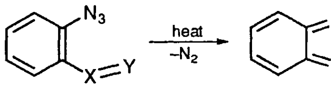


Scheme 1

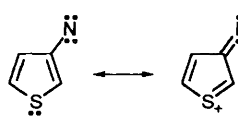
The neighbouring group effect of nitro on the azide pyrolysis rate should, ideally, be measured against the rate for an azidothiophene in which there is no neighbouring group.[3] Rate constants for thermolysis of 2-azidothiophene and 3-azidothiophene were recently reported by Spinelli and Zanirato,[4] and are very high: 8×10^{-2} and 1.17×10^{-4} s^{-1}, respectively in *p*-chlorotoluene solvent at 120 °C. Azidobenzene reacts much slower ($k_1 = 3.78 \times 10^{-6}$ s^{-1} at 120 °C in decalin solution).[5] Thus, the thermolyses of azidothiophenes are inherently fast and it is doubtful if the introduction of a neighbouring group makes them much faster. Unfortunately, the published data do not lend themselves to quantitative comparisons, the ester group in the 2-position of the azidothiophenes having a significant influence[1] which can only be roughly estimated.

The question of whether neighbouring group effects in the pyrolyses of azidothiophenes are larger or smaller than in azidobenzenes is an important one to resolve. In this paper, we report rates for some 2-substituted 3-azidothiophenes in order to address this question with adequate data. The behaviour of 2-azido heterocycles will be addressed in a later paper.

Results and Discussion

Rate constants for various 3-azidothiophenes, and 4-methoxy-1-azidobenzene, are reported in Table 1. Addition of a radical chain inhibitor was essential in order to obtain first-order kinetics from 1-azido-4-methoxybenzene. This inhibitor was normally used with the azidothiophenes also, though in several runs where it was omitted there was no change in the rate constant. Arrhenius parameters, and relative rates for the 3-azidothiophenes, are reported in Table 2.

Rate of Thermolysis of 3-Azidothiophene.—The reported rate[4] of thermolysis of 3-azidothiophene (*p*-chlorotoluene solution) is 31 times faster than that of azidobenzene[5] in decalin solution. Our data for methyl 3-azidothiophene-2-carboxylate (Table 3) in these two solvents indicate that the change of solvent has only a small effect (1.54-fold) so that there is a real 20-fold rate difference in favour of 3-azidothiophene over azidobenzene. We suggest that the advantage is derived from conjugative stabilization of the nitrene-like transition state (structure **3**).



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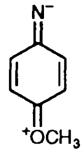

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A similar stabilization of a nitrene-like transition state, **4**, has been reported for 1-azido-4-methoxybenzene by Smith and Hall.[6] In their hands, 1-azido-4-methoxybenzene thermolysed 4.9 times as fast as azidobenzene at 141 °C in decalin solution, though they did report that there were deviations from the expected first-order kinetic behaviour. Walker and Waters[7] report a larger rate factor (11.7-fold) for these two compounds in both decalin and ethyl benzoate solutions at 132 °C; they too reported poor first-order kinetic behaviour for azidobenzene in decalin solution. These deviations from first-order behaviour are doubtless due to the competing induced decomposition reported by Dyall and Smith.[5] This induced pathway can be eliminated by addition of a free radical chain inhibitor, and we have remeasured the rates for 1-azido-4-methoxybenzene under these conditions (see Table 1). The reactions showed precise first-order kinetic behaviour as far as three half-lives, and in agreement with Smith and Hall[6] the methoxy group was found to increase the rate of azidobenzene by 4.5-fold in decalin solution. The 20-fold effect found with 3-azidothiophene is in

Table 1 Rates of thermal decomposition of aryl azides[a]

Aryl azide	T/°C	$k_1/10^{-4}\ s^{-1}$	Inhibitor (mol mol^{-1} azide)
3-Azido-2-cyanothiophene	120.0	1.16	14
	120.0	1.09	4
	130.0	3.28	9
	130.0	3.28	9
	140.0	9.46	5.7
	140.0	9.64	6.7
	150.0	24.9	6.5
	150.0	23.3	5.1
Methyl 3-azidothiophene-2-carboxylate	130.0	0.867	0.9
	130.1	0.850	0.9
	144.0	3.05	0
	144.0	3.03	0.9
	151.5	6.45	0.9
	151.5	6.62	1.7
	160.0	11.9	1.7
	160.0	12.1	0.9
2-Acetyl-3-azidothiophene	100.0	0.517	0
	99.2	0.517	2.7
	109.2	1.32	0
	110.1	1.60[b]	0
	116.9	2.80	2.7
	116.4	2.90	0
	123.5	5.15[b]	2.5
	124.1	5.40[b]	4.9
	130.6	8.60	2.7
	130.9	9.30	2.7
3-Azido-2-nitrothiophene	99.9	1.89	4.6
	99.2	1.86	2.9
	109.8	5.20	2.6
	110.0	5.48	3.5
	115.1	7.53	4.0
	114.7	8.04	3.0
	123.7	19.2	2.0
	125.0	21.0	2.2
1-Azido-4-methoxybenzene[c]	120.0	0.170	2.1
	120.0	0.170	3.8
	130.0	0.526	2.3
	130.0	0.519	4.6
	140.0	1.53	1.6
	140.0	1.54	4.2
	150.0	4.35	2.4
	150.0	4.29	4.5

[a] In decalin; the free radical inhibitor is 2,6-di-*tert*-butyl-4-methylphenol. [b] Rate constants measured from disappearance of the carbonyl band in the IR spectrum were 1.84×10^{-4}, 4.85×10^{-4} and $5.17 \times 10^{-4}\ s^{-1}$ at 110.1, 123.5 and 124.1 °C, respectively. [c] E_{act} 149.1 ± 0.2 kJ mol^{-1}, S_{act} 32.3 ± 0.6 J K^{1} mol^{-1}. At 120 °C, 4-methoxy-1-azidobenzene reacts 4.5 times as fast as azidobenzene.

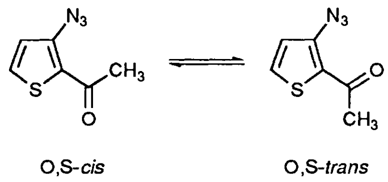
Table 2 Arrhenius parameters[a] and relative rates for the decomposition of 3-azidothiophenes in decalin

2-Substituent in 3-azidothiophene	k_{rel} (at 120 ° C)	E_{act}/ kJ mol^{-1}	S_{act}/ J K^{-1} mol^{-1}
H[b]	1	128.7 ± 1.6	−3.5 ± 4.1
2-CN	1.5	142.0 ± 1.1	29.8 ± 2.7
2-CO_2Me	0.42	129.5 ± 1.7	−12.4 ± 4.1
2-COMe	5.0	115.0 ± 1.5	−28.5 ± 4.1
2-NO_2	17.4[c]	116.6 ± 2.0	−13.7 ± 5.4

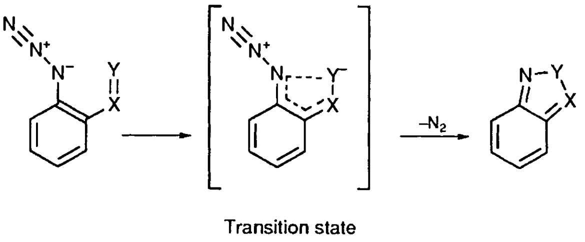
[a] Errors are expressed as 90% confidence limits. [b] Data for 3-azidothiophene are taken from ref. 4. The k_1 value calculated from their data for 120 °C and *p*-chlorotoluene as solvent ($1.17 \times 10^{-4}\ s^{-1}$) has been reduced by 1.54-fold (see Table 3) to $7.60 \times 10^{-5}\ s^{-1}$ to estimate the value for decalin as solvent. [c] For *p*-chlorotoluene as solvent, k_{rel} is 25.7 at 110.1 °C using our experimental value of $k_1 = 1.08 \times 10^{-3}\ s^{-1}$ for 3-azido-2-nitrothiophene.

Table 3 Solvent effect on rates of thermolysis of 3-azidothiophenes

2-Substituent in 3-azidothiophene	T/°C	k_1/s^{-1} (*p*-chlorotoluene)	k_1/s^{-1} (decalin)	Ratio
2-CO_2Me	144.6	5.06×10^{-4}	3.28×10^{-4}	1.54
2-NO_2	110.1	1.08×10^{-3}	5.27×10^{-4}	2.05



Scheme 2



Scheme 3

line with the generally large conjugative effects observed in thiophene compounds,[8] and the degree of negative charge on nitrogen at the transition state (see 3) must be considerable. We believe that this charge is the key to understanding the neighbouring group effects.

Neighbouring Group Effects on the Rate of Thermolysis of 3-*Azidothiophene*.—The rate enhancement by the 2-acetyl group in 3-azidothiophene (see Table 2) is surprisingly small (5-fold), whereas in azidobenzene the factor is reported[5] to be 413. This weak neighbouring group effect in 3-azidothiophene could possibly be attributed to an overwhelming preference[9] for the O,S-*cis* conformation (Scheme 2). This conformation is obviously unreactive in the electrocyclic mechanism[10] which is generally accepted for the neighbouring group effect (Scheme 3). However, there is no such conformational preference when nitro is the neighbouring group, and again the measured rate enhancement is far smaller for 3-azido-2-nitrothiophene (17.4-fold in decalin solvent, and 25.7-fold in *p*-chlorotoluene, see Table 3) than in 2-nitroazidobenzene (1060-fold).

Despite the very small magnitudes of these rate enhancements in the 3-azidothiophenes, the neighbouring group effect is real. Both the 2-nitro and the 2-acetyl compounds react significantly faster than the 2-cyano compound in which the substituent effects are comparable but the linear geometry of the cyano group makes a neighbouring group participation impossible. Moreover, the combination of negative S_{act} values and lowered E_{act} values for the 2-acetyl and 2-nitro compounds (see Table 2) is typical of neighbouring group effects in aryl azide decomposition.[10] The data in Table 2 show that methoxycarbonyl is not an effective neighbouring group; it actually *lowers* the rate of 3-azidothiophene by a very small factor but the origin of this effect is not readily apparent.

It remains to explain why these neighbouring group effects in 3-azidothiophenes are so small. Our work on azidobenzenes[11] supports the transition state shown in Scheme 3, in which the neighbouring group has taken negative charge onto itself from the azido group and is using this high electron density to bond across onto the essentially neutral inner nitrogen atom of the azido group. We deemed this electron distribution essential for an effective neighbouring group distribution. This requirement is in conflict with the electron distribution (structure **3**) which is responsible for the inherently high rates of thermolysis of all the 3-azidothiophenes, so that the transition state can derive little stabilization from involvement of the neighbouring group.

Products of Thermolysis.—2-Nitro-3-azidothiophene is reported[12,13] to yield thieno[3,2-*c*]furazan 1-oxide on thermolysis, though this compound decomposes in boiling toluene.[12] By analogy, 2-acetyl-3-azidothiophene should lose nitrogen on heating to yield 3-methylthieno[3,2-*c*]isoxazole. Our rate measurements on this azide are consistent with this expectation, the azido and carbonyl bands in the IR spectrum disappearing at the same rate (see Table 1) without appearance of any new carbonyl band. In a product run, where the azide was decomposed in boiling toluene, the product was contaminated with brown gum. Chromatography afforded a low-melting solid containing small amounts of 2-acetylthiophene-3-amine. Crystallization gave a white solid, m.p. 56–57 °C, which had no amine or carbonyl bands in the IR spectrum. The material was unstable at room temperature and was not pure by TLC. Only a poorly-resolved ^{1}H NMR spectrum could be obtained, though this was consistent with the expected structure. This white solid underwent a slow change into a high-melting material and could not be further characterized. There is a literature report[14] of the parent compound, thieno[3,2-*c*]isoxazole, being isolated in low yield from thermolysis of 3-azidothiophene-2-carbaldehyde.

Experimental

Synthesis of Azides.—All products have been checked for purity by TLC (silica gel G, $CHCl_3$ elution). Precursor amines were synthesized by published procedures and had appropriate m.p. and spectra (both IR and ^{1}H NMR). *J*-Values are given in Hz.

Methyl 3-*azidothiophene*-2-*carboxylate and* 2-*acetyl*-3-*azidothiophene.* The corresponding amine (5 mmol) was dissolved in conc. HCl (5 cm^3), chilled to −5 °C, and then treated dropwise during 5 min with a chilled solution of $NaNO_2$ (6 mmol) in water (2 cm^3), the temperature being kept below −4 °C. The mixture was stirred a further 10 min at −5 °C, after which urea (50 mg) was added to remove the excess of nitrous acid. After 5 min, the mixture was filtered to remove traces of solids and the filtrate was added in a steady stream to a stirred slurry of NaN_3 (7.7 mmol) and sodium acetate (15.09 g) in ice–water (25 cm^3). Frothing occurred, and the solid azide separated. The product was collected by filtration after a further 20 min. *Methyl* 3-*azidothiophene*-2-*carboxylate* was obtained in 89% yield, m.p. 67–68 °C. Recrystallization from aqueous methanol afforded white needles, the m.p. being unchanged (Found: C, 39.3; H, 2.3; N, 22.3. $C_6H_5N_3O_2S$ requires C, 39.34; H, 2.75; N, 22.9%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2125, 2104 (N_3) and 1702 (C=O); δ_H($CDCl_3$; 90 MHz) 3.88 (3 H, s, CH_3), 6.91 (1 H, d, *J* 5.3, 4-H) and 7.48 (1 H, d, *J* 5.3, 5-H); *m*/*z* 183 (M^+, 10%), 155 ($M - N_2$, 15), 125 (14), 97 (21) and 58 (100).

2-Acetyl-3-azidothiophene was obtained in 79% yield, m.p. 59–60 °C (decomp.); it crystallized from aqueous methanol as white micro-needles of the same m.p. as before (Found: C, 42.8; H, 3.2; N, 24.7. $C_6H_5N_3OS$ requires C, 43.10; H, 3.01; N, 25.14%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2163, 2117 (N_3), 1654sh and 1649 (C=O); δ_H($CDCl_3$; 90 MHz) 2.56 (3 H, s, $COCH_3$), 7.01 (1 H, d, *J* 5.3, 4-H) and 7.59 (1 H, d, *J* 5.3, 5-H); *m*/*z* 167 (M^+, 2%), 139 ($M - N_2$, 6) and 42 ($CH_2{=}C{=}O^+$, 100). The NMR spectrum is in satisfactory agreement with the one reported by Paulmier *et al.*[12] but we differ on the IR frequency of the carbonyl band (lit.,[12] 1700 cm^{-1}); these authors did not further characterize their compound.

3-*Azido*-2-*nitrothiophene.* Diazotization of the corresponding amine in conc. HCl by the method above was not satisfactory, but use of 50% sulfuric acid (a medium used by Paulmier *et al.*)[12] gave the azide in 67% yield. This compound crystallized from light petroleum as feathery pale yellow needles, m.p. 82–83 °C (lit.,[12,13] 81 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 2164, 2112 (N_3), 1546 and 1336 (NO_2).

3-*Azido*-2-*cyanothiophene.* Direct nucleophilic substitution of 3-bromo-2-cyanothiophene was attempted, using powdered dry LiN_3 in dry DMF as recommended by Choi *et al.*[15] for a similar substrate. Yields were poor; the best was 19% obtained after 48 h at 60 °C, with 53% of the starting material recovered. Longer reaction times (8 days at 60 °C) or higher temperatures (80 °C for 48 h) gave less recovery of the starting material but also lower yields of the azide. The pure azide, separated by thick layer chromatography on silica (chloroform elution) had ν_{max}/cm^{-1} 2220 (CN) and 2139 and 2111 (N_3); *m*/*z* 150 (M^+, 7.8%), 122 ($M - N_2$, 23.9), 95 (12.6), 70 (100). The published method of synthesis,[16] *via* 3-bromothiophene-2-carbaldehyde, is clearly superior.

1-*Azido*-4-*methoxybenzene.* The corresponding amine was diazotized in aqueous sulfuric acid and then added to NaN_3 buffered with sodium acetate, as above. The azide was recovered by diethyl ether extraction, and phenolic material was removed by washing with sodium carbonate solution before evaporating the diethyl ether. The pale tan solid azide (yield, 92%) had m.p. 31.0–32.5 °C (lit.,[7] 34 °C).

Rate Measurements.—The azides were heated in decalin solution in an oil-bath, and the internal temperature of the solution was measured. Concentrations were in the range 0.005 to 0.01 mol dm^{-3}. At suitable time intervals, samples were withdrawn and added to an ice-cold tube to stop the reaction. The absorbances of the azide band were measured with a Fourier transform IR spectrometer, using a solution cell of 0.5 mm thickness. Runs were followed for at least one, and sometimes as many as three, half-lives and ten samples were taken from each run. In all cases, the infinity absorbance was zero, and the runs were strictly first-order, the plots of ln (absorbance) *versus* time having correlation coefficients better than 0.999.

Under high resolution, there were several overlapping azide bands near 2120 cm^{-1}. With 3-azido-2-cyanothiophene (bands at 2137 and 2108 cm^{-1}) and 3-azido-2-nitrothiophene (bands at 2162 and 2108 cm^{-1}) the two bands were well-resolved and absorbance measurements on them both gave the same rate constants.

Products of Thermolysis of 2-*Acetyl*-3-*azidothiophene.*—The azide (110 mg) was heated in boiling toluene (10 cm^3) for 5.5 h (calculated as 4.5 half-lives). A small amount of brown gum was deposited. Chromatography in dichloromethane over a silica column separated a yellow band from a brown residue; the band was eluted with dichloromethane–diethyl ether and yielded a low-melting point solid (63 mg). The IR spectrum indicated traces of 2-acetylthiophene-3-amine (ν_{max}/cm^{-1} 3498 and 3352 for NH) as well as a major component. Crystallization from chloroform–hexane afforded colourless plates mixed with brown gum, and on standing the mother liquor deposited a white solid (20 mg) no longer soluble in chloroform and melting above 270 °C. Further crystallization of the gummy solid gave colourless plates (5 mg), m.p. 56–57 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1640 (sh), 1628 and no NH bands; δ_H($CDCl_3$; 90 MHz) 2.60 (3 H, s), 6.92 (1 H, broadened d, $J \approx 8$), 7.49 (1 H, broadened d, $J \approx 8$). The NMR spectrum was poorly resolved and the signals broadened with time. TLC revealed a major and a minor component in the NMR sample.

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