

^{15}N -CIDNP Measurements and *Ab Initio* Calculations on the Nitration of Dithieno[3,4-*b*:3',4'-*d*]pyridine *N*-Oxide

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^{15}N NMR studies indicate that radical ion coupling is involved in the nitration of the title compound. During the reaction under mildly acidic conditions at 40 °C strong emission signals appear, while at 0 °C signal enhancement is observed. Orientation effects of the ring system under mildly and strongly acidic conditions have been investigated by means of *ab initio* RHF/3-21G(*) and ROHF/3-21G(*) calculations.

In a previous paper we reported our experimental findings on the reaction-condition-dependent orientation effects of dithieno[3,4-*b*:3',4'-*d*]pyridine *N*-oxide during nitration.¹ If the reaction was attempted with nitric acid in trifluoroacetic acid (TFA) above 40 °C the substrate was completely decomposed (Fig. 1). At 0 °C the only nitrated product which could be isolated was the 6-nitro isomer **2**. However, this reaction also gave decomposition products of the ring system. Nitration of **1** under aprotic conditions,¹ in sulfolane with NO_2BF_4 , gave the same isomer **2**. Under strongly acidic conditions in TFA/sulfuric acid mixture, the nitration resulted in 1- and 8-nitro isomers, without a trace of the 6-nitro derivative. Such acidity-dependent directing effects were also reported for several bi- and tri-cyclic aromatic *N*-oxides (Table 1). Based on kinetic measurements, Gleghorn *et al.*^{5,8} concluded that nitration of quinoline *N*-oxide and isoquinoline *N*-oxide takes place through the conjugate acid under strongly acidic conditions, while under mildly acidic conditions the free base is involved in some way. As the $\text{p}K_a$ values of the quinoline *N*-oxide and **1** are of the same magnitude, it is highly probable that the same is true for the latter substrate. Another interesting feature is the similar orientation effects of the pyridine fused ring systems and their *N*-oxides under strongly acidic conditions. Moodie *et al.*⁷ demonstrated that the nitration of quinoline and isoquinoline takes place through the protonated form over a broad acidity range. We also found that addition of water to the nitrating mixture does not influence the distribution of dithieno[3,4-*b*:3',4'-*d*]pyridine isomers, in contrast to its *N*-oxide (Fig. 2). The $\text{p}K_a$ values of dithieno[3,4-*b*:3',4'-*d*]pyridine and of quinoline and isoquinoline (Table 1) are also similar, suggesting that its conjugated acid is nitrated, even if a considerable amount of water is present in the reaction mixture. The oxidation of the nitrogen atom decreases the basicity by 4–5 orders of magnitude which means that only under strongly acidic conditions can the nitration of the protonated form compete with that of the free base.

Results

^{15}N CIDNP Measurements.—The nitration reactions were carried out using 99% ^{15}N -labelled nitric acid in TFA(D) and followed by ^{15}N NMR spectroscopy. Running the reaction at 40 °C, strong emission signals were observed (Fig. 3, S1), followed by the total decomposition of the starting material. Disappearance of the H^{15}NO_3 signal accompanied the nuclear polarization. Mononitrated derivatives of **1** could not be obtained from this reaction mixture. Addition of sodium azide, to suppress nitrous acid catalysis, delayed, but did not hinder, the appearance of the emission signals (S1). Decomposition

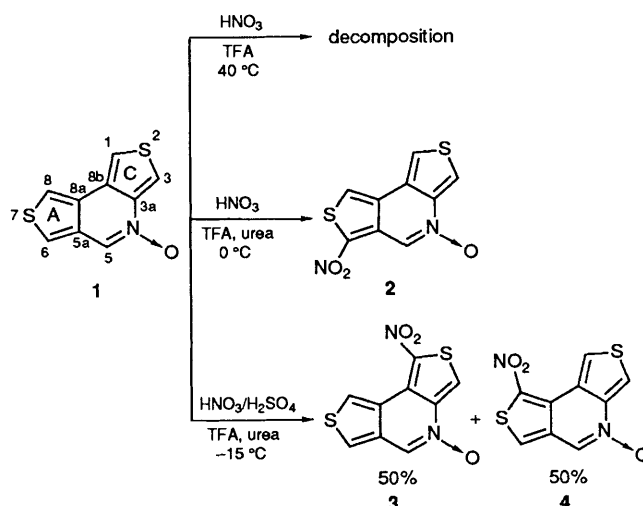


Fig. 1 Nitration of dithieno[3,4-*b*:3',4'-*d*]pyridine *N*-oxide under different reaction conditions

of aromatic *N*-oxides under similar conditions or higher temperatures has also been reported.^{9,10}

Running the reaction at lower temperature (0 °C) resulted in small but reproducible enhanced absorption of the ^{15}N signal of **2**. The reaction could be accelerated by addition of sulfuric acid. In order to avoid the protonation of the *N*-oxide, deuterated water was also added. It was attempted to suppress the nitrous acid catalysis by adding urea, rather than sodium azide because the latter decomposed with gas evolution in the presence of sulfuric acid. (The explosion of a sealed NMR tube containing highly corrosive acids may seriously damage the probe!) The reaction conditions were optimized to get the largest enhancement (S2, Fig. 3). Using conditions listed in the caption of Fig. 3, the half-life of the reaction is about 10 min. The largest enhancement (S2) of the ^{15}N signal of **2** in the beginning of nitration is 2.5 times relative to its intensity after completion of the reaction. This nuclear polarization indicates that radicals are involved in the nitration.^{12–14} According to the application of Kaptein's rule to the aromatic radical cation–nitrogen dioxide pair,^{12,14} if the nitration of an aromatic compound occurred by electron transfer from the aromatic to $^{15}\text{NO}_2$, followed by combination of the radicals formed, the ^{15}N NMR spectrum could show enhanced absorption but not emission. In a recent publication¹³ Johnston, Ridd and Sandall proposed two possibilities for the formation of the radical pair for this case: (i) homolysis of the C–N bond in a Wheland intermediate (*e.g.* nitration of durene); (ii) direct electron

Table 1 Comparison of physical data and orientation effects of some bi- and tri-cyclic pyridines and their *N*-oxides

Compound	pK_a	E°/V	Substituted position		Ref.
			m.a. ^a	s.a. ^b	
1	0.22 ± 0.02	1.20	6	1, 8	1 ^c
1-N^d	4.23 ± 0.02	2.10	1, 8	1, 8	2 ^c
Quinoline <i>N</i> -oxide	0.70	1.54	4	5, 8	3–5
Quinoline	4.87	1.97	5, 8	5, 8	3, 6, 7
Isoquinoline <i>N</i> -oxide	1.01	1.60	5, 6, 8	5, 8	3, 4, 8, 9
Isoquinoline	5.40	1.84	5, 8	5, 8	3, 6, 7
Benzo[<i>c</i>]cinnoline <i>N</i> -oxide			9	7, 10	10
Benzo[<i>c</i>]cinnoline	2.1 –3.5 ^f	1.72		1, 4 ^e	6, 10, 11

^a Mildly acidic conditions. ^b Strongly acidic conditions. ^c And this work. ^d Non-*N*-oxide of **1**. ^e Equivalent of 7, 10 positions of the corresponding *N*-oxide. ^f Second protonation constant.

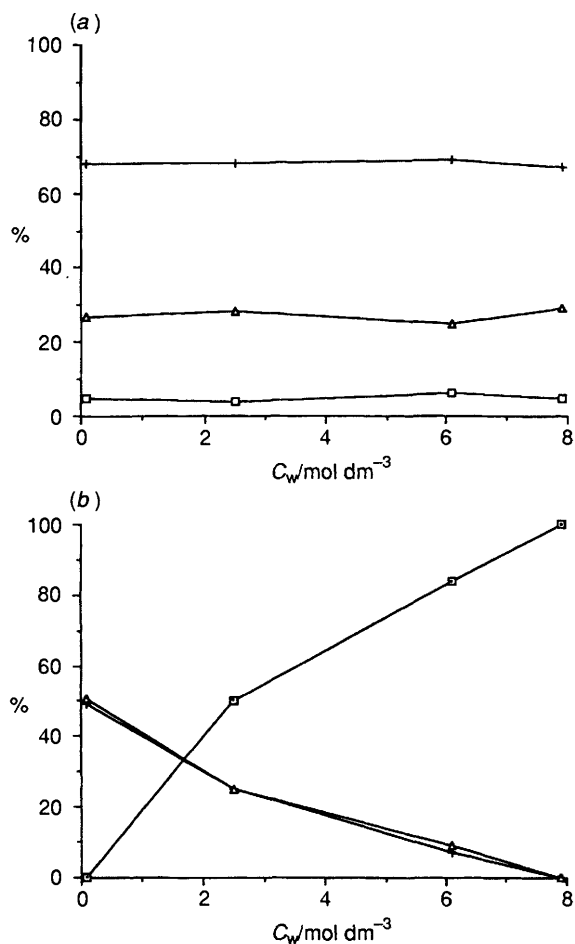


Fig. 2 Isomer distribution as a function of the added water for nitration of (a) dithieno[3,4-*b*:3',4'-*d*]pyridine and (b) its *N*-oxide (**1**). [H_2SO_4] = 2 mol dm⁻³; [HNO_3] = 0.5 mol dm⁻³; [urea] = 0.5 mol dm⁻³; in TFA. Legends: 1-nitro, +; 8-nitro, Δ; 3-nitro, □; 6-nitro, ◻.

transfer before the formation of the Wheland intermediate (e.g. nitration of naphthalene or 2-methylnaphthalene). Ebersson *et al.*¹⁵ suggested that the Wheland intermediates of perylene ($E^\circ = 1.3$ V) and the easily oxidizable aromatics tend to form a radical pair by homolytic fission of the C–N bond. Recombination of this radical pair is assumed to be a highly endothermic process. The formation of side products might be the result of decomposition of the aromatic radical cation. Since the oxidation potential of the unprotonated **1** (Table 1) is even lower than that of perylene, we believe that the radical pair formation during the nitration of **1** might be the result of the homolytic fission of the Wheland intermediate.

It should be pointed out that the measured ¹⁵N NMR signal

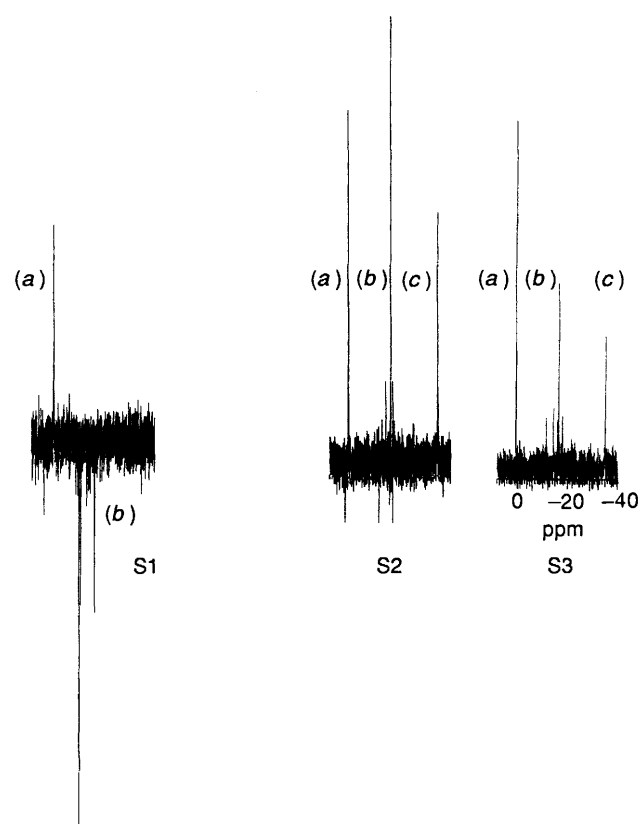


Fig. 3 ¹⁵N NMR spectra during nitration of **1**. S1: Nitration in TFA at 40 °C. Nuclear polarization after 45 min; [$Ph-^{15}NO_2$] = 0.3 mol dm⁻³; [$H^{15}NO_3$] = 0.5 mol dm⁻³; [NaN_3] = 0.5 mol dm⁻³; [D_2O] = 1.2 mol dm⁻³; [**1**] = 1.6 mol dm⁻³; in TFA. S2, 3: Nitration in TFA– D_2SO_4 mixture at 0 °C. Initial spectrum (1.5–6 min, S2) and final spectrum (52–56.5 min, S3); [$Ph-^{15}NO_2$] = 0.3 mol dm⁻³; [$H^{15}NO_3$] = 0.5 mol dm⁻³; [urea] = 0.5 mol dm⁻³; [D_2O] = 7 mol dm⁻³; [D_2SO_4] = 2 mol dm⁻³; [**1**] = 1.6 mol dm⁻³; in TFA. Assignment of the peaks: (a) [¹⁵N]nitrobenzene standard; (b) 6-nitrodithieno[3,4-*b*:3',4'-*d*]pyridine *N*-oxide; (c) $H^{15}NO_3$.

enhancement accounts for a small portion of formation of **2** through the radical pair recombination pathway. Nitration of naphthalene¹³ under similar conditions ($t_{1/2}$ ca. 10 min) resulted in signal enhancement to a similar extent (h_i/h_∞ ca. 2). The contribution of the electron transfer path to the overall reaction was estimated as being as small as 1%. However, according to Ebersson,¹⁵ in the case of the easily oxidizable aromatics, the recombination of the radical pair does not necessarily follow the fission of the Wheland intermediate. On the other hand, if under the same reaction conditions the radical pairs were formed both by diffusion together of the components (leading

Table 2 Results of *ab initio* calculations

Position of substitution	N-O ^a		N ^b		N-H ^c	N-H(TS) ^d
	<i>E</i> _{tot} ^e	<i>E</i> _{rel} ^f	<i>E</i> _{tot} ^e	<i>E</i> _{rel} ^f	<i>E</i> _{rel} ^{f,g}	<i>E</i> _{rel} ^{f,g}
1	-1464.190 399	0.0	-1389.841 828	0.0	0.0	0.0
3	-1464.184 199	16.3	-1389.842 458	-1.7	-9.2	7.3
6	-1464.199 725	-24.5	-1389.826 276	40.8	39.2	33.9
8	-1464.183 724	17.5	-1389.836 986	12.7	-9.3	5.9

^a Wheland intermediates of **1**. ^b Wheland intermediates of dithieno[3,4-*b*:3',4'-*d*]pyridine. ^c Wheland intermediates of dithieno[3,4-*b*:3',4'-*d*]pyridinium. ^d Transition states for dithieno[3,4-*b*:3',4'-*d*]pyridinium. ^e Total energy in atomic units. ^f Energy relative to 1-substitution, in kJ mol⁻¹. ^g From ref. 2.

to emission signals) and by dissociation of Wheland intermediates, the resultant polarization would be weaker than normally observed. In this case the radical pathway would contribute to the overall reaction to a larger extent than is expected from the observed nuclear polarization.

Ab-initio Calculations.—All the structures which are presented herein are optimized on the RHF/3-21G(*) level. The d functions on sulfur atoms only were included. Spin densities for the radical cation of **1** were calculated by the spin restricted open-shell Hartree-Fock (ROHF) method, because the spin unrestricted procedure (UHF) gave unacceptable high spin contamination. In this calculation the optimized geometry of **1** was used.*

Nitration of the conjugated acid. By analogy with the nitration of (iso)quinoline *N*-oxide, it is supposed that under strongly acidic conditions the conjugated acid of **1** is nitrated. The protonation certainly stabilizes it against oxidation. Unfortunately, the oxidation potentials in sulfuric acid are not available, but a related property, the ionization potential (*E*_i) was calculated. *E*_i obtained for the free base is 8.1 eV, while for the conjugate acid it is 12.5 eV. The *E*_i values corrected¹⁶ by the estimated effects of the solvent (TFA) are 7.5 eV and 11.5 eV for the free base and conjugated acid respectively. Since the latter *E*_i value is already high enough¹⁷ to exclude the possibility of an ET pathway, the orientation effects of the conjugated acid are discussed within the framework of the electrophilic substitution mechanism.

It was demonstrated^{2,18} that the calculated Wheland intermediate stabilities of the *N*-protonated heterocycles do not (or poorly) correlate with the isomer distribution of nitration. The electrostatic repulsion between the positively charged reactants (*i.e.* the conjugated acid and nitronium ion) raise an activation barrier to the formation of the Wheland intermediate. If the transition state (TS) has an 'early' or 'half-way' nature, the field effects arising from the protonated part of the aromatic ring may be stronger than the inductive or resonance effects, which determine the Wheland intermediate stability. The activation barrier heights calculated² for the non-*N*-oxide of **1** are in good agreement with the experimentally found position preferences (Table 2). It was also shown¹⁸ that the electrostatic potential of the aromatic ring at those points where the nitronium ion is situated in the TS for nitration at different ring positions, correlates well with the calculated TS energies. This is due to the ionic nature of the interactions, which determine the stability of TS complexes. The calculation of electrostatic potential maps is much simpler and cheaper than the localization of TSs. It was supposed that, similar to the non-*N*-oxide case,² the nitronium

ion would be situated in a plane parallel to the ring plane in the vicinity of the attacked position in the TS (π -type TS complex). This plane would be about 2.6 Å above the ring plane, as for the non-*N*-oxide. The electrostatic map calculated for the protonated non-*N*-oxide¹⁸ [Fig. 4(a)] is quite similar to that of the *N*-oxide [Fig. 4(b)]. In agreement with the experimental findings, the main differences are: (i) the higher repulsion energy in the vicinity of the 3-position, and (ii) more equal potential in the vicinity of the 1- and 8-positions for the *N*-oxide than in the other case. Nitration of the 6-position seems to be highly disadvantageous in both cases.

Nitration of free base. The CIDNP measurements suggest that the nitration of the free base follows a radical mechanism at least partially. However, it is probable that the main reaction pathway is an ionic process. If the radical pair is formed by fission of the Wheland intermediate even this radical reaction path is preceded by an ionic step (*i.e.* formation of the Wheland intermediate).

A possible ionic pathway could be a classical electrophilic substitution. Since the free base is uncharged, the Wheland intermediate model is expected to predict correctly the orientation preferences. The gas phase experimental¹⁹ and theoretical²⁰ results show that there is no intrinsic activation barrier between the positively charged nitronium ion and uncharged aromatics. It was proposed²⁰ that in the solvent phase the nitronium ion should overcome a desolvation barrier. The positional selectivity is produced after this barrier and close correlation is expected between the stability of Wheland intermediates and position preferences.

The Wheland intermediate for substitution at the 6-position was found to be the most stable of the possible substitutions on the thiophene rings (Table 2). Effects arising from substitution on the ring nitrogen have also been investigated. *N*-Protonation has rather weak effects on the Wheland intermediate stability in comparison with that of dithieno[3,4-*b*:3',4'-*d*]pyridine. It decreases somewhat the stability of the 1-substituted Wheland intermediate. In contrast, oxidation of the ring nitrogen dramatically changes the orientation effects. It alters the position preference from 3 > 1 > 8 ≫ 6 to 6 ≫ 1 > 3 ≈ 8.

Atomic spin densities for the radical cation of **1** are given in Fig. 5. Spin densities are rather low at the thiophene α positions with the highest value at the 6-position. It is relatively high at the pyridine α position (5-position). Although the 5-nitro derivative has not been detected in the reaction mixture of **1**, it has been obtained as a minor product in the nitration of dithieno[2,3-*b*:3',2'-*d*]pyridine *N*-oxide.¹ Spin densities are largest at oxygen and nitrogen atoms, suggesting that these may be reaction centres for further radical transformations.

Experimental

***pK*_a Measurements.**—The ionization constant for **1** was determined by a photometric method using Varian CARY 2290 spectrophotometer. The Bunnett-Olson method was applied²¹

* Internal coordinate systems (in Z-matrix form) and optimized geometrical parameters are available as supplementary material, Supp. Pub. No. 56903, 7 pp. See 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1992, issue 1.

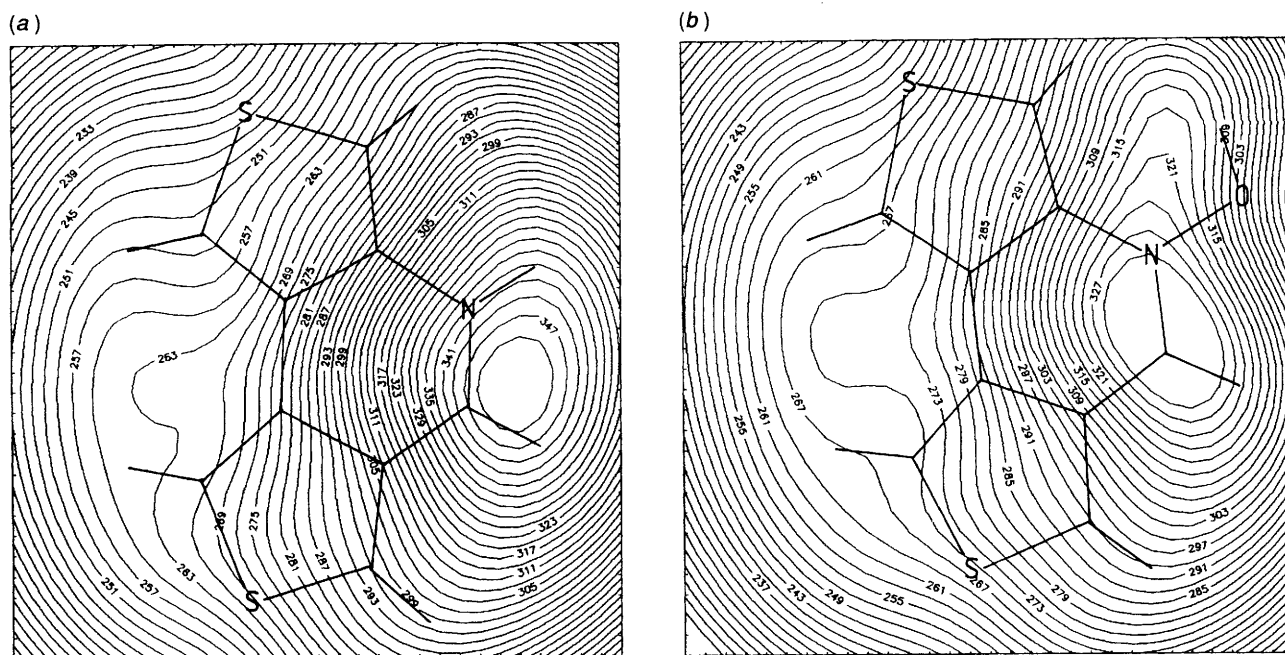


Fig. 4 Electrostatic potential 2.6 Å above (a) dithieno[3,4-*b*:3',4'-*d*]pyridinium and (b) its *N*-oxide. The energy levels are given in kJ mol⁻¹.

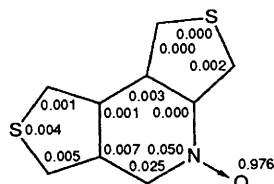


Fig. 5 ROHF/3-21G(*) spin densities calculated for the radical cation of **1**. Expectation value of $\langle S^2 \rangle = 0.75$.

using the H_A acidity function values (recommended²¹ for *N*-oxides) in evaluation of experimental data. The ionization constant for dithieno[3,4-*b*:3',4'-*d*]pyridine was determined by potentiometric titration (with 0.01 mol dm⁻³ sodium hydroxide solution) of the chloride salt with a Radiometer PHM92 titrigraph.

¹⁵N NMR Measurements.—The aromatic compound and the standard ([¹⁵N]nitrobenzene 98%, purchased from Berlin-Chemie) were initially dissolved in TFA (0.4 cm³). The [¹⁵N]nitric acid (99% ¹⁵N, purchased from MSD isotopes) D₂O and eventually sulfuric acid were mixed with another portion of TFA (0.4 cm³) containing the required amount of sodium azide or urea (for exact concentrations see caption of Fig. 3). After 10 min at the appropriate temperature (40 °C or 0 °C) the two solutions were mixed and poured into an NMR tube. The runs, which were followed by ¹⁵N NMR spectroscopy (resonance frequency: 30.4 MHz), were carried out on a Varian XL-300 instrument. The spectra involved 25 pulses, each of 15 μs with an acquisition time of 0.8 s and 10 s delay. ¹⁵N shifts observed relative to [¹⁵N]nitrobenzene: 6-[¹⁵N]nitrodithieno[3,4-*b*:3',4'-*d*]pyridine *N*-oxide: -16.9 ppm; [¹⁵N]nitric acid: -35 ppm.

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