protonation mechanism[25] is not observed because of the relative difficulty of O-protonation in *N*-acyl imines and the availability of a low energy path for imine hydrolysis in these compounds.[2,24]

Acknowledgment. This work was supported, in part, by a grant from the National Institutes of General Medical Sciences (GM 38449-01). A grant of computer time on the Cray Y-MP8/864 at the Ohio Supercomputer Center is also gratefully acknowledged (POS075-1), as is the help of the Miami University Academic Computer Service in installing and testing GAUSSIAN86 at Miami. We would also like to thank Professor Gilbert Gordon of this department for the use of his rapid scan stopped flow spectrophotometer and Dr. Istvan Fabian for his technical assistance with this instrument.

Supplementary Material Available: Table I listing hydrolysis rate constants for **1a** and **1b** and Table IV listing optimized STO-3G and 3-21G structures for **1–5a** and **1–5b** (14 pages). Ordering information is given on any current masthead page.

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Experimental and Theoretical Study of Orientation in the Nitration of Dithieno[3,4-*b*:3′,4′-*d*]pyridine

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The nitration of dithieno[3,4-*b*:3′,4′-*d*]pyridine was investigated. Despite the similarity of the electrophilic reaction centers, high positional selectivity was found. Thus, the 1-, 8-, and 3-nitro isomers were obtained in the relative amounts 78%, 20%, and 2%, respectively. In spite of the unusually large size of the molecular systems, the structure and electronic properties of the Wheland intermediates (sigma complexes) and the transition states were calculated at the ab initio 3-21G* level. Harmonic frequencies have been calculated to characterize the stationary points obtained. The Wheland intermediate model failed to predict the site preferences, probably due to steric hindrance. However, the energies found for the transition-state complexes are in good agreement with the experimental findings. The transition-state geometry of the ring system shows greater similarity to the parent structure than to the Wheland intermediate. Orientation effects could be explained by the electron distribution of the transition-state structures.

One of the greatest successes of theoretical organic chemistry is the explanation of the orientating effects of substituents in benzene derivatives in electrophilic substitution reactions.[1] However, although these qualitative rules give reliable results in predicting the isomer distribution in the nitration of aromatic hydrocarbons, they often fail to interpret the results found in the substitution of heterocyclic compounds. This is a consequence of the quite complicated electronic and steric effects, particularly in systems containing several rings and heteroatoms.

There is a considerable current interest in effects that arise from the fusion of several nonequivalent monocycles. Klemm[2] pointed out that the thienopyridine systems should be particularly pertinent for a study of the effects of ring interactions of the monocyclic components (thiophene and pyridine).

We investigated the nitration reaction of dithieno[3,4-*b*:3′,4′-*d*]pyridine (1). This ring system is especially interesting as it contains four nonequivalent thiophenic α-positions. The C_{2v} symmetry of the benzo analogue is decreased only by the nitrogen atom. These two facts suggest a similar reactivity for all the electrophilic centers. In contrast, the experimental results showed high positional selectivity.

The present combined experimental and theoretical investigation was undertaken to gain more insight into the nature of the directing and activating effects in this dithienopyridine ring system.

Experimental Results

The parent compound 1 was nitrated in strong acidic medium (TFA) with nitric acid. Modie et al. demonstrated that the nitration of quinoline and isoquinoline takes place through the conjugate acid under similar conditions.[3] Since the pK_a value for the thienopyridines and isoquinoline are of the same magnitude,[4] it is highly probable that the same is true for the dithieno analogue 1. This is supported by the fact that the nitrate salt of 1 can be precipitated by adding nitric acid to its ethereal solution. Under these conditions, nitration of thiophene rings take place partly via nitrosation followed by oxidation.[5] In order to avoid this side reaction, on determination of isomer distribution, urea was added to remove the nitrous acid.[5] Without this precaution the amount of the 8-nitro derivative is somewhat higher in the reaction mixture (60% 1-nitro, 38% 8-nitro, and 2% 3-nitro derivative). The results of the competitive nitration (eq 1) show that position 1 (2) is the most reactive followed by position 8 (4) and position 3 (3). We could not detect any nitration in position 6 nor in position 5. The nitro isomers are all crystalline products with high melting points. Their sol-

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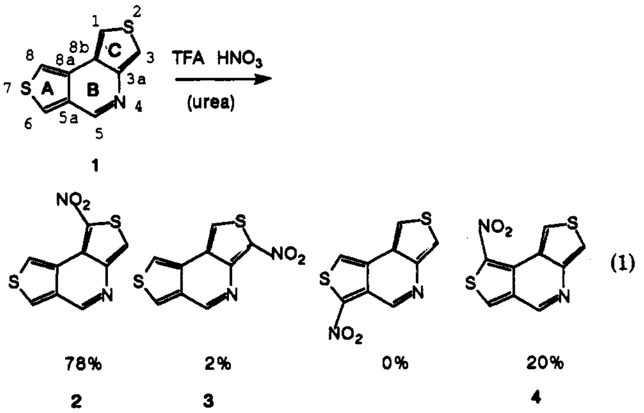

1, 2, 3, 4

(1)

ubility is rather low in common solvents. The 1-nitro isomer (**2**) was difficulty soluble in the eluent system used for the chromatography, which explains the rather low isolated yield. The higher activity of positions 1 and 8 was surprising because steric hindrance was expected for these positions.

The structure determination of the various isomers was carried out by NMR and authentic synthesis. Gronowitz et al.[6] emphasized the usefulness of the characteristic long-range coupling between H^5 and H^8 for structure determination of thienopyridine systems. This phenomenon also appears in dithienopyridines[7] and is conserved in the nitrated products (Table I). The simultaneous presence of the long-range couplings J_{58} and J_{68} of the thiophene protons resulted a pseudoquartet in the ^{1}H NMR spectrum of the nitro isomers **2** and **3**. This proved that the substitution must have taken place in ring C. Neither from these results nor from other standard NMR measurements could the correct position of the nitration (namely, whether position 1 or 3 has reacted) be determined. Identification of the 1-nitro derivative was therefore carried out by an authentic synthesis (Figure 1). 4-Bromo-5-nitro-3-thiophenecarboxylic acid[8] was converted into its carbamate **5**. The Pd(0)-catalyzed coupling[7] reaction of **5** and the 4-formyl-3-thiopheneboronic acid[9] resulted in a dithienopyridine derivative, which is identical with the 1-nitro derivative (**2**) obtained from the nitration reaction (eq 1). These findings also proved the structure of the minor product **3**. The lack of the long range coupling in the ^{1}H NMR spectrum of the nitro derivative **4** suggests that the substitution takes place at position 8. This is confirmed by the evidence obtained from its carbon–proton coupled spectrum. As a consequence of the molecular structure, only $^1J_{CH}$ ($\approx$190 Hz) and $^3J_{CH}$ ($\approx$4 Hz) couplings are expected for the hydrogen-bearing carbon atoms. Both types of interactions appear for the four tertiary carbon atoms in the ^{13}C–H coupled spectrum of **4** (Table II). This coupling scheme is only possible for the 8-nitro derivative. In all the other cases (except for the highly unlikely 5 substitution), one of the $^3J_{CH}$ couplings should be missing, as demonstrated for the 1-nitro derivative **2** (Table II).

Theoretical Investigations. There are two essentially different mechanisms to describe the nitration reactions: ionic, electrophilic substitution[1,10] (S_E2) and the radical, electron-transfer mechanism[10] (ET). The standard electrode potential (E^0) (measured by cyclic voltammetry in acetonitrile) found[11] for **1** is 2.10 V, too high for an ET nitration.[12] On the other hand, the first ionization potential calculated for the protonated starting material B (Figure 2) is 12.3 eV. Such a high ionization potential leads to a large charge-transfer ionization energy ($h\nu_{CT}$) by Pedersen's model for electron-transfer nitration,[13] which also seems to exclude the possibility of an electron-transfer mechanism. We therefore suppose that the nitration of **1** can be discussed within the framework of the S_E2 mechanism.[1] In this approach, the attacking agent is the nitronium ion, and the reaction consists of two steps: the first step is the formation of the high-energy intermediate (Wheland intermediate), and the second step is the elimination of a proton from the reaction center. The absence of a kinetic isotope effect in protic media shows that the latter step cannot be rate determining.[14] We also suppose that the rate-determining step, and thus the step that determines the isomer distribution, is the formation of the Wheland intermediate.[1,15,16] Thienopyridines and dithienopyridines are nitrated with high substrate and positional selectivity,[2,6,17] which seems to confirm[10] this assumption.

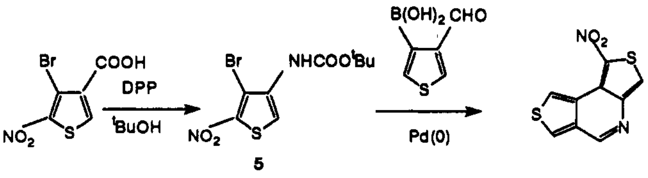

Figure 1. Authentic synthesis for 1-nitro derivative.

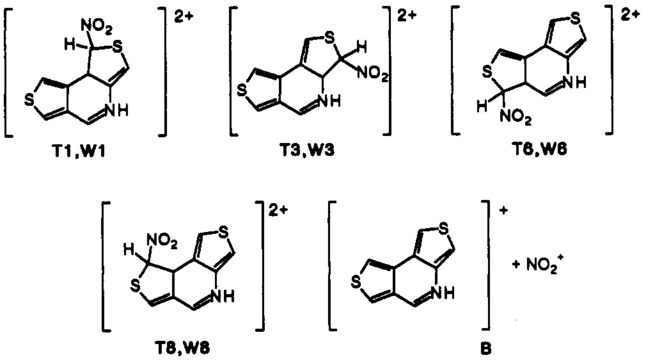

Figure 2. Schematic structure of the calculated complexes.

There is an increasing number of publications discussing aromatic electrophilic substitution by means of theoretical methods. Although the major part of these calculations deals with the examination of the nitration of benzene or benzene derivatives,[18,19] some substitution reactions of heterocyclic ring systems have also been reported.[20,21]

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Table I. Proton NMR Shifts (ppm) and Coupling Constants (Hertz) in $CDCl_3$

	H^1	H^3	H^5	H^6	H^8	$^3J_{13}$	$^3J_{68}$	$^4J_{58}$[a]
2	–	8.11	8.95	8.14	9.34	–	3.1	0.9
3	8.02	–	9.61	7.89	8.05	–	3.1	0.4
4	9.28	7.96	8.68	8.19	–	3.4	–	–

[a] Long-range couplings.

Table II. Carbon NMR Shifts and Carbon–Proton Coupling Constants of 1- and 8-Nitro Isomers in 80% Formic Acid 20% Acetone-d_6 Solvent Mixture

	C^1	C^3	C^{3a}	C^5	C^{5a}	C^6	C^8	C^{8a}	C^{8b}
2									
δ (ppm)	151.4	131.6	138.6	151.8	136.1	149.0	137.2	133.6	128.8
$^1J_{CH}$ (Hz)		196.0		192.7		196.0	198.4		
$^3J_{CH}$ (Hz)		–		2.9		5.3	5.0		
4									
δ (ppm)	125.4	137.2	140.3	154.3	134.6	153.3	150.2	134.3	128.1
$^1J_{CH}$ (Hz)	194.7	198.1		194.0		197.5			
$^3J_{CH}$ (Hz)	5.1	5.0		3.4		2.5			

Table III. Calculated Bond Lengths (in Angstroms) for Transition States and Wheland Intermediates

bond[a]	T1	W1	T3	W3	T6	W6	T8	W8	B[b]
C^1S^2	1.726	1.824	1.691	1.664	1.696	1.678	1.698	1.654	1.706
S^2C^3	1.697	1.661	1.732	1.818	1.700	1.690	1.704	1.721	1.705
C^3C^{3a}	1.362	1.398	1.371	1.506	1.354	1.361	1.352	1.343	1.352
$C^{3a}C^{8b}$	1.429	1.382	1.426	1.371	1.439	1.449	1.439	1.463	1.438
$C^{8b}C^1$	1.374	1.513	1.372	1.413	1.363	1.377	1.364	1.403	1.355
$C^{3a}N^4$	1.406	1.400	1.400	1.347	1.407	1.383	1.410	1.398	1.410
N^4C^5	1.307	1.309	1.319	1.350	1.292	1.307	1.296	1.302	1.301
C^5C^{5a}	1.404	1.404	1.392	1.372	1.432	1.412	1.420	1.411	1.409
$C^{5a}C^{8a}$	1.449	1.462	1.450	1.461	1.431	1.367	1.443	1.412	1.446
$C^{8a}C^{8b}$	1.450	1.407	1.450	1.445	1.436	1.410	1.443	1.376	1.451
$C^{5a}C^6$	1.376	1.366	1.384	1.399	1.378	1.500	1.374	1.399	1.374
C^6S^7	1.679	1.693	1.671	1.656	1.719	1.826	1.685	1.660	1.680
S^7C^8	1.717	1.689	1.721	1.723	1.681	1.624	1.727	1.828	1.719
C^8C^{8a}	1.353	1.375	1.350	1.348	1.383	1.466	1.371	1.519	1.351
C^1H^1	1.070	1.087	1.069	1.075	1.068	1.068	1.068	1.066	1.067
C^3H^3	1.070	1.075	1.071	1.089	1.068	1.069	1.068	1.068	1.067
N^4H^4	1.007	1.009	1.006	1.015	1.011	1.012	1.009	1.011	1.005
C^5H^5	1.072	1.072	1.072	1.072	1.072	1.069	1.072	1.072	1.071
C^6H^6	1.070	1.070	1.070	1.071	1.072	1.087	1.071	1.076	1.069
C^8H^8	1.068	1.066	1.068	1.068	1.069	1.075	1.071	1.085	1.067
AN^A	2.610	1.510	2.577	1.501	2.540	1.506	2.723	1.514	–
O^XN^A	1.126	1.232	1.129	1.216	1.141	1.228	1.121	1.235	1.111
O^YN^A	1.125	1.229	1.131	1.250	1.142	1.236	1.121	1.225	1.111

[a] In order to avoid much blank space the carbon atom attacked (C^1, C^3, C^6, and C^8) is denoted by A. [b] Separated reactants, see Figure 2.

Calculations on larger molecular systems (for instance, fused heterocycles) have been carried out on a semiempirical level,[19,21] while ab initio calculations have been published for benzene derivatives[18] and even for a heterocycle.[20] It also appears from these papers that calculations of the structure of the Wheland intermediate give more reliable results than those which examine the various reactivity indices of the aromatic substrate.

Computational Aspects. The GAUSSIAN86[22] and CADPAC[23] computer programs were used on a Cray XMP-48 supercomputer (National Superdator Center, Linköping) to perform the present calculations. Standard, single-determinant, restricted Hartree–Fock (RHF) calculations were carried out using the split valence 3-21G* basis set. The d orbitals on the sulfur atoms were included. The reason for using d functions was to account for the polarization of the electron distribution[24] of the sulfur-containing ring system. Stationary structures were optimized by using Schlegel's gradient technique.[25] A flexible internal coordinate system (available as supplementary material) was constructed in order to speed up the convergence of the geometry optimization. The optimization procedure was carried out with no restrictions on the internal coordinates, and continued until the largest remaining force was less than 0.002 au for the Wheland intermediate structures or 0.0005 au for the transition states.

Results and Discussion

The calculated geometry parameters for the possible isomers (Figure 2) are listed in Tables III and IV, the charge densities in Table V and the energies in Table VI. The eigenvalues of the second-derivative matrix for the Wheland intermediates (W1, W3, W6, and W8) were calculated at the AM1 level,[26] giving all positive values,

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(26) The resulted 3-21G* structures were reoptimized by AM1 method resulting substantially similar geometries. The AM1 second derivatives were calculated at these AM1 geometries.

Table IV. Calculated Bond Angles (Degrees) for Transition States and Wheland Intermediates

angle[a]	T1	W1	T3	W3	T6	W6	T8	W8	B[b]
$C^1S^2C^3$	91.9	91.0	91.9	90.9	93.0	94.3	92.7	94.0	92.5
$S^2C^3C^{3a}$	111.8	116.2	110.4	106.7	110.6	110.6	110.9	110.7	110.7
$C^3C^{3a}C^{8b}$	113.4	114.1	113.3	113.3	113.5	112.8	113.4	113.3	113.7
$C^{3a}C^{8b}C^1$	110.9	110.6	111.0	111.1	110.8	111.0	110.8	109.7	110.9
$C^{8b}C^1S^2$	111.8	107.9	113.1	117.1	112.0	111.4	112.1	112.3	112.2
$C^{8b}C^{3a}N^4$	120.4	121.4	120.2	122.6	119.6	118.8	119.9	118.8	119.9
$C^{3a}N^4C^5$	122.4	122.0	122.2	121.7	123.4	123.7	122.9	122.4	122.7
$N^4C^5C^{5a}$	120.9	119.9	121.1	120.0	120.3	119.4	120.7	120.2	121.2
$C^5C^{5a}C^{8a}$	121.1	120.3	121.0	121.1	120.3	120.5	120.8	120.9	120.8
$C^{5a}C^{8a}C^{8b}$	117.0	117.2	116.8	115.5	118.3	121.1	117.4	119.1	117.2
$C^{8a}C^{8b}C^{3a}$	118.2	119.2	118.6	119.1	118.0	116.6	118.2	118.5	118.2
$C^{8a}C^{5a}C^6$	112.2	112.2	112.1	111.4	112.9	113.9	112.5	113.6	112.7
$C^{5a}C^6S^7$	111.5	111.4	111.5	111.6	110.5	106.3	112.1	116.5	111.3
$C^6S^7C^8$	93.0	93.6	93.2	93.9	92.8	92.8	92.6	91.7	93.0
$S^7C^8C^{8a}$	111.8	112.1	111.7	111.5	112.6	115.7	111.6	107.8	111.8
$C^8C^{8a}C^{5a}$	111.4	110.7	111.5	111.6	111.0	111.0	111.2	110.4	111.3
$C^{8b}C^1H^1$	125.8	110.5	126.0	123.3	127.1	127.7	127.1	125.5	126.8
$S^2C^1H^1$	120.8	109.7	120.9	119.5	120.9	120.9	120.8	122.1	121.1
$C^{3a}C^3H^3$	127.0	124.1	127.0	110.3	127.9	127.8	127.7	128.2	127.7
$S^2C^3H^3$	121.2	119.7	120.8	109.3	121.5	121.7	121.1	121.1	121.6
$C^{3a}N^4H^4$	118.2	118.8	118.6	117.3	117.4	118.4	117.6	118.2	117.7
$C^5N^4H^4$	119.4	119.1	118.9	120.8	119.2	117.9	119.4	119.4	119.6
$C^{5a}C^5H^5$	121.5	122.1	121.7	123.4	121.3	121.9	121.1	121.6	121.1
$N^4C^5H^5$	117.6	118.0	117.2	116.6	118.3	118.8	118.2	118.2	117.8
$C^{5a}C^6H^6$	126.8	127.1	126.7	126.3	127.1	113.6	126.6	123.9	126.9
$S^7C^6H^6$	121.7	121.5	121.8	122.2	121.5	109.6	121.4	119.7	121.9
$C^{8a}C^8H^8$	127.9	126.7	127.9	128.5	126.4	123.5	126.3	111.3	127.5
$S^7C^8H^8$	120.3	121.2	120.3	120.0	121.0	120.8	120.4	110.2	120.7
AN^AO^X	96.4	116.5	101.3	117.2	101.7	115.9	96.1	115.7	-
$O^XN^AO^Y$	162.9	128.7	162.0	129.1	155.5	129.6	166.8	128.8	180.0
$C^{8b}C^1N^A$	96.2	114.3	-	-	-	-	-	-	-
$S^2C^1N^A$	90.4	108.5	-	-	-	-	-	-	-
$C^{3a}C^3N^A$	-	-	99.9	112.3	-	-	-	-	-
$S^2C^3N^A$	-	-	84.4	112.6	-	-	-	-	-
$C^{5a}C^6N^A$	-	-	-	-	99.8	112.2	-	-	-
$S^7C^6N^A$	-	-	-	-	79.3	109.0	-	-	-
$C^{8a}C^8N^A$	-	-	-	-	-	-	90.1	113.1	-
$S^7C^8N^A$	-	-	-	-	-	-	103.2	108.8	-
$O^YN^AAH^A$	1.1	-92.1	9.9	-74.8	-16.8	-80.7	131.6	-99.0	-
$C^8C^{8a}C^{8b}C^1$	1.0	-4.2	-2.9	3.6	3.2	2.1	-0.8	-2.6	0.0

[a] In order to avoid much blank space the carbon atom attacked (C^1, C^3, C^6, and C^8) is denoted by A. [b] Separated reactants, see Figure 2.

Table V. Atomic Charges Calculated from the Mulliken Analysis for Transition States and Wheland Intermediates

	T1	W1	T3	W3	T6	W6	T8	W8	B[a]
C^1	-0.597	-0.324	-0.419	-0.277	-0.433	-0.440	-0.452	-0.350	-0.451
S^2	0.602	0.780	0.595	0.780	0.689	0.776	0.665	0.788	0.585
C^3	-0.413	-0.297	-0.580	-0.313	-0.426	-0.438	-0.429	-0.453	-0.441
C^{3a}	0.392	0.383	0.429	0.603	0.385	0.448	0.389	0.458	0.385
N^4	-1.031	-1.026	-1.045	-1.057	-0.999	-1.011	-1.013	-1.022	-1.023
C^5	0.437	0.450	0.429	0.418	0.429	0.413	0.438	0.457	0.424
C^{5a}	-0.274	-0.243	-0.282	-0.275	-0.246	-0.173	-0.283	-0.308	-0.271
C^6	-0.379	-0.392	-0.371	-0.355	-0.523	-0.317	-0.371	-0.274	-0.397
S^7	0.696	0.769	0.707	0.778	0.668	0.870	0.648	0.769	0.622
C^8	-0.465	-0.380	-0.467	-0.475	-0.444	-0.272	-0.610	-0.322	-0.476
C^{8a}	0.055	-0.002	0.076	0.099	-0.071	0.051	0.052	0.205	0.077
C^{8b}	-0.077	0.061	-0.107	-0.159	-0.098	-0.109	-0.121	-0.169	-0.083
H^1	0.344	0.427	0.355	0.407	0.334	0.344	0.319	0.390	0.310
H^3	0.356	0.403	0.347	0.441	0.344	0.362	0.342	0.365	0.309
H^4	0.446	0.459	0.440	0.485	0.459	0.470	0.453	0.467	0.429
H^5	0.391	0.410	0.390	0.412	0.388	0.422	0.388	0.406	0.359
H^6	0.359	0.379	0.360	0.382	0.368	0.428	0.365	0.404	0.328
H^8	0.326	0.381	0.333	0.344	0.366	0.416	0.337	0.425	0.314
N^A	1.140	0.382	1.112	0.377	0.987	0.380	1.185	0.387	1.286
O^X	-0.156	-0.337	-0.152	-0.358	-0.162	-0.331	-0.155	-0.344	-0.143
O^Y	-0.147	-0.282	-0.149	-0.257	-0.155	-0.289	-0.148	-0.276	-0.143

[a] Separated reactants, see Figure 2.

and thus verifying that these structures are real minima on the potential energy surface[27] (Table VI). It can be seen that the relative energies (E_{rel}, Table VI) of the Wheland intermediate do not reflect the experimental findings very well. The site preference resulting from this model is 8 = 3 > 1 > 6, in contradiction with the experimental order 1 > 8 > 3 > 6. The most surprising finding is the poor stability of the 1-substituted complex (W1) compared to the 3-substituted complex (W3). In order to get more reliable results, and to explore the deficiencies of the Wheland intermediate approach, we also calculated the

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Table VI. Calculated Energies and the Characterization of the Stationary Points

	E_{total}, au	ΔE,[a] kJ/mol	E_{rel},[b] kJ/mol	NES[c]	IF,[d] cm^{-1}	E_{zpv},[e] kJ/mol	E_{corr},[f] kJ/mol
W1	−1390.072 748	59.6	0.0	0	–	–	–
W3	−1390.076 237	50.4	−9.2	0	–	–	–
W6	−1390.057 799	98.8	39.2	0	–	–	–
W8	−1390.076 279	50.3	−9.3	0	–	–	–
T1	−1390.012 260	218.4	0.0	1	i227	353.1	0.0
T3	−1390.009 476	225.7	7.3	1	i285	352.8	7.0
T6	−1389.999 561	251.7	33.9	1	i286	353.1	33.9
T8	−1390.009 987	224.3	5.9	1	i179	353.2	6.0
B	−1187.635 382						
NO_2^+	−202.460 060						

[a] Calculated from the isodesmic equation 2. [b] Relative to species substituted at position 1 (W1 and T1, respectively). [c] Number of the negative eigenvalues of the second derivative matrix. [d] Imaginary frequencies. [e] Zero-point vibration energies (scaled by 0.89). [f] Energies corrected by zero-point vibration contribution relative to T1.

Table VII. Points of the Reaction Profile

RC,[a] Å	E_{total}, au	ΔE,[b] kJ/mol
2.0	−1390.038 693	149.0
2.2	−1390.026 743	180.4
2.4	−1390.018 447	202.2
2.8	−1390.012 679	217.3
3.1	−1390.015 522	209.8
3.3	−1390.022 441	191.7

[a] Reaction coordinate (C–N^A distance). [b] Calculated from isodesmic equation 2.

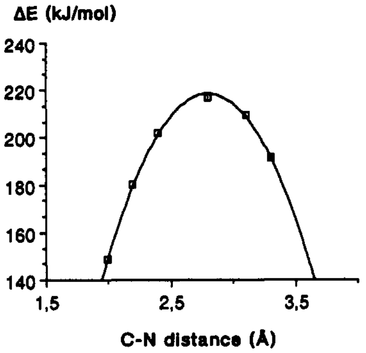


Figure 3. The energy dependence of the reaction coordinate.

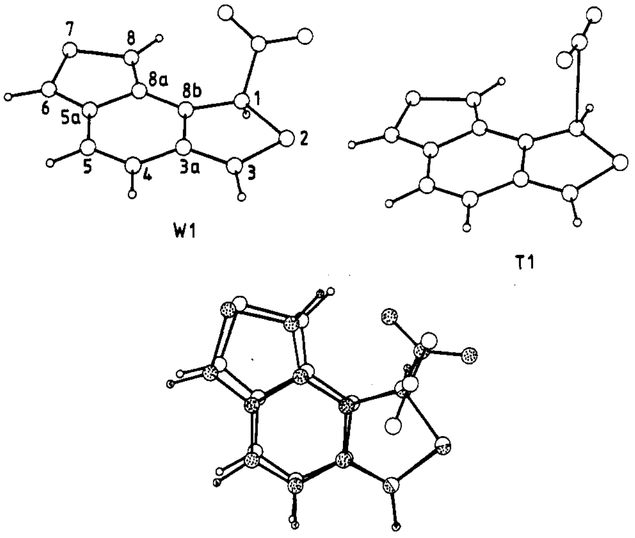
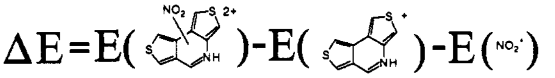


Figure 4. Calculated Wheland intermediate and transition state for 1-nitro derivative.

energies and structures of the corresponding "genuine" transition states. The search for the first-order saddle point was started from the Wheland intermediate structure. This treatment also guaranteed finding the transition state along a continuous line connecting reactants and products.[27] In order to map out the reaction profile for the formation of the Wheland intermediate, we chose the distance between the attacked carbon arom and the nitrogen of the nitro group as a reaction coordinate. This was kept fixed, while all the remaining internal coordinates were optimized simultaneously to obtain a point on this profile. The results for the 1-substituted case can be seen in Table VII and Figure 3. Finally, a simple parabola was fitted to the calculated points. The deviation from this parabola was surprisingly small. From the reaction coordinate value of the highest energy and the optimized structure of the nearest point a trial geometry was constructed, which was optimized further with no restrictions on the geometry parameters. All the transition state structures were characterized by calculating the ab initio 3-21G* eigenvalues of the second-derivative matrix, giving one and only one negative eigenvalue, which satisfies the criterion for the transition state given by McIver et al.[27] (Table VI). The vibrational zero-point energy corrections to the relative energies were scaled (scaling factor: 0.89) to account for their general overestimation at this computational level.[24] The relative energies obtained for the transition state are in considerably better agreement with the experimental findings than those for the Wheland intermediates.

The energy difference between substitutions at positions 1 and 3 (T1 and T3) is in the range of the expected experimental values.[28] The relative energies compared to the separated reactants were calculated by means of the isodesmic equation 2 (Table VI). Although the HF approach certainly overestimates the experimental activation energy, the barrier height from both sides (B ⟹ T ≈200 kJ/mol, W ⟹ T ≈150 kJ/mol) seems to be high enough to ensure that the formation of the Wheland intermediate is an irreversible reaction step. This is in agreement with experimental findings concerning the S_E2 nitration,[29] suggesting that the possibility of thermodynamic control can be dismissed.



(2)

Comparing the structures of the different species reveals that the transition-state geometry of the dithienopyridine ring system resembles more the unsubstituted species (B)

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(28) A rough estimation of the experimental energy difference: Supposing that the difference in the entropies of activation is close to zero ($\Delta S^{\ddagger} \approx 0$), the energy difference can be formulated as $\Delta E \approx RT \ln (k_2/k_3)$. Using the fact that for the parallel reactions $k_2/k_3 \approx c_2/c_3 \approx 39$ (eq 1), this energy difference is about 8 kJ/mol.

(29) According to Taylor: "Although in principle all electrophilic substitutions are reversible, in practice, the reverse reaction is too slow to be significant in most cases. Two reactions in which this is not completely true under commonly used conditions are sulfonation and Friedel–Crats alkylation." (ref 15)

than the Wheland intermediate (W). A similar observation was reported by Hirao et al.[30] for transition state structure in S_N2 reaction of alkyl bromides. The largest geometrical deviation in the B–T relation is 0.04 Å (Table III) for bond lengths (T6, C^6S^7 bond) and 0.9° (Table IV) for bond angles (among others T6, the $N^4C^5C^{5a}$ angle). The geometrical difference between the Wheland intermediate and transition state is particularly large at the reaction center. Even the thiophene ring is distorted in the Wheland intermediate. This difference reaches 0.15 Å (T8–W8, C^8C^{8a} bond) and 16.7° (T3–W3, $C^{3a}C^3H^3$ angle). The geometry differences between W1 and T1 are visualized in Figure 4. The differences concerning the geometry of the nitro group and the hydrogen atom are also typical for the other case of substitution. The bond angles (Table IV) between the nitrogen atom of the nitro group and the ring system are close to tetrahedral for W1 (114.3 and 108.5°), while rather perpendicular for T1 (96.2 and 90.4°). The hydrogen atom at the reaction center is also in a nearly tetrahedral position for W1 (110.5 and 109.7°), while it is practically in the ring plane for T1 (125.8 and 120.8°). The deviation of this hydrogen from planarity is less than 0.3° for the transition-state structures. The ONO angle of the nitro group for T1 (162.9 degrees) is close to 180°, the equilibrium bond angle of the nitronium ion, while in W1 (128.7°) it is similar to the bond angle of the nitro group in aromatic nitro compounds. The Hammond postulate predicts a less endotermic reaction for such an "early" transition state. This somewhat unexpected because the substrate has already a positive charge and to receive a further one (by nitronium ion) should be disadvantageous. Nevertheless, the possibility for extensive delocalization of the positive charges on the 12-membered aromatic ring system, where the two sulfur atoms serve particularly good electron "source", considerably reduces the endothermicity.

There is a unique difference between the transition state and Wheland intermediate structures for substitution at positions 1 and 8 (W1–T1 and W8–T8) compared to positions 3 and 6 (W3–T3 and W6–T6). This is the influence of the attacking nitro group on the "distant" thiophene ring (in the case of 1-substitution on ring A). This effect is considerably larger for W1 than for T1. Projecting the two structures on to each other (Figure 4), it can be seen that ring A of the Wheland intermediate (dotted structure) is shifted in comparison to the transition state. Of course there is no such interaction for substitutions in positions 3 and 6. This steric effect gives a reasonable explanation for the lower stability of W1 compared to W3, suggesting an incorrect energy sequence for the site preference. This finding shows that particularly for the angularly annelated ring systems, approximating the transition state of the reaction by means of its Wheland intermediate may be inadequate. The bond distance between the nitrogen atom of the nitro group and the carbon atom attacked changes from 2.540 Å (T6) to 2.723 Å (T8). This difference is due to the fact that this "bond" is very weak. The diagonal force constant (3-21G* level) is about 0.017 au, which is about 30 times smaller than that for normal C–N bond. The larger geometrical differences among the various isomers concerning the nitro group in relation to the ring system can be explained in a similar way.

The charge densities (Table V) for the atoms in the ring systems for the transition states also show greater similarity to the unsubstituted parent compound than to the Wheland intermediate. It is worth pointing out that the full charge on the nitro group ranges from +0.811 (T3) to +0.882 (T8) for the experimentally found isomers, while the free nitronium ion bears a +1.0 charge. This slight difference suggests that there is no large electron movement between the nitronium ion and the ring system in the transition state. This emphases the electrostatic nature of the interaction between the reactants, in agreement with the theory of S_E2 mechanism[1,10,15] which is classified as a purely ionic process. In the Wheland intermediate the nitro group draws more than one electron from the positively charged ring system. The full charge on the nitro group ranges between −0.233 (W8) and −0.240 (W6).

The different site preferences can also be explained by the charge distribution in the transition state. Considering ring A substitutions (T6, T8), it can be seen that as a consequence of the large positive charge on the nitro group, the carbon atom in the reaction center is negatively charged. It is surrounded by a positively charged sulfur atom (S^7) and a carbon atom (C^{8a}) in T8. In contrast, for T6 the carbon atom in the neighboring position (C^{5a}) is negatively charged, and thus increase of the negative charge in the reaction center leads to increasing repulsion between C^6 and C^{5a} which is, of course, disadvantageous. This effect is most likely the cause of the lower stability of T6 versus T8 and the absence of the 6-substituted derivative in the reaction mixture from the nitration (eq 1). There is not such a spectacular difference between the electronic structures of T1 and T3 (ring C). The lower stability of T3 may be due to the fact that the negative charge on C^{8b} is slightly increased. This atom is in the neighboring position to the atom C^1 bearing a large negative charge. It is remarkable that in spite of the protonation the ring nitrogen bears a quite large negative charge (certainly the consequence of its highest electronegativity in the ring system). The positive charge partly remained on the proton H^4 (0.43–0.46 electrons) and delocalized on the ring system. The finding, that the protonation does not alter the sign of the charge on nitrogen N^4, suggests that it does not induces substantial changes in the electronic structure and relative energies.

Due to the large size of the molecular systems (167 orbital on 3-21G* level) and the necessity of the accurate geometry optimization (57 geometrical variables) using a larger basis set or a more advanced theoretical approach would make these calculations exceedingly expensive[31] (not to mention the extremely high disk space requirements). A large number of transition-state energies calculated on HF level were published recently for organic reactions following ionic mechanism[30,32] (S_N2 alkylation, aldol reaction, pinacol rearrangement, isomerization of aldoximes, Michael addition, etc.). These publications demonstrate the reliability of the single determinant approach at least for the relative activation energies of ionic processes.

The calculated structures are those for gas-phase monomers; the true species are undoubtedly solvated. Nevertheless, we believe that as a consequence of the structural similarities of the transition-state structures and the extensive delocalization of atomic charges, specific solvent effects do not influence the relative energy sequence found for the nitration.

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Experimental Section

NMR spectra were recorded on a Varian XL-300 spectrometer. The high-resolution mass spectral data were obtained on a Finnigan 4021 spectrometer. The GLC analyses were carried out on a Varian 3700 gas chromatograph.

Nitration of Dithieno[3,4-*b*:3′,4′-*d*]pyridine (1). Compound 1[7] (0.6 g, 3.2 mmol) was dissolved in 10 mL of TFA. Concentrated HNO_3 (0.54 mL, 12.8 mmol) was added to the solvent stirred for 7 h on the room temperature. The solvent was evaporated, and the residue was neutralized with $NaHCO_3$ solution. The raw material was chromatographed on a silica gel column using ethylacetate/ether, 1:1, as eluent. Isolated yields: 1-nitro derivative (2), 0.22 g (28.6%); 8-nitro derivative (4), 0.25 g (32.5%). The minor product the 3-nitro derivative (3), was isolated by column chromatography of the reaction mixture, using cyclohexane/ethyl acetate, 2:1, as eluent. Melting points: 212-4 °C (2), 258-60 °C (3), and 229-30 °C (4). Mass spectra: m/e 236 (2, 3, 4). Anal. Found for 2: C, 45.7; H, 1.6. For 3: C, 45.5; H, 1.9; N, 11.6. For 4: C, 45.5; H, 1.7; N, 11.7. Calculated: C, 45.8; H, 1.7; N, 11.9.

Determination of Isomer Distribution. To 50 mg (0.26 mmol) of 1 dissolved in 3 mL of TFA was added 0.083 mL (1.25 mmol) of 65% HNO_3 and urea (19 mg, 0.32 mmol). The reaction was interrupted after stirring for 1 h and 25 °C. The neutralized reaction mixture was separated on a DG1701 30-m capillary column. Temperature program: heating period, 150-250 °C, 5 °C/min, followed by 20 min hold time at 250 °C. Retention times: 24.4 min for 2, 26.2 min for 4, and 27.2 min for 3.

***tert*-Butyl *N*-(4-Bromo-5-nitro-3-thienyl)carbamate (5).** 4-Bromo-5-nitro-3-thiophenecarboxylic acid[8] (2.5 g, 10 mmol) was converted to its carbamate.[7] After column chromatography in cyclohexane/ethyl acetate, 7:1, as eluent, 1.8 g (55%) of product was obtained. ^1H NMR ($CDCl_3$): δ (ppm) 7.85 (s, 1 H), 6.96 (s, 1 H), 1.53 (s, 9 H). Mass spectra: m/e 322, 324. Anal. Found: C, 33.2; H, 3.2; N, 8.6. Calculated: C, 33.5; H, 3.4; N, 8.7.

1-Nitrodithieno[3,4-*b*:3′,4′-*d*]pyridine (2). Starting from 0.4 g (1.2 mmol) of carbamate 5 and 0.4 g (1.2 mmol) of carbamate 5 and 0.4 g (2.6 mmol) of 4-bromo-3-thiopheneborornic acid, 0.16 g (55%) of nitro derivative 2 was synthesized via a Pd(0)-catalyzed coupling reaction.[7]

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Supplementary Material Available: Internal coordinate systems (in Z-matrix form), optimized geometrical parameters, and vibrational frequencies of transition states (13 pages). Ordering information is given on any current masthead page.

Concerning the Mechanism of the Reaction of $LiAlH_4$ with Alkyl Halides

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A detailed study of the mechanism of reaction of $LiAlH_4$ with alkyl halides has been carried out with special emphasis on the use of radical probes. The data presented strongly support the validity of using radical probes in this reaction as an indication of an electron-transfer process. These studies also suggest a radical chain process (hydrogen atom transfer) in addition to the halogen atom transfer process on which we reported earlier. Studies to determine the influence of impurities as well as a potential metal-halogen exchange process are also reported.

Introduction

The reduction of alkyl halides to the corresponding hydrocarbons by $LiAlH_4$ is a well-known reaction (eq 1) that has been studied in some detail.[1] In 1984 we reported

$$RX + LiAlH_4 \rightarrow RH + AlH_3 + LiX \qquad (1)$$

that the results of a mechanistic study of this reaction indicated evidence for electron transfer in the cases of reaction of primary (neopentyl type) and secondary alkyl iodides with $LiAlH_4$ in THF.[2] Although we have reported evidence for electron transfer in reactions of alkyl halides with other reagents,[3] it is only in the case of reduction of alkyl halides with $LiAlH_4$ that the presence of electron transfer has been questioned. Newcomb has argued from both kinetic[4] and probe studies[5] that such reductions proceed by a polar S_N2 mechanism, and more recently Newcomb and Curran have summarized a joint position supporting a polar mechanism, for the reaction of $LiAlH_4$ with alkyl iodides, arguing against the involvement of an electron-transfer process.[6] We have responded to the above arguments and have concluded that the evidence is overwhelming that electron transfer is indeed involved in this reaction and that the opposing arguments are invalid.[7] The following presentation represents our completed studies in this area; thus, at this time, we wish to summarize recent communications from our laboratory and add new data and discussion that strongly support the position that electron transfer is involved in the reaction of primary and secondary alkyl iodides with $LiAlH_4$ in THF solvent.

Results and Discussion

The most impelling argument that we presented in 1984 in favor of an electron-transfer pathway for the reaction

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