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Evidence for a Strong Enaminic Character of 3,4-Diaminothiophene: A Fast Carbon–Carbon Coupling with 4,6-Dinitrobenzofuroxan

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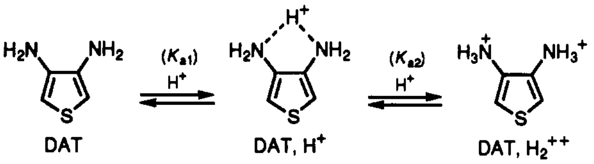
While exhibiting a nitrogen basicity comparable to that of aniline, 3,4-diaminothiophene (DAT) does not show any tendency to react as a nitrogen nucleophile with a highly electrophilic compound like 4,6-dinitrobenzofuroxan (DNBF). Depending upon the experimental conditions employed, the addition of DNBF takes place at C-2 to give a carbon-bonded monoadduct (**3,H**) or at C-2 and C-5 to give a C,C-diadduct (**4,H**) which exists as a mixture of two diasteromers. Both the acid and base forms of these adducts have been characterized. A kinetic study of the monocomplexation of DAT and its 2,5-dideuteriated analog have been carried out at various pH in 50% H_2O–50% Me_2SO. The results show that electrophilic attack by DNBF is the rate-limiting step of the formation of the adduct **3,H**. The measured rate constant for DNBF addition is very high ($k_1 = 9 \times 10^5$ L mol^{-1}s^{-1}), emphasizing the very strong nucleophilic character of the C_α positions of DAT and supporting the idea that this compound is strongly enaminic in nature.

It has been recently pointed out that 4,6-dinitro-2,1,3-benzoxadiazole 1-oxide, more commonly known as 4,6-dinitrobenzofuroxan (DNBF), is a very suitable electrophile to assess the reactivity of very weak carbon nucleophiles.[1] A number of π-excessive aromatics (anilines, phenols or phenoxide anions, 1,3,5-trimethoxybenzene) or heteroaromatics (pyrroles, indoles, furans, thiophenes) have thus been found to react under smooth conditions with DNBF, affording quantitatively stable carbon-bonded σ-adducts which are formally the products of S_EAr substitution of the benzene or hetarene rings.[1-5] The coupling of DNBF with aniline which gives first the N-adduct **1a** under kinetic control but finally affords the C-adduct **2a** as the thermodynamically stable product (Scheme I) is representative for these reactions which in some cases could be investigated in detail by kinetics.[5,6] The results obtained have provided interesting mechanistic information on the factors influencing the course of the substitutions.[5]

Although we will show that it exhibits an acid-base behaviour comparable to that of anilines, undergoing complete nitrogen protonation in acid media, so far 3,4-diaminothiophene (DAT) has been found to suffer exclusively electrophilic substitution at the unsubstituted α-carbon(s).[7] In an attempt to assess the carbon nucleophilicity of this compound,[8] a thorough structural and kinetic investigation of the reaction of DAT with DNBF was carried out and is reported in this paper. The results reveal that DNBF addition takes place exclusively at the α-position(s) of DAT, as depicted in Scheme II, thus supporting the idea that DAT exhibits a very strong enaminic character.[9] Some data pertaining to the reaction of 1,2-diaminobenzene (DAB) with DNBF are also reported for purpose of comparison.

Results

Protonation Behavior of DAT (eq 1). Because of the poor solubility of DAT in aqueous solution, we have studied the protonation behavior of this compound in a few H_2O–Me_2SO mixtures, using a standard potentiometric procedure (see Experimental Section).[10] The results obtained at 25 °C are given in Table I, together with those for the protonation of aniline and 1,2-diaminobenzene under similar experimental conditions.



(1)

We also investigated the protonation behavior of DAT by ^1H NMR in Me_2SO solution, adding increasing amounts of a strong acid, namely methanesulfonic acid. The pH dependence of the chemical shifts of the $H_{2,5}$ protons upon

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[1] (a) Terrier, F. In *Nucleophilic Aromatic Displacements*; Feuer, H., Ed.; VCH Publishers: New York, 1991; p 142, 262. (b) Terrier, F. *Chem. Rev.* **1982**, *82*, 77. (c) Buncel, E.; Crampton, M. R.; Strauss, M. J.; Terrier, F. In *Electron-Deficient Aromatic- and Heteroaromatic-Base Interactions*; Elsevier: Amsterdam, 1984; p 166 and 296.

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[3] (a) Strauss, M. J.; Renfrow, R. A.; Buncel, E. *J. Am. Chem. Soc.* **1983**, *105*, 2473. (b) Buncel, E.; Renfrow, R. A.; Strauss, M. J. *J. Org. Chem.* **1987**, *52*, 488.

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[9] Paulmier, C.; Outurquin, F. *Janssen Chem. Acta* **1987**, *5*, 9.

[10] (a) Halle, J. C.; Gaboriaud, R.; Schaal, R. *Bull. Soc. Chim. Fr.* **1969**, 1851. (b) *Ibid.* **1970**, 2047. (c) Vega, C. A.; Halle, J. C. *Ibid.* **1970**, 124. (c) Achassi-Sorkhabi, H.; Halle, J. C.; Terrier, F. *J. Chem. Res.* **1978**, (S) 196, (M) 2545.

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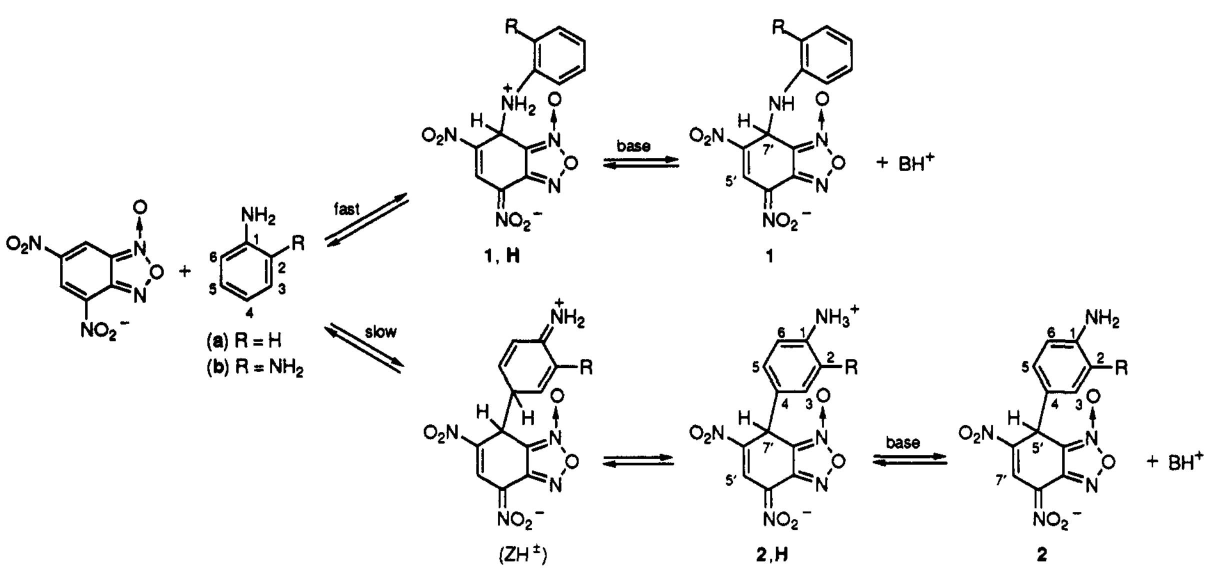
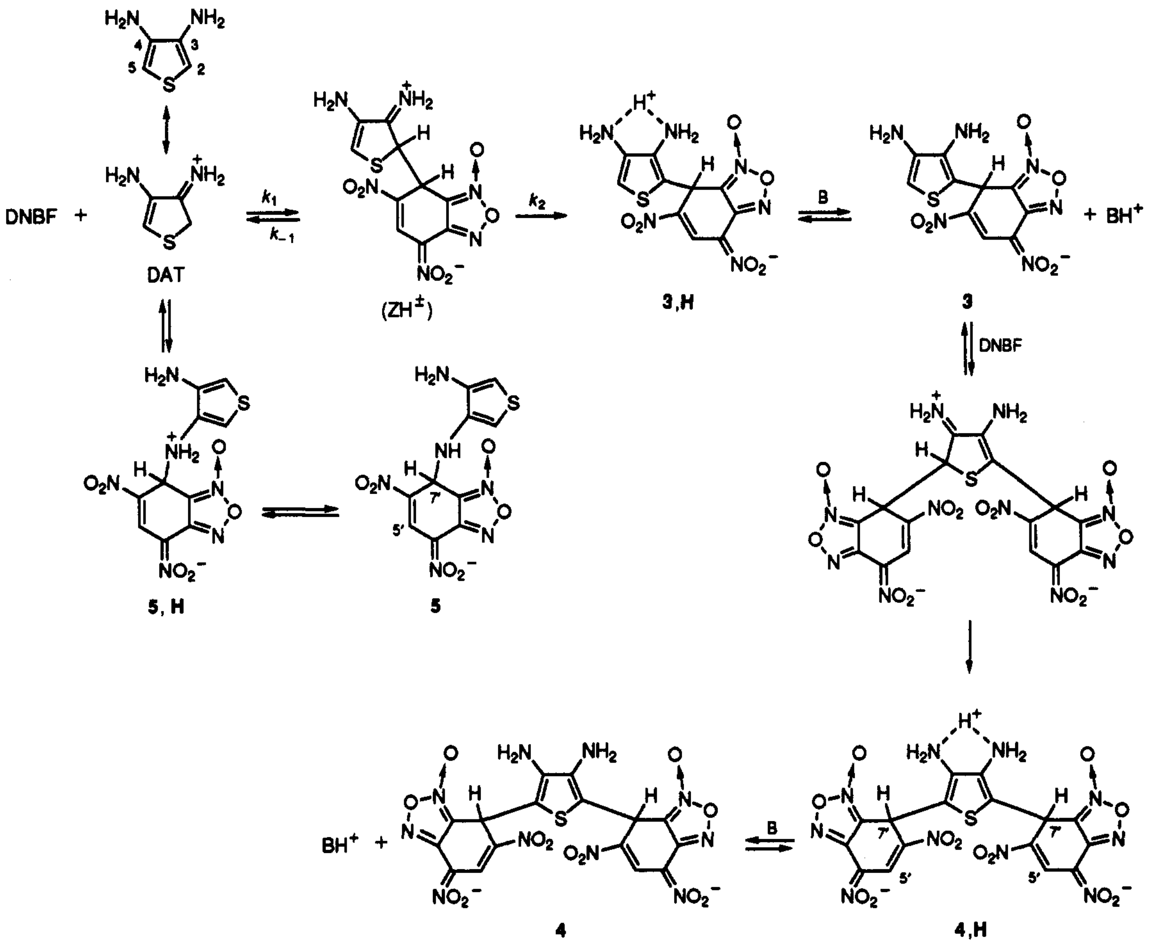
Scheme I



Scheme II



the acid concentration is shown in Figure 1. As can be seen, the addition of 1 equiv of acid results in the quantitative formation of the monocation DAT,H^+ while about 3.4 equiv of CH_3SO_3H are required to achieve complete formation of the dication DAT,H_2^{++}. Based on the observed chemical shifts variations, a pK_{a2} value of $\simeq 1.6 \pm 0.2$ can be estimated for the equilibrium DAT,H^+ $\rightleftarrows$ DAT,H_2^{++} in pure Me_2SO. More importantly, no evidence for protonation at the α-C carbons could be found.

DNBF Complexation with DAT. Structural Studies. The addition of 1 equiv of DNBF to a Me_2SO solution of DAT at room temperature resulted in the formation of an approximately 1:1 mixture of two products that we could identify as the zwitterionic monoadduct **3,H** and the diadduct in its monoprotonated form **4,H.** ^1H NMR spectra (in Me_2SO-d_6) show in particular the presence of the AX systems expected for the negatively charged DNBF moieties of such carbon-bonded σ-complexes.[2-4,6] In the case of **4,H**, the observation of two very close $H_{5'}$ singlets at 8.60_6 and 8.59_4 suggests that this diadduct species exists as a 1:1 mixture of two diastereomers, a situation which is reminiscent of that observed for the diadduct resulting

Table I. Comparison of the pK_a Values for Protonation of Aniline, 1,2-Diaminobenzene, and 3,4-Diaminothiophene in Various H_2O–Me_2SO Mixtures at $t = 25°$

		% Me_2SO by volume							
		0	10	30	50	70	80	85	90
aniline	pK_{a1}	4.58	–	4.08	3.73	3.41^a 3.25	3.16		
DAB	pK_{a1}	4.47^b	4.43	4.26	4.17	3.87	4.02	4.19	4.59
	pK_{a2}	1.30	–	–	1.10^c	–	–	–	–
DAT	pK_{a1}	–	4.29	4.13	3.96	3.70	3.74	3.88	4.30
	pK_{a2}	–	–	–	0.98^c	–	–	–	–

^{a} Reference 19. ^{b} P. Vetesnik, J. Bielavsky, J. Kavalek and M. Vecera, *Collect. Czech. Chem. Commun.* **1968**, *33*, 2902. ^{c} Estimated error on pK_{a2}: 0.05 pK unit.

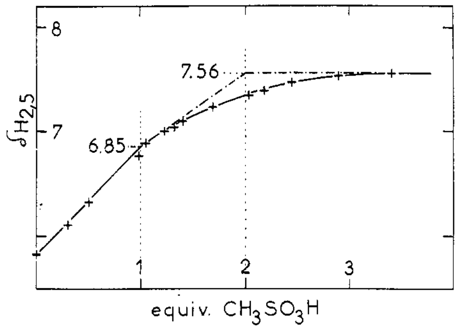


Figure 1. Effect of the addition of methanesulfonic acid on the chemical shift of the $H_{2,5}$ protons of DAT in Me_2SO.

Table II. ^1H NMR Data for the Base and Acid Forms of DAT and Related DNBF Adducts^a

compound	δ_{H2}	δ_{H5}	$\delta_{H5'}$	$\delta_{H7'}$
DAT	5.83_4	5.83_4		
DAT,H^+	6.85_0	6.85_0		
3^b		5.72_8	8.60_8	5.72_8
3,H		7.09_1	8.66_6	5.98_3
4^b		–	$8.55_5/8.54_5$	$5.69_5/5.69_2$
4,H		–	$8.60_6/8.59_4$	6.05_2

^{a} Chemical shifts (ppm) relative to Me_4Si as internal standard. Solvent Me_2SO-d_6; $t \simeq 20$ °C. ^{b} **3** and **4** were generated by addition of DABCO to Me_2SO solutions of **3,H** and **4,H** (see text).

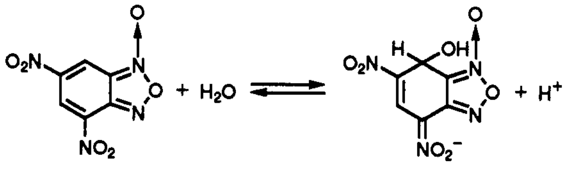
from the DNBF complexation by unsubstituted thiophene.[2a] Also consistent with the formation of **4,H** was the presence of a singlet at 6.86 with an intensity similar to those of the $H_{5'}$ and $H_{7'}$ signals. This singlet corresponds exactly to the thiophene ring protons of the protonated form of the unreacted DAT which serves as the counterion. In the case of **3,H**, the $H_{5'}$ and $H_{7'}$ signals of the DNBF moiety ($\delta_{H5'} = 8.66$; $\delta_{H7'} = 5.98$) go along with a signal at $\delta = 7.09$ assignable to the single ring proton H_5 of the protonated thiophene DAT moiety.

Other illustrative experiments of the behavior of DAT have been carried out. Use of an excess of DAT over DNBF was found to favor the formation of the monoadduct **3,H** relative to that of the diadduct **4,H** while contributing partially or totally to the conversion of these species to their conjugate bases **3** and **4**. Only in the presence of a large excess (8–10 fold) of DAT, the anionic monoadduct **3** was the only species observed. Complete conversion of the nitrogen acids **3,H** and **4,H** into their conjugate bases **3** and **4** was more conveniently achieved by adding 1.5 equiv of 1,4-diazabicyclooctane (DABCO) to a solution resulting from the mixing of equimolar amounts of DAT and DNBF. As can be seen in Table II, the deprotonation of **3,H** and **4,H** is accompanied by marked high-field shifts of the $H_{5'}$ and $H_{7'}$ signals of these adducts. Interestingly, the zwitterionic monoadduct **3,H** could be isolated as a crystalline solid from experiments carried out at −60 °C in THF. Dissolution of this compound in Me_2SO-d_6 gave a NMR spectrum identical to those recorded in in situ experiments. The structure of **3,H** was also confirmed by mass spectra experiments. In any of the above NMR experiments, signals ascribable to the N-adduct **5** could be detected in the recorded spectra.

The complexation of DNBF by DAB in Me_2SO solution was also studied by ^1H NMR. The spectra recorded immediately after mixing of equimolar amounts of the two reagents showed the signals typical for the N- and C-adducts **1b** and **2b,H**. Very rapidly, the resonances of the various protons of **2b,H** increased at the expense of those of **1b** which eventually disappeared. We succeeded in isolating the zwitterionic complex **2b,H** as a crystalline solid. Dissolution of this solid in Me_2SO gave rise to a NMR spectrum identical to that recorded in the in situ generation of **2b,H**. Addition of 1 equiv of DABCO to the solution of **2b,H**, afforded this complex into its basic form **2b**. The structure of **2b,H** was also confirmed by mass spectra experiments.

The most representative NMR data for the DAT-DNBF and DAB-DNBF systems are summarized in Tables II and III, together with similar data previously reported by Buncel et al. for the DNBF–aniline systems.[3b]

Kinetic Studies. The reaction of DAT with DNBF was kinetically studied at 25 °C under pseudo-first-order conditions with respect to DAT as the excess component in 50% H_2O–50% Me_2SO. Experiments were carried out by mixing various HCl solutions of DNBF ($\simeq 3 \times 10^{-5}$ M) with equal volumes of various solutions of the diamine (10^{-3}–10^{-2} M) in a stopped-flow apparatus. The HCl concentrations of the DNBF solutions were chosen so as to afford after mixing, H^+ concentrations in the range (5×10^{-3}) – 0.1 M; $I = 0.1$ M (KCl). Under these experimental conditions, the diamine was essentially present in its monocationic form DAT,H^+ or in a mixture of this species with the dication DAT,H_2^{++}, but only one relaxation time corresponding to the quantitative formation of the C-adduct **3,H** ($\lambda_{max} = 480$ nm) was observed in all cases. Also, no interference between the formation of this adduct and that of the hydroxy adduct **6** according to eq 2 was detected.[11]



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(2)

The most reasonable mechanism for the complexation process is depicted in Scheme II which involves the attack of DNBF by equilibrium concentrations of the diamine. The general expression for the observed first-order rate constants k_{obsd}, for the formation of **3,H**, as derived under the assumption that the zwitterion $ZH^{\pm}$ is a low concentration ("steady-state") intermediate, is given by :

$$k_{obsd} = \frac{k_1 k_2}{k_{-1} + k_2} \frac{K_{a1}K_{a2}}{K_{a1}K_{a2} + K_{a2}[H^+] + [H^+]^2} [DAT]_0 \tag{3}$$

which reduces to:

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Table III. ^{1}H NMR Data for the Base and Acid Forms of DAB and Aniline and Their DNBF-Related Adducts[a]

compound	δ_{H2}	δ_{H3}	δ_{H4}	δ_{H5}	δ_{H6}	$\delta_{H5'}$	$\delta_{H7'}$	$^3J_{5,6}$	$^4J_{3,5}$
DAB[b,d]	–	------ $6.53_4/6.41_4$ ------							
DAB,H$^+$[b,d]		------ $7.01_2/6.86_7$ ------							
1b		------ 7.01_8 (br s) ------				8.67_4	6.38_4		
2b	–	6.31_9	–	6.27_5	6.37_1	8.66_2	5.01_3	7.8	1.9
2b,H$^+$		6.84_7	–	6.81_1	6.89_8	8.71_3	5.20_2	8.0	1.6
1a[c]	------ 6.9 (multiplet) ------					8.74	6.08		
2a[c]		6.96/6.61[d]	–	6.96/6.61[d]		8.78	5.18		
2a,H[c]		7.41/7.26[d]	–	7.41/7.26[d]		8.79	5.40		

[a] Chemical shifts (ppm) relative to Me_4Si as internal standard; solvent Me_2SO-d_6; t = 20 °C. [b] Coupling constants (Hz) for both DAB and DAB,H: $^3J = 7.8$ and 7.5, $^4J = 1.5$, $^5J = 0.5$. [c] Data taken from refs 3b and 4c. [d] AA′BB′ patterns.

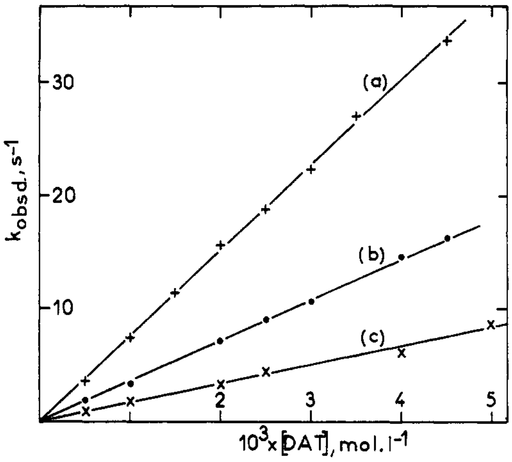

Figure 2. Influence of the DAT and HCl concentrations on the observed first-order rate constant for the complexation of DNBF in 50:50 (v/v) H_2O–Me_2SO at t = 25 °C; (a) [HCl] = 0.01 mol L^{-1}; (b) [HCl] = 0.025 mol L^{-1}; (c) [HCl] = 0.05 mol L^{-1}.

Table IV. Summary of Rate Parameters for the Formation of the C-Adduct 3,H According to Scheme II in 50% H_2O–50% Me_2SO[a]

[H$^+$], mol L^{-1}	k, L mol^{-1} s^{-1} [b]	k_1, L mol^{-1} s^{-1} [d]
0.005	20600	9.63×10^5
0.01	8500	8.31×10^5
0.015	5700	8.72×10^5
0.025	3600 (3575)[c]	9.95×10^5
0.050	1636 (1450)[c]	1.087×10^6
0.10	571	9.95×10^5

[a] t = 25 °C, I = 0.1 M (KCl). [b] Experimental values. [c] k values for the reaction of DNBF with 2,5-dideuteriated DAT. [d] k_1 values calculated from the k values by means of eq 5 with $K_{a1} = 1.12 \times 10^{-4}$ and $K_{a2} = 0.105$ (see Table I).

$$k_{obsd} = \frac{k_1 k_2}{k_{-1} + k_2} \frac{K_{a1}K_{a2}}{[H^+]([H^+] + K_{a2})} [DAT]_0 = k[DAT]_0 \tag{4}$$

at the different pH studied ($K_{a1} \ll [H^+]$). In accordance with eq. 4, excellent linear plots of k_{obsd} vs the total diamine concentration ($[DAT]_0 = [DAT] + [DAT,H^+] + [DAT,H_2^{++}]$) were obtained at each pH (Figure 2). Table IV summarizes the values of the corresponding second-order rate constants k which were readily determined from the slopes of these plots.

Also given in Table IV are the k values corresponding to a series of experiments carried out with the 2,5-dideuteriated diamine (DAT-d_2). As can be seen, the results do not reveal a significant influence of the nature of the isotopic substitution at C_α on the rates of formation of the monoadduct 3,H; the measured k^H/k^D ratios are 1.1 ± 0.1. This absence of a significant isotope effect shows that proton removal from the zwitterionic intermediate $ZH^\pm$ is rapid and that the rate-determining step of the complexation is the nucleophilic addition step, i.e. $k_2 \gg k_{-1}$.[5,12–15] Accordingly, the expression of the second-order rate constant k takes on the simplified form of eq 5:

$$k = k_1 \frac{K_{a1}K_{a2}}{[H^+]([H^+] + K_{a2})} \tag{5}$$

from which a value of the second-order rate constant k_1 for the addition of DAT to DNBF was readily obtained at each pH (Table IV). The results afford the following average value in 50% H_2O–50% Me_2SO: $k_1 = 9 \times 10^5$ L mol^{-1} s^{-1}.

Discussion

Nitrogen Basicity of DAT. It can be seen from Table I that the pK_{a1} values associated with the first protonation equilibrium of DAT and DAB are very similar in each of the H_2O–Me_2SO mixtures studied. In addition, these pK_{a1} values compare well, after statistical correction, with the pKa values of aniline, at least in the mixtures containing up to 50% Me_2SO, eg. $pK_{a1,corr}^{DAT} = 3.66$, $pK_{a1,corr}^{DAB} = 3.87$, $pK_{a1}^{A} = 3.73$ at t = 25 °C in 50% H_2O–50% Me_2SO. The results fit well the NMR observation that the protonation of DAT occurs at nitrogen, as do those of DAB and aniline. Also to be noted is the similarity of the pK_{a2} values pertaining to the formation of the dications DAT,H_2^{++} and DAB,H_2^{++} in 50% H_2O–Me_2SO.

In accordance with the general observation that acid-base equilibria of the type RNH_3^+/RNH_2 are considerably less affected than equilibria of the type $RCOOH/RCOO^-$ or $ArOH/ArO^-$ on transfer from a protic to a dipolar aprotic solvent,[10,16–23] the pK_{a1} values of DAT, DAB, and aniline do not suffer considerable variations on going from water or 90% H_2O–10% Me_2SO to 10% H_2O–90% Me_2SO. However, it is interesting that this solvent transfer induces

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especially little changes in the basicity of DAT and DAB; the pK_{a1} values of each of these derivatives are essentially the same in 90% H_2O–10% Me_2SO and 10% H_2O–90% Me_2SO, while it results in a moderate but regular decrease in the basicity of aniline. This different behavior can probably be understood in terms of the different requirements for solvation of the DAT, H^+, and DAB,H^+ cations as compared to a common primary ammonium cation like anilinium ion. Due to the greater ability of Me_2SO relative to water to act as a strong hydrogen-bond acceptor,[17,21,24] the water molecules of the solvation shell of this latter cation are progressively replaced by Me_2SO molecules on going from water-rich media to Me_2SO-rich media. In contrast, the possible stabilization of the monocations DAT,H^+ and DAB,H^+ by intramolecular hydrogen bonding in the diamine systems must reduce the importance of the solvation shift, accounting for the decreased sensitivity of the corresponding pK_{a1} values to the increase in the Me_2SO content.

Carbon Nucleophilicity of DAT. Buncel and coworkers as well as Spear et al. have shown that the reaction of DNBF with aniline involves the competitive formation of the nitrogen- and carbon-bonded σ-adducts **1a** and **2a,H** according to the mechanism shown in Scheme I.[3,4] The key point in this mechanism is that the formation of the N-bonded adduct **1a** occurs very rapidly but is reversible while the formation of the C-bonded adduct **2a,H** is slower but occurs irreversibly; hence, **2a,H** is obtained quantitatively as the thermodynamically favored product.

On the basis of the similarity of the nitrogen basicities of the three derivatives, we could reasonably anticipate that DAB and DAT would react with DNBF similarly to aniline, attacking first via their nitrogen atom to form the N-adducts **1b** or **5** under kinetic control but affording the C-adducts **2b,H** or **3,H** as the thermodynamically controlled products. While the successful NMR identification of **1b** as a transient species confirmed the expectation of a similar behavior of the DAB–DNBF and aniline–DNBF systems in Me_2SO, the failure to detect the formation of the N-adduct **5** prior to that of the C-adduct **3,H** under all experimental conditions used in Me_2SO reflects a noteworthy difference in the behavior of the DAT–DNBF system. Even in the presence of a large excess of DAT over DNBF, no evidence for the formation of **5** could be obtained.

Although one cannot exclude that other experimental conditions which would be more favorable to the detection of **5** could exist, the present observation that DNBF addition exclusively occurs at the C_α position of DAT in Me_2SO is consistent with the general reactivity pattern found for the reactions of this heterocyclic diamine with a number of structurally different electrophiles.[7–9] This also supports the idea that DAT exhibits an especially high nucleophilicity. In this regard, the high rate constant k_1 measured for the formation of the C-adduct **3,H** in 50% H_2O–50% Me_2SO, a solvent where again we failed to detect an initial formation of the N-adduct **5**, is very revealing: $k_1 \simeq 9 \times 10^5$ L mol^{-1}s^{-1}. As shown in Table V, this k_1 value is notably higher that similar k_1 values previously reported for DNBF addition at the C_α or C_β positions of various pyrrole or indole derivatives.[5,25] Thus, the difference in nucleophilic carbon reactivity is about 20 between DAT and the most basic pyrrole studied, i.e. 1,2,5-trimethylpyrrole ($pK_a^{C_\beta} = -0.49$).

Table V. Carbon Nucleophilicity of Various π-Excessive Heterocycles toward DNBF in 50% H_2O–50% Me_2SO[a]

carbon nucleophile	$pK_a^{H_2O}$	k_1, L mol^{-1} s^{-1}
5-cyanoindole	−6.00[b]	1.14 (1.13)[f]
5-bromoindole	−4.30[b]	46.2
pyrrole	−3.79,[c] (−4.09)[e]	260[e]
indole	−3.46[d]	555 (500)[f]
5-methoxyindole	−2.90[b]	2613 (2140)[f]
N-methylindole	−2.32[d]	3510
1,2,5-trimethylpyrrole	−0.49,[c] (−0.79)[e]	12000[e]
2-methylindole	−0.28[d]	9900
5-methoxy-2-methylindole	+0.13	40500 (34000)[f]
2,5-dimethylindole	+0.26[d]	42400

[a] t = 25 °C; data taken from refs 5 and 25. [b] $pK_a^{H_2O}$ values taken from Challis, B. C.; Millar, E. M. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1111, 1618. [c] $pK_a^{H_2O}$ values taken from Chiang, Y.; Whipple, E. B. *J. Am. Chem. Soc.* **1963**, *85*, 2736. [d] $pK_a^{H_2O}$ values taken from Hinman, R. L.; Lang, J. *J. Am. Chem. Soc.* **1984**, *86*, 3796. [e] Statistically corrected pK_a and k_1 values. [f] k_1 values for the corresponding 3-deuteriated indoles.

Of particular interest in Table V is the observation that pyrrole or indole compounds with close thermodynamic C-basicities exhibit roughly similar carbon nucleophilicities. If one assumes in a first approximation that the DAT behavior fits the correlation found for the nitrogen heterocycles, a pK_a^{CH} value of about 1.5–2 can be estimated for the protonation at C_α of this thiophene derivative. Clearly such a value accounts fairly well for the finding of an essentially complete N-protonation of DAT in the H_2O–Me_2SO mixtures studied ($pK_a^{NH_3} \simeq 4$) while it also implies a notable enaminic character of this heterocyclic diamine. This confirms previous suggestions made by different authors regarding the general behavior of 3-aminothiophenes.[7–9,26,27]

Our measurement of a k^H/k^D ratio of 1.1 ± 0.1 is worthy of comment since it reveals that electrophilic attack by DNBF is undoubtedly the rate-limiting step of the complexation of DAT. While this situation resembles that observed in all DNBF–pyrrole and indole systems listed in Table V, it differs markedly from that observed in the DNBF complexation (eq 6) by electron-rich benzenes like 1,3,5-trimethoxybenzene (TMB) or 3,5-dimethoxyaniline (DMA).[25] In these instances, k^H/k^D ratios of the order of 3–4 have been measured in various H_2O–Me_2SO mixtures, indicating that proton removal from the benzenonium intermediates **7** and **9** is largely rate-limiting.

According to various authors,[12,28–30] rate-limiting proton transfer in S_EAr reactions is most often encountered when the reaction site of the nucleophilic reagent is sterically strained or when the bonded electrophilic moiety shows a low or moderate capability to promote the ionization of the C–H bond in the arenonium or hetarenium intermediate. In view of the especially strong electron-withdrawing capability exhibited by a 4,6-dinitrobenzofuroxan

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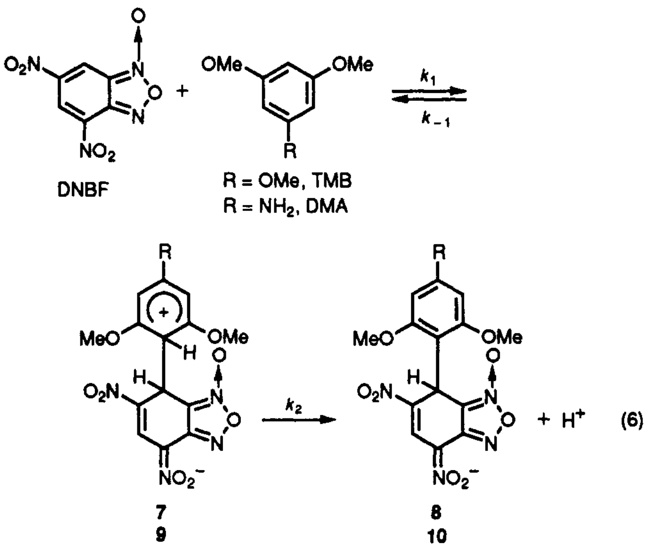

(6)

structure,[5] including when it bears a negative charge,[11,31,32] an abnormally low acidity of the reacting C–H bond seems to be excluded in all intermediates involving DNBF as the electrophile moiety. Thus, it is more reasonable to attribute the different behavior of the five-membered ring heterocycles–DNBF systems compared to the benzene–DNBF systems to major differences in the steric requirements of the reactions. As pointed out earlier by Illuminati, σ-adduct formation at a substituted or unsubstituted α or β position of a thiophene or a pyrrole ring is not subject to important steric hindrance, even when there is a substituent in the adjacent position.[33,34] Contrasting with this behavior, steric factors are largely predominant in governing the feasibility of σ-complex formation at a diortho-substituted benzene ring position.[1,33–35] In the present case of the TMB– and DMA–DNBF systems, the steric hindrance might affect the reactions in two different ways. First, it could operate in the intermediates 7 and 9, decreasing their stability compared with that of hetarenium analogs like $ZH^{\pm}$ in Scheme II and favoring the step of return to the reactants (k_{-1}) relative to the proton elimination step (k_2). However, it could also affect the final substitution products 8 and 10 due to a greater difficulty for the two methoxy groups to lie after rearomatization in the plane of the benzene ring. This situation will correspond to a decrease in the rate of proton elimination, thereby contributing to make this step at least partially rate-determining. Interestingly, our results relate well to some literature data. Thus, Jackson and co-workers as well as Butler and co-workers have reported that S_EAr substitutions of various pyrrole and indole derivatives by 4-nitrobenzenediazonium cation, a somewhat less bulky but a weaker electrophilic reagent than DNBF, do not exhibit any isotope effect.[14,15] In contrast, the S_EAr substitution of 1-bromo-2,4,6-trimethoxybenzene by bromine in DMF to give 1,3-dibromo-2,4,6-trimethoxybenzene shows an isotope effect of 3.6 at 25 °C.[36] Even larger isotope effects have been found in the sulfonation reaction of 1,2,4,5-tetramethylbenzene in nitromethane (k^H/k^D = 5.6 at 0 °C).[37]

Experimental Section

Materials. 4,6-Dinitrobenzofuroxan (DNBF) was prepared according to the procedure of Drost: mp 172 °C (lit. 172–174.5 °C[4b,11,38]). 3,4-Diaminothiophene (DAT) was prepared as described previously: mp 96 °C (lit. 96 °C[8]). 1,2-Diaminobenzene (DAB) was a commercially available product (Aldrich) that we recrystallized twice from methanol: mp 102 °C (lit.102–103[39]). Me_2SO was stirred with calcium hydride and distilled under vacuum. Me_2SO-d_6 was dried by storing over molecular sieves.

Deuteriation of DAT to give 2,5-dideuterio-N,N,N',N'-tetradeuteriothiophene (DAT-d_6) was effected according to the H^+-catalyzed exchange process previously described by Paulmier et al.[7] Dissolution of DAT-d_6 in water–Me_2SO solutions was found by NMR to restore only the signals assigned to the NH_2 protons in a few minutes, as expected from the known lability of these hydrogen atoms. For this reason, the kinetic experiments carried out to measure the effect of isotopic substitution at C-2, C-5 on the rates of complexation of DAT by DNBF have been described in Results as referring to reactions involving 2,5-dideuteriothiophene (DAT-d_2) as the starting deuteriated substrate. In fact, similar rates were obtained whether isolated samples of DAT-d_2 or DAT-d_6 were used as starting materials.

The zwitterionic DNBF monoadduct of DAT, **3,H**, was prepared as follows: a solution of 23 mg of a freshly recrystallized sample of DAT (0.2 mM) in 2 mL of dry THF was prepared in a small reactor equipped with a septum and cooled at -60 °C with an acetone–CO_2 bath. To this solution was added dropwise by means of a syringe a solution of 45 mg DNBF (0.2 mM) in 2 mL of THF which was previously cooled at -60 °C. A red-orange solution was thus obtained which was allowed to warm up slowly. At about -30 °C, a dark orange solid began to precipitate which was collected by filtration at room temperature. After rapid washing with copious amounts of dry diethyl ether, the crystals were dried under vacuum and stored at -20 °C under argon and in the dark (40 mg; 60% yield, not optimized): decomposition occurs at $\simeq$100 °C. As with most DNBF adducts studied so far, attempts to obtain satisfactory elemental analysis have failed. However, dissolution of the solid in Me_2SO-d_6 gave NMR spectra identical to those recorded in the in situ generation of **3,H** in this solvent. Also, the visible spectra were typical of a C-bonded σ-adduct of DNBF, exhibiting a strong maximum at λ_{max} = 480 nm in 50/50 (v/v) H_2O–Me_2SO. Definitive evidence that we isolated the zwitterionic adduct **3,H** comes from mass spectra experiments performed with the FAB technique: m/z = 340.

The zwitterionic DNBF monoadduct of DAB, **2b,H**, was prepared according to the procedure reported by Buncel et al. for the analogous adduct **2a,H** of aniline.[3] To 0.4 g of DNBF suspended in 10 mL of methanol was added 0.19 g (1 equiv) of DAB. Within a few minutes, the DNBF had disappeared and an orange precipitate formed. This was filtered, washed with cooled methanol and dry ether, and dried in vacuo to give 0.5 g (84%) of **2b,H** (mp = 150 °C). As for **2a,H**, satisfactory elemental analysis could not be obtained but both the NMR and mass spectra (FAB technique; m/z = 333) confirmed the structure of the adduct **2b,H** (λ_{max} = 484 nm in 50/50 (v/v) H_2O–Me_2SO).

pK_a Measurements. The pK_{a1} values of DAT in all H_2O–Me_2SO mixtures studied were simply obtained from potentiometric measurements carried out by using buffer solutions with [DAT]/[DAT,H^+] ratios equal to 1:2, 1:1, and 2:1. These solutions were prepared so that the molarity of the cationic species DAT,H^+ was equal to 0.01 M. Under these experimental conditions, the pK_{a1} values at I = 0.01 M (Table I) were thus deduced from the measured pH values of the buffers by means of eq 7.

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$$\mathrm{p}K_{\mathrm{a1}} = \mathrm{pH} - \log\frac{[\mathrm{DAT}]}{[\mathrm{DAT,H^+}]} \qquad (7)$$

The pK_{a1} values of DAB and the pKa values of aniline were similarly measured.

The pK_{a2} values for protonation of DAT according to eq 1 were obtained in 50/50 (v/v) H_2O–Me_2SO by titrating a 5×10^{-2} M solution of this dibasic species with a 1 M HCl solution at t = 25 °C. The titration was carried out by measuring the emf of the following cell: glass Electrode; test solution in 50/50 (v/v) H_2O–Me_2SO; KCl (saturated), Hg_2Cl_2; Hg, by means of an electronic pH-meter (Tacussel Isis 20000) equipped with a Tacussel glass electrode (TCB,HA) and a Tacussel saturated calomel reference electrode (C_8). The glass electrode was standardized with buffer solutions previously calibrated at 298 K in the same solvent mixture by use of the absolute hydrogen electrode.[10] The titration curve confirmed that the first protonation is essentially complete after addition of 1 equiv of HCl and afforded a pK_{a1} value consistent within experimental error with the value previously determined from DAT buffer solutions. On the other hand, the titration curve showed that 4 equiv of HCl are required to achieve the formation of the dication $\mathrm{DAT,H_2^{++}}$. From a conventional treatment of the pH data corresponding to the addition of HCl in the range of 1.5–2.5 equiv, a satisfactory pK_{a2} value of 0.98 ± 0.05 could be obtained.[40]

Kinetic Measurements. Stopped-flow determinations were performed on a Durrum stopped-flow spectrophotometer, the cell compartment of which was maintained at 25 ± 0.3 °C. All kinetic runs were carried out in triplicate under pseudo-first-order conditions with a DNBF concentration of ca. 1.5×10^{-5} M and DAT concentrations in the range (5×10^{-4})–(5×10^{-3}) M. In a given experiment, the rates were found to be reproducible to ±2–3% and to be similar whether the process was followed by monitoring the increase in absorbance at $\lambda_{\max}$ = 480 nm of the adduct **3,H** or the decrease in absorbance at $\lambda_{\max}$ = 415 nm of the parent DNBF substrate as a function of time.

Spectroscopy. UV-visible spectra were determined with a Kontron-Uvikon spectrophotometer. NMR spectra were recorded in Me_2SO-d_6 with TMS as internal standard using a Bruker AM-250 spectrometer equipped with an ASPECT 3000 computer. Mass Spectrometry experiments were performed using a Nermag R1010C quadrupole mass spectrometer and a Spectral-30 data system (Delsi-Nermag, Argenteuil, France). FAB mass spectra were obtained using a M-scan atom gun (M-Scan Ltd, Ascot, UK). Xenon atoms at 8 KeV formed from a beam of 200 μA flux were employed. The FAB target consisted of a copper probe of 3 mm² surface area, machined to an incidence angle of 45°, relative to the primary beam. Samples were dissolved in Me_2SO. One milliliter of the solution was deposited onto triethanolamine (TEA) as the matrice. All FAB experiments were performed in triplicate. Detection in negative ion was performed.

Acknowledgment. We are grateful to Professor Catherine Lange (Centre de Spectroscopie, Faculté des Sciences de Rouen) for mass spectra determinations by the FAB technique.

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