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Assessing the Nitrogen and Carbon Nucleophilicities of 2-Aminothiazoles through Coupling with Superelectrophilic 4,6-Dinitrobenzofuroxan

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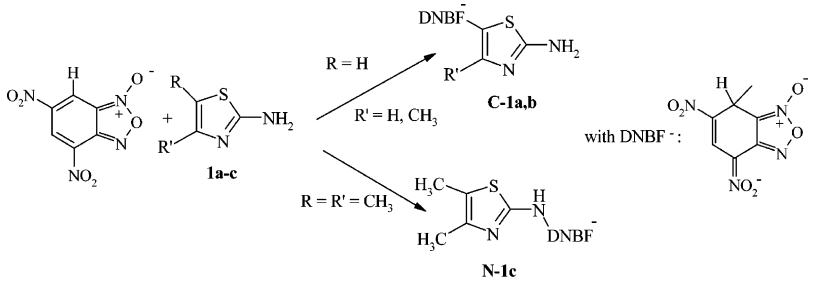
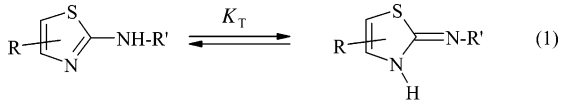


The reactions of 2-aminothiazole (**1a**), 4-methyl-2-aminothiazole (**1b**), and 4,5-dimethyl-2-aminothiazole (**1c**) with superelectrophilic 4,6-dinitrobenzofuroxan (DNBF) have been studied in acetonitrile and a 70/30 (v/v) H_2O/Me_2SO mixture. While exhibiting a somewhat higher nitrogen basicity than that of anilines, **1a** and **1b** do not react as nitrogen nucleophiles, affording exclusively anionic C-bonded σ-adducts (**C-1a** and **C-1b**) through electrophilic S_EAr substitution of the thiazole ring by DNBF. Only in the case of the 4,5-dimethyl derivative **1c** a N-adduct, **N-1c**, was obtained. On the basis of $^1H-^{15}N$ correlations, it is demonstrated that this adduct, **N-1c;1c,H**$^+$, is derived from DNBF addition at the exocyclic amino group and not at the endocyclic nitrogen center of **1c**. Rate constants have been determined in the two solvents for the formation of the adducts, revealing a reactivity sequence which accounts well for the finding that **1a** and **1b** behave preferentially as carbon rather than nitrogen nucleophiles. The enaminic character of these thiazoles is assessed through an estimation of the pK_a values for their C-protonation in aqueous solution as well as through a positioning of their reactivity on the nucleophilicity scale recently developed by Mayr et al. (*Acc. Chem. Res.* **2003**, *36*, 66). With *N* values of the order of 6.80 and 5.56, **1b** and **1a** have a carbon nucleophilicity comparable to that of *N*-methylindole and indole, respectively.

Introduction

2-Aminothiazoles, also referred to as thiazol-2-amines, represent an interesting class of versatile nucleophiles, being susceptible to electrophilic attack at each of the two nitrogen centers as well as the ring carbon C-5.[1] Regarding the nitrogen competition, the amino−imino tautomerism of eq 1 is an important factor determining the preferred site of electrophilic addition.[1−3] Most 2-aminothiazole derivatives exist in the amino aromatic form A, for example, $K_T = 4.67 \times 10^{-5}$ for the parent unsubstituted 2-aminothiazole (R = R′ = H).[3a] However, the B form can predominate when strong electron-withdrawing groups are bonded to the exocyclic nitrogen.[3]



(1)

Despite a 10^4-fold greater basicity of the imino nitrogen of the B form ($pK_a^{H_2O} = 9.65$),[3a] it is the endo aza nitrogen that is

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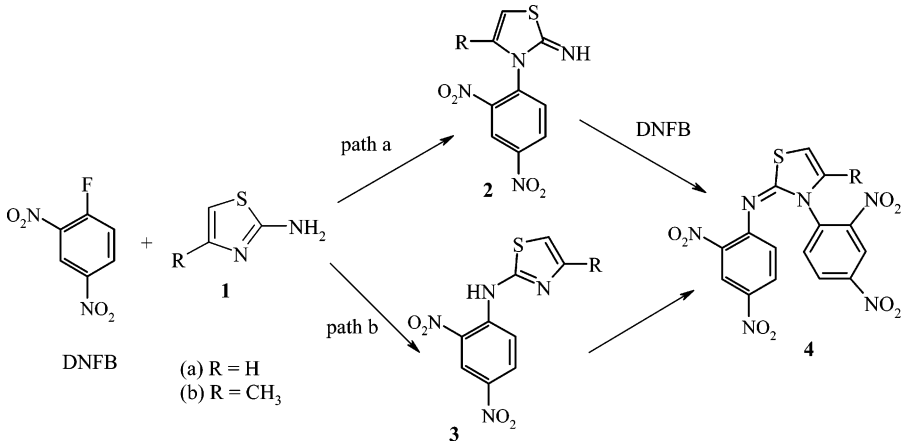
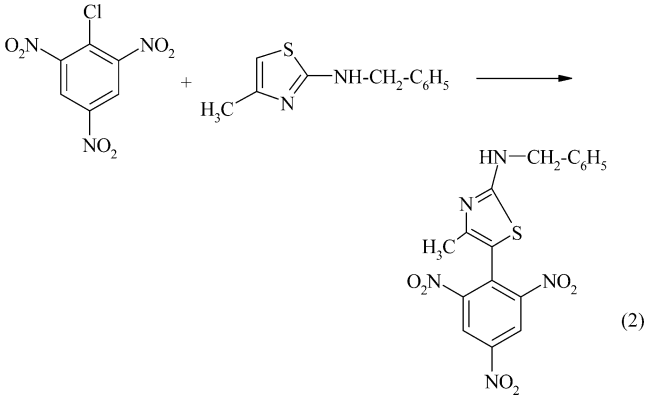
SCHEME 1



the most basic center of the A form ($pK_a^{H_2O} = 5.32$),[3] which is the preferred reactive site in nucleophilic aromatic substitutions of activated aryl halides, such as 2,4-dinitrofluorobenzene (DNFB) by **1a** (Scheme 1, path a).[1,4] Because a second and much faster reaction occurs at the imino nitrogen of the monosubstituted product **2a**, the diadduct **4a** is obtained as the major product, even when the reaction is carried out in the presence of excess **1a**. However, when the approach of the electrophile from the aza center is sterically hindered by the presence of an alkyl substituent at C-4, such as **1b** (R = CH_3), the reaction takes place first at the amino nitrogen (Scheme 1, path b). In this instance, the rate of reaction is low and the diadduct (**4b**) is obtained in low yield. Overall, Scheme 1 is an illustration of the consecutive ambident nitrogen reactivity of 2-aminothiazoles.[4a]

Much less attention has been devoted to the reactivity of aminothiazoles acting as carbon nucleophiles.[1] Besides a few electrophilic substitutions at the ring carbon C-5 by common electrophilic reagents (NO_2^+, Cl^+, Br^+, $Ar-N_2^+$, ...), C−C couplings with protonated aldehydes and picryl chloride have been reported.[1] In this latter instance, steric hindrance around the two nitrogen centers is a major factor governing the substitution process, as exemplified in eq 2, which refers to the picryl chloride/4-methyl-*N*-benzylaminothiazole system.[5]



(2)

We and others have discovered that 4,6-dinitrobenzofuroxan is an extremely strong neutral electrophile in various processes, including addition to very weak carbon nucleophiles.[6−15] A number of π-excessive arenes (anilines, phenols, or phenoxide ions)[9,13,16,17] or heteroarenes (pyrroles, indoles, furans, thiophenes)[18,19] have thus been found to react under smooth conditions with DNBF, affording quantitatively stable carbon-bonded σ-adducts of type **C-5** or **C-6**, which are formally the

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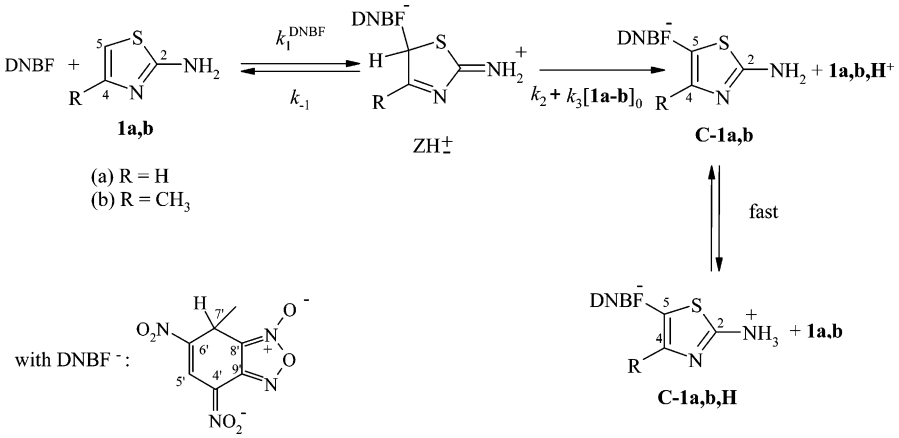
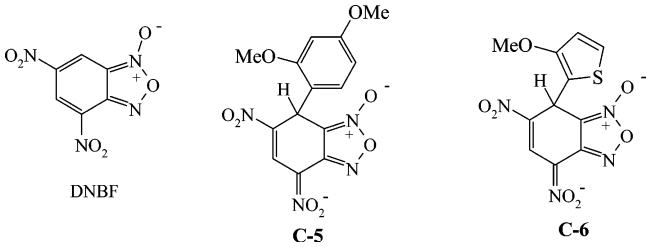
SCHEME 2



products of S_EAr substitution of the benzene or hetarene rings. Interestingly, most of these reactions could be investigated in detail by kinetics, an approach which has allowed us to quantify the weak carbon nucleophilicity of many of the aforementioned π-excessive substrates as well as to delineate the C versus N reactivity of such ambident nucleophiles as anilines or aminothiophenes.[16,19]

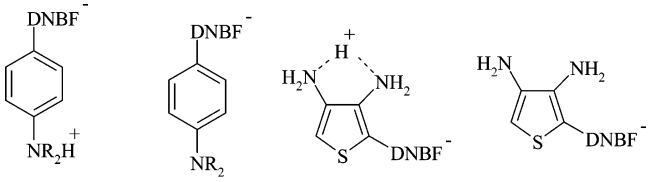


In this paper, we report on a structural and kinetic investigation of the reactions of DNBF with 2-aminothiazole **1a** ($pK_a^{H_2O} = 5.32$),[3] 4-methyl-2-aminothiazole **1b** ($pK_a^{H_2O} = 5.95$),[20a] and 4,5-dimethyl-2-aminothiazole **1c** ($pK_a^{H_2O} = 6.29$),[20b] in acetonitrile and a 70/30 (v/v) H_2O/Me_2SO mixture. As will be seen, combining the effect of the successive substitution of **1a** by the two methyl groups with an appropriate modulation of the experimental conditions (solvent, pH, etc.) has allowed us to assess accurately the nitrogen and carbon nucleophilicities of the aminothiazole structure.

Results

A. Structural Studies: 1. Complexation of DNBF by 1a and 1b. The reactions of DNBF with **1a** and **1b** were studied by mixing equimolecular amounts of the two reagents in acetonitrile solution, resulting after addition of diethyl ether in the quantitative formation of the zwitterionic adducts **C-1a,H** and **C-1b,H**, which were readily collected as orange solids (see structures in Scheme 2). Dissolution of these solids in Me_2SO-d_6 gave ^1H and ^{13}C NMR spectra (see Experimental Section) which confirmed the exclusive formation of these C-bonded complexes. Representative data are summarized in Table S1, together with those for the parent substrates.

As a major diagnostic feature in the ^1H NMR spectra of **C-1a,H** and **C-1b,H** is the $H_{7'}$ resonance which appears at 5.60 and 5.74 ppm, respectively, being in the range commonly found for many C-bonded DNBF adducts (e.g., $\delta = 5.40$ ppm for **C-7,H** and 5.42 ppm for **C-5**).[9b,17] Also in accord with previous observations showing that the chemical shift of the $H_{5'}$ proton located between the two NO_2 groups of the negatively charged DNBF moiety depends very little on the nature of the C-bonded structure, the $H_{5'}$ resonance for **C-1a,H** and **C-1b,H** is the same ($\delta = 8.64$ ppm) and close to those found for related adducts (e.g., $\delta = 8.62$ ppm for **C-6** and $\delta = 8.79$ ppm for **C-7,H**).



a) R=H
b) R=CH3

Regarding ^{13}C NMR data, there are two noteworthy results: (a) in accord with the $sp^2 \rightarrow sp^3$ rehybridization resulting from the complexation of the DNBF moiety, there is a strong upfield shift of the $C_{7'}$ resonance (from 120.80 ppm for DNBF to ~32 ppm for **C-1a,H** and **C-1b,H**); (b) the substitution of **1a** and **1b** by DNBF induces a significant low-field shift of the resonance of the C_5 carbon of the thiazole ring ($\Delta\delta \sim 13$ ppm). This latter result is mainly the reflection of the fact that a negatively charged DNBF structure exerts a notable $-I$ effect (vide infra).[6] Interestingly, carrying out the σ-complexation of **1a** and **1b** by DNBF either in the presence of a 2-fold excess of the parent aminothiazole or in the presence of a stronger base, such as DABCO, leads to the complete conversion of the two zwitterionic adducts **C-1a,H** and **C-1b,H** into their conjugate bases, that is, the anionic adducts **C-1a** and **C-1b**. As can be seen in Table S1, the process is accompanied by an appreciable shift to high field of some especially sensitive resonances, for example, δH_4 moves from 7.25 to 6.97 for **C-1a,H** and $\delta H_{7'}$ moves from 5.74 to 5.60 for **C-1b,H**. A similar trend prevailed in the deprotonation of zwitterionic adducts, such as **C-7H** and

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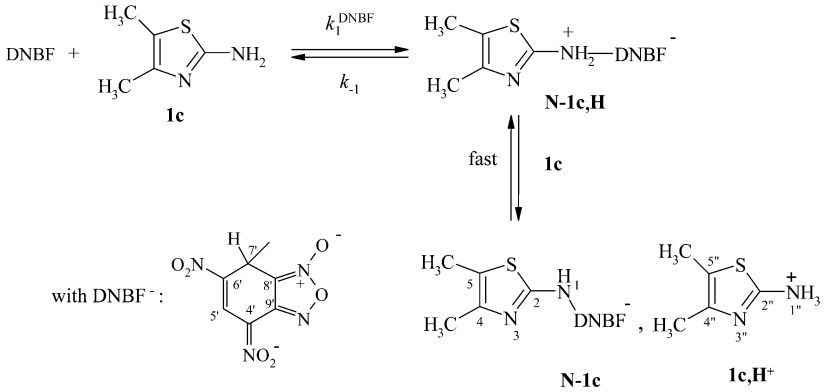
SCHEME 3



C-8H.[9b,19b,c] The zwitterionic character of **C-1a,H** and **C-1b,H** also agreed with mass spectroscopy data (see Experimental Section).

2. Complexation of DNBF by 1c. Treatment of DNBF with a 2-fold excess of **1c** in acetonitrile solution, followed by addition of diethyl ether, resulted in the precipitation of an orange solid corresponding to the 4,5-dimethylthiazolium salt of the adduct **N-1c** (Scheme 3). Because of the strong acidifying effect exerted by a negatively charged DNBF moiety,[6] the deprotonation of the NH_2^+ group of the initially formed zwitterion **N-1c,H** by **1c** acting as a base reagent is a facile process, accounting for the adduct **N-1c;1c,H**$^+$ being the thermodynamically stable product of the interaction and therefore for the need of 2 mol of **1c** to drive the overall equilibrium process to completion in acetonitrile solution.

The bonding of DNBF at a nitrogen center is supported by the presence of a relatively low-field $H_{7'}$ resonance ($\delta H_{7'}$ = 6.00 ppm) in the ^{1}H NMR spectra. Also, the related $\delta C_{7'}$ resonance appears at lower field than in the case of the C-adducts **C-1a** and **C-1b** ($\delta C_{7'}$ = 46.1 ppm; see Table S1). As previously emphasized by many authors,[6,7,21] the change in hybridization from sp^2 to sp^3 resulting from a σ-complexation process occurring at an unsubstituted aromatic or heteroaromatic ring position, here $C_{7'}$, has the expected effect to induce a high-field shift of the related proton and carbon resonances. The evidence, however, is that this resonance is very sensitive to the nature of the atom or group bonded to that position, the shielding increasing with decreasing the electronegativity of the attached atom, that is, according to the sequence O < N < C. On this ground, the finding of a $H_{7'}$ resonance at 6.00 ppm and a $C_{7'}$ resonance at 46.1 ppm leaves little doubt regarding the N-bonded structure of the DNBF adduct of 4,5-dimethyl-2-aminothiazole **1c**. As a matter of fact, the $H_{7'}$ resonance of **N-1c** is very similar to that of the anionic aniline complex **C-7** ($\delta H_{7'}$ = 6.08 ppm).[9b] ^{1}H−^{15}N correlations based on long-range coupling are clearly in favor of structure **N-1c**. In the spectra, correlations can be observed between the exocyclic nitrogen N_1 (δ = 87.1 ppm) and $H_{7'}$ (δ = 6.00 ppm), between the endocyclic nitrogen N_3 (δ = 245.0 ppm) and the methyl group at C-4 (δ = 2.05 ppm); concomitantly, the correlation between the endocyclic nitrogen N_3'' (δ = 180.5 ppm) and the methyl group at C-4″ (δ = 2.08 ppm) of the thiazolium counterpart is observed (Figure 1a). This latter correlation is similar to that observed with the 4,5-dimethylaminothiazolium bromide (Figure 1b). To be noted is that all the ^{15}N NMR data collected from the various correlations are in full agreement with a recent review on the use of long-range ^{1}H−^{15}N correlations in the structural determination of organic compounds.[22,23]

B. Kinetic Studies. Because of the poor solubility of the reagents in aqueous solution, we have investigated the kinetics of the σ-complexation of DNBF by **1a**−**c** in acetonitrile and a 70/30 (v/v) H_2O/Me_2SO mixture. All experiments were conducted at 20 °C (acetonitrile) and 25 °C (H_2O/Me_2SO) under first-order conditions with respect to the thiazole at hand as the excess component.

1. Reactions in Acetonitrile: Experiments were carried out by mixing directly a 3×10^{-5} mol dm^{-3} solution of DNBF with the thiazole solutions ([**1a**−**c**]$_0$ = 2×10^{-3} to 5×10^{-2} mol dm^{-3}). In all cases, only one relaxation time was observed (Figures S_1−S_3), corresponding to the direct formation of the anionic C-adducts **C-1a** and **C-1b** through Scheme 2 and of the anionic N-adduct **N-1c** through Scheme 3.

In formulating Scheme 2, account was taken that the rearomatization of the thiazole moiety of the "Wheland−Meisenheimer" intermediate ZH± can proceed via a spontaneous[24] or solvent-assisted pathway (k_2)[25] as well as a base-catalyzed process involving the parent aminothiazole as the effective catalyst (k_3[**1a**−**b**]$_0$).[27] On the basis of this scheme, the general expression for the observed first-order rate constant, k_{obsd}, for the formation of **C-1a** and **C-1b**, as derived under the

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(24) The rearomatization of ZH± is driven by the recovery of the π-aromatic character of the aminothiazole moiety. Obviously, the process involves the expulsion of a proton which, depending upon the experimental conditions (mixing of equimolar amounts of the reagents or excess of **1a** or **1b**) binds instantaneously to the amino group of the resulting anionic adducts **C-1a** and **C-1b**, to give **C-1a,H** or **C-1b,H**, or to the amino group of the parent thiazole at hand to afford **C-1a** and **C-1b**. The situation is similar to the one encountered in the DNBF/aniline system.[9] For simplicity, the two situations are expressed through the single equilibrium **C-1a,b** + **1a,b,H**$^+$ ⇔ **C-1a,bH** + **1a,b** in Scheme 2.

(25) The available results do not allow one to discriminate unambiguously between the two possible pathways. However, solvent assistance by acetonitrile is not expected to be here a reasonable pathway, at least on the basis of the relative pK_a values of acetonitrile (pK_a ~ −10)[26] and aminothiazole in water.

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(27) A referee has suggested that the nitronate or *N*-oxide functionalities of the resulting anionic σ-adducts might also act as base catalysts to promote the deprotonation of ZH±. While this proposal is consistent with the fact that such functionalities exhibit a much higher basicity in dipolar solvents than in aqueous solution,[28] it is not borne out by the results obtained under our experimental conditions, where the concentration of the σ-adducts cannot exceed that of DNBF, that is, it is very low ($\leq 3 \times 10^{-5}$ M).

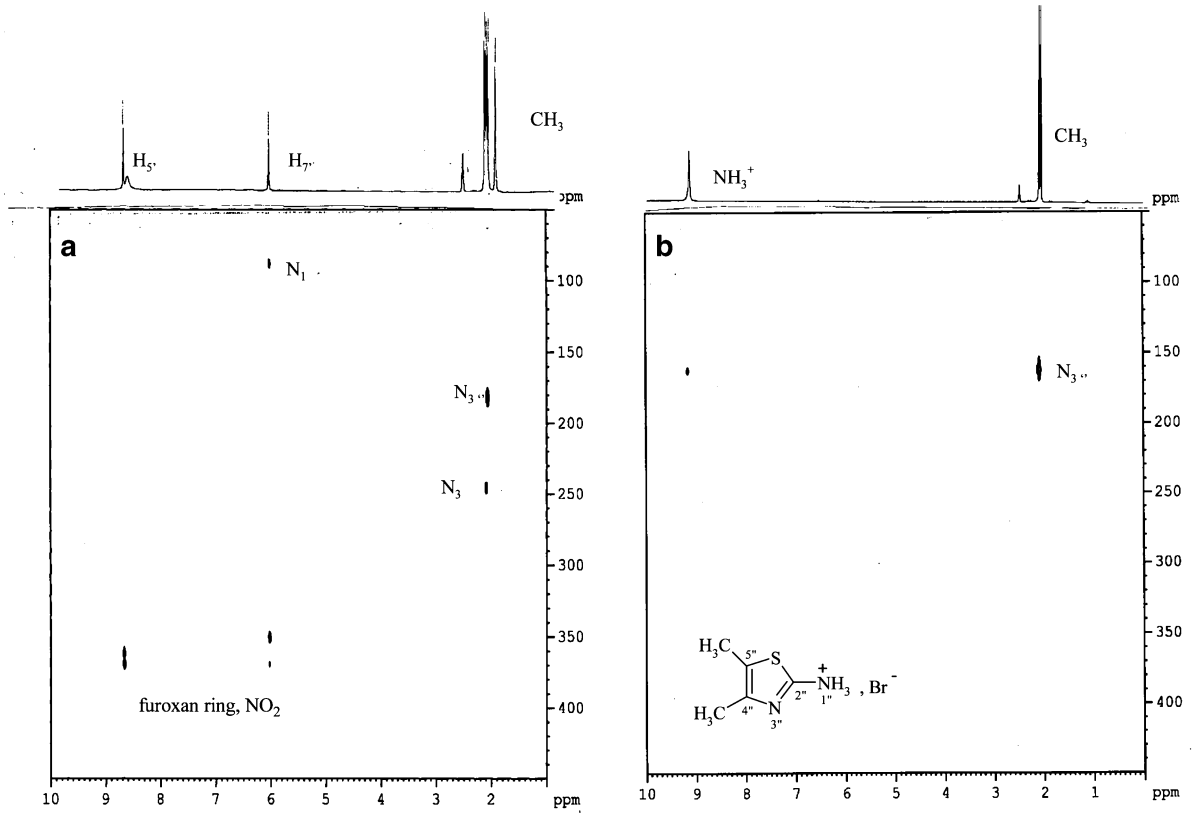


FIGURE 1. (a) $^{1}H-^{15}N$ correlation for the adduct **N-1c;1c,H**$^{+}$. (b) $^{1}H-^{15}N$ correlation for 4,5-dimethylaminothiazolium bromide.

assumption that the zwitterions ZH± are low concentration intermediates is given by

$$k_{obsd} = \frac{k_1^{DNBF}k_2[\mathbf{1a-b}]_0}{k_{-1} + k_2 + k_3[\mathbf{1a-b}]_0} + \frac{k_1^{DNBF}k_3[\mathbf{1a-b}]_0^{\,2}}{k_{-1} + k_2 + k_3[\mathbf{1a-b}]_0} \quad (3)$$

Importantly, it was found that a good straight line with zero intercept was obtained in each of the two systems studied when the k_{obsd} values were plotted versus the thiazole concentration (Figures 2 and 3), a situation which indicates that the base-catalyzed pathway is not operative at all in the second step of Scheme 2. Thus, eq 3 reduces to the simplified form of eq 4:

$$k_{obsd} = \frac{k_1^{DNBF}k_2}{k_{-1} + k_2}[\mathbf{1a-b}]_0 = k[\mathbf{1a-b}]_0 \quad (4)$$

making the determination of the second-order rate constant k from the slopes of the k_{obsd} versus $[\mathbf{1a-b}]_0$ plots straightforward. These values are given in Table 1 together with the k values corresponding to experiments carried out with the two 5-deuterated thiazoles **1-a,d** and **1-b,d**. As can be seen, the rates of formation of **C-1a** and **C-1b** depend to some extent on the nature of the isotopic substitution at C-5. The k^H/k^D ratios are equal to 1.89 and 2.50 for **C-1a** and **C-1b**, respectively. This indicates that the nucleophilic addition step is not fully rate determining in the formation of these two adducts, especially **C-1b**, in acetonitrile. In this regard, it is of interest to note that the finding of appreciable KIE is in itself consistent with **1a** and **1b** reacting as carbon nucleophiles in an overall process involving C−H bond breaking.

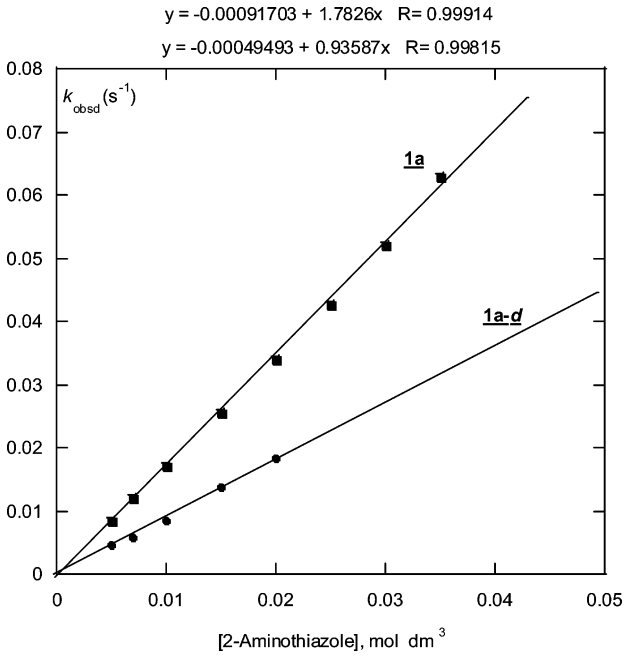


FIGURE 2. Effect of the concentration and of the isotopic substitution at C-5 of 2-aminothiazole **1a** on the observed rate of formation of the DNBF adduct **C-1a** at $T = 20$ °C in acetonitrile.

Notwithstanding that the calculations require several assumptions,[17] it is possible, using the observed KIE values, to derive the rate constant k_1^{DNBF} for the two couplings of Scheme 2 from the measured composite rate constant k. If one neglects as a first approximation secondary isotope effects on k_1^{DNBF} and k_{-1} and assumes that the rearomatization of the ZH± intermediates

TABLE 1. Summary of Rate Parameters for Formation of the Adducts C-1a, C-1b, and N-1c According to Schemes 2 and 3 in 70/30 (v/v) H_2O/Me_2SO and Acetonitrile[a]

			Acetonitrile		70/30 (v/v) H_2O/Me_2SO		
thiazole	pK_a[b]	adduct	k $dm^3\ mol^{-1}\ s^{-1}$	k_1^{DNBF}	$[H^+]$ $mol\ dm^{-3}$	k $dm^3\ mol^{-1}\ s^{-1}$	k_1^{DNBF} $dm^3\ mol^{-1}\ s^{-1}$
1a	5.32	**C-1a**	1.78 (0.93)[c]	2.06[d]	0.1	2.64×10^{-3} (2.75×10^{-3})[c]	55 (58)[c]
					0.125	2.04×10^{-3} (2.12×10^{-3})[c]	53.3 (55.4)[c]
					0.25	1.18×10^{-3}	61.7
1b	5.95	**C-1b**	18.6 (7.03)[c]	26.4[d]	0.1	5.8×10^{-3} (6×10^{-3})[c]	518 (535)[c]
					0.25	2.3×10^{-3}	513
1c	6.29	**N-1c**	8.97	8.97			

[a] $T = 20$ °C for acetonitrile; $T = 25$ °C for 70/30 (v/v) H_2O/Me_2SO. [b] Refs 3 and 20. [c] Values referring to **1a**−***d*** or **1b**−***d***. [d] Corrected for the observed KIE, as described in ref 17.

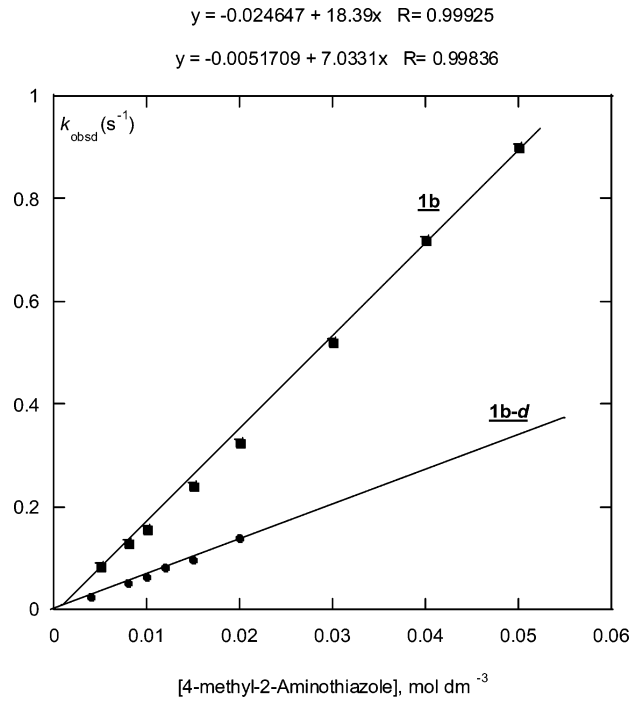


FIGURE 3. Effect of the concentration and of the isotopic substitution at C-5 of 4-methyl-2-aminothiazole **1b** on the observed rate of formation of the DNBF adduct **C-1b** at $T = 20$ °C in acetonitrile.

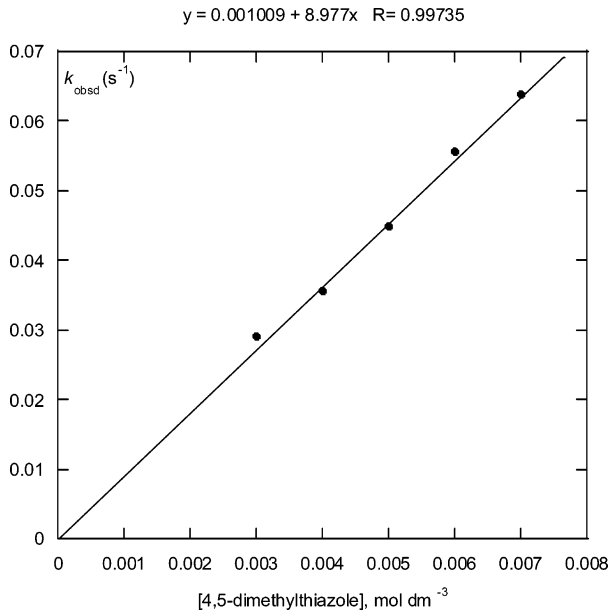


FIGURE 4. Effect of the concentration of 4,5-dimethyl-2-aminothiazole **1c** on the observed rate of formation of the DNBF adduct **N-1c** at $T = 20$ °C in acetonitrile.

proceed through essentially symmetrical transition states with no notable variation in the value of the related k_2^H/k_2^D ratio on going from aqueous to acetonitrile solutions (i.e., 7.8),[29−32] the following estimates of the actual k_1^{DNBF} rate constant can be obtained from the measured k^H/k^D ratios: $k_1^{DNBF} = 2.06\ dm^3\ mol^{-1}\ s^{-1}$ for **C-1a**, $k_1^{DNBF} = 26.4\ dm^3\ mol^{-1}\ s^{-1}$ for **C-1b** (Table 1).[33] While these latter values may better reflect the actual reactivity of DNBF toward **1a** and **1b**, they are not profoundly changed from the composite rate constants. Accordingly, referring to the k values or the k_1^{DNBF} values in our forthcoming discussion of the reactivity of **1a** and **1b** will have no effect on the overall picture that emerges from our results.

For purpose of comparison, the reactions of DNBF with 3,4-diaminothiophene and *N*,*N*-dimethylaniline, proceeding in two steps similar to those depicted in Scheme 2 to afford the previously characterized C-adducts **C-8** and **C-7b**, respectively, have been kinetically studied in acetonitrile with no evidence for KIE. From the data in Figures S4 and S5, the following k_1^{DNBF} values have been obtained: $k_1^{DNBF} = 3970$ and $0.05\ dm^3\ mol^{-1}\ s^{-1}$ for **C-8** and **C-7b**, respectively.

As shown in Figure 4, plotting the values of the observed first-order rate constant, k_{obsd}, for formation of the N-adduct **N-1c** versus the **1c** concentration afforded a straight line passing through the origin. This implies that the formation of the zwitterionic intermediate **N-1c,H** is rate-limiting in Scheme 3, in accord with the strong acidifying effect exerted by the negatively charged DNBF moiety which makes the proton transfer step thermodynamically very favorable.[6,34] Then, k_{obsd}

(28) Bug, T.; Lemek, T.; Mayr, H. *J. Org. Chem.* **2004**, *69*, 7565.
(29) Challis, B. C.; Millar, E. M. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1618.
(30) Kresge, A. J.; Chiang, Y. *J. Am. Chem. Soc.* **1962**, *84*, 3976.
(31) Gruen, L. C.; Long, F. A. *J. Am. Chem. Soc.* **1967**, *89*, 1287.
(32) Smith, P. J. In *Isotopes in Organic Chemistry* (Vol. 2) and *Isotopes in Hydrogen Transfer Processes*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1976; Chapter 6, p 260.
(33) Should the reactions proceed through somewhat unsymmetrical transition states, the value of the k_2^H/k_2^D ratio will be lowered, but again the calculated k_1^{DNBF} value does not fundamentally differ from the experimentally measured k value. Thus for $k_2^H/k_2^D = 5$, we will have $k_1^{DNBF} = 2.25$ for **C1-a** and $k_1^{DNBF} = 28$ for **C1-b**.

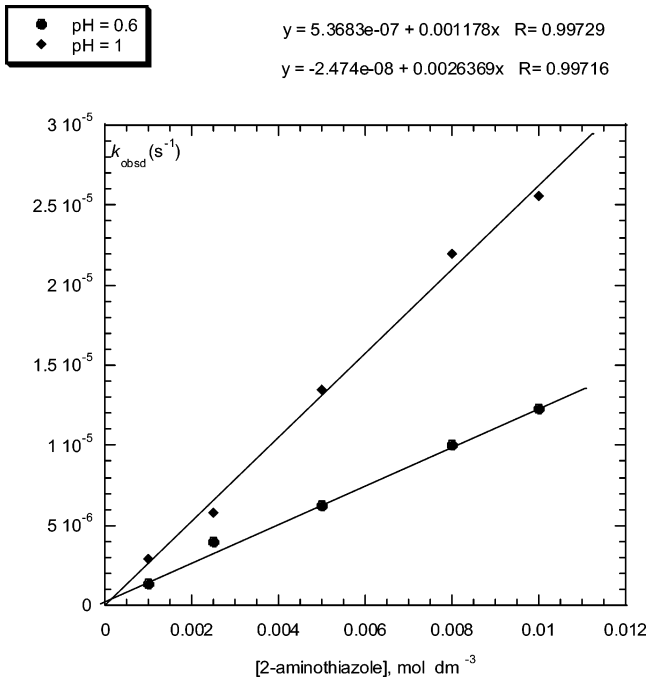
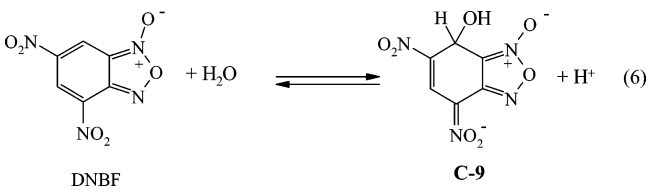


FIGURE 5. Effect of the thiazole and H^+ concentrations on the observed rate of formation of the DNBF adduct **C-1a,H** at $T = 25$ °C in 70/30 (v/v) H_2O/Me_2SO.

is simply given by eq 5. From the slope of the line of Figure 4, one readily obtained $k_1^{DNBF} = 8.97$ dm^3 mol^{-1} s^{-1} (Table 1).

$$k_{obsd} = k_1^{DNBF}[\mathbf{1c}]_0 \qquad (5)$$

2. Reactions in 70/30 (v/v) H_2O/Me_2SO. As previously reported,[6] DNBF has a strong tendency to react according to eq 6 in aqueous solution. The pK_a for formation of the hydroxyl adduct **C-9** is equal to 3 at 25 °C in 70/30 (v/v) H_2O/Me_2SO.[6,35] To avoid any interference between this process and the σ-complexation reactions of DNBF with **1a**−**c**, we have investigated the kinetics of these interactions at low pH in this solvent, a strategy that we have successfully used in studies of DNBF/anilines and DNBF/aminothiophene systems.[16,19] Experiments were thus carried out by mixing HCl solutions of DNBF ($\sim 3 \times 10^{-5}$ mol dm^{-3}) with equal volumes of various solutions of **1a**−**c** (2×10^{-3} to 0.04 mol dm^{-3}) in a stopped flow apparatus. The HCl concentrations of the DNBF solutions were chosen to afford, after mixing, H^+ concentrations of 0.1, 0.125, and 0.25 mol dm^{-3}. The final ionic strength was maintained at 0.25 mol dm^{-3} by addition of KCl as needed. Under these rather acidic conditions, where the parent aminothiazoles **1a**−**c** were present essentially in their protonated forms, direct conversion of DNBF to the adducts **C-1a,H** and **C-1b,H** (these acid forms must predominate at the pH at hand), but not to the N-adduct **N-1c** was found to occur.



Returning to Scheme 2, **C-1a,H** and **C-1b,H** must now form through attack of DNBF by equilibrium concentrations of **1a** and **1b**, with the expression of the observed first-order rate constant, k_{obsd}, being given by eq 7 in the absence of base catalysis of the second step (vide infra). In this equation, [**1a**−**b**]$_0$ represents the total thiazole concentration used in a given experiment and K_a is the acidity constant describing the N-protonation behavior of the amino reagent.[3,20] As in acetonitrile experiments, eq 7 is derived under the assumption that the zwitterions ZH± are low concentration ("steady-state") intermediates.

$$k_{obsd} = \frac{k_1^{DNBF}k_2}{k_{-1} + k_2}\frac{K_a}{K_a + [H^+]}[\mathbf{1a}-\mathbf{b}]_0 \qquad (7)$$

$$k_{obsd} = \frac{k_1^{DNBF}k_2}{k_{-1} + k_2}\frac{K_a}{[H^+]}[\mathbf{1a}-\mathbf{b}]_0 = k[\mathbf{1a}-\mathbf{b}]_0 \qquad (8)$$

In view of the rather moderate variations suffered by the pK_a values of nitrogen bases on going from water to a 70/30 (v/v) H_2O/Me_2SO,[36] eq 7 reduces to eq 8 at the high H^+ concentrations employed ($K_a \ll [H^+]$). In accord with eq 8, excellent linear plots of k_{obsd} versus the total concentration of the thiazole reagent were obtained, both for the **1a** and **1b** systems, at the two or three H^+ concentrations studied (Figure 5). Relevant values of the second-order rate constant k are given in Table 1.

Contrasting with the acetonitrile behavior, no significant variations in the k values were observed when using the 5-deuterated thiazoles **1a,d** and **1b,d**, that is, the nucleophilic addition step is rate determining in 70/30 (v/v) H_2O/Me_2SO mixture, implying $k_2 \gg k_{-1}$. Hence, eq 7 takes on the simplified form of eq 9. From this equation, values of the second-order rate constant k_1^{DNBF} for the C-addition of **1a** and **1b** to DNBF could be estimated at each H^+ concentration studied, assuming as a first approximation that the pK_a values of the thiazole reagents are about the same in H_2O and 70/30 (v/v) H_2O/Me_2SO. As can be seen in Table 1, there is a good agreement between the different sets of determinations. For purpose of discussion, the average k_1^{DNBF} values for **1a** and **1b** are compared in Table 2 with similar data previously reported for DNBF addition to aniline, 3-aminothiophene, 3-methoxythiophene, and a number of 5-X-substituted indoles as well as a few pyrrole derivatives in the same 70/30 (v/v) H_2O/Me_2SO mixture.[16,18,19,37]

$$k_{obsd} = \frac{k_1^{DNBF}K_a}{[H^+]}[\mathbf{1a}-\mathbf{b}]_0 \qquad (9)$$

Discussion

Nitrogen versus Carbon Nucleophilicity of Aminothiazoles 1a−c. Buncel and co-workers as well as Spear et al. have

(34) (a) Bernasconi, C. F. *MTP Int. Rev. Sci.: Org. Chem. Ser. 1* **1973**, *3*, 33. (b) Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147. (c) Asghar, B. H.; Crampton, M. R. *Org. Biomol. Chem.* **2005**, *3*, 3971.
(35) Terrier, F.; Sorkhabi, H. A.; Millot, F.; Hallé, J. C.; Schaal, R. *Can. J. Chem.* **1980**, *58*, 1155.
(36) (a) Hallé, J. C.; Schaal, R.; Di Nallo, A. *Anal. Chim. Acta* **1972**, *60*, 197. (b) Edward, J. T.; Farrell, P. G.; Hallé, J. C.; Kirchnerova, J.; Schaal, R.; Terrier, F. *Bull. Soc. Chim. Fr.* **1979**, I-124.
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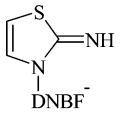
TABLE 2. Comparison of the Carbon Nucleophilicities of Aminothiazoles 1a and 1b with Those of Various π-Excessive Arenes and Heteroarenes in 70/30 (v/v) H_2O/Me_2SO

compound	$pK_a^{H_2O}$ [a]	k_1^{DNBF} $dm^3\ mol^{-1}\ s^{-1}$
1,3-dimethoxybenzene[b]	−9	1[f,g]
1,3-dihydroxybenzene[b]	−7.83	3.2 [f,g]
3-methoxythiophene[c]	∼ −6.5 to −7	0.72
5-cyanoindole[d]	−6.00	2.8
aniline	−7.1[h]	4.6[f]
N,*N*-dimethylaniline[e]	∼ −6.8[h], −6[e]	7[f]
1,3,5-trimethoxybenzene[b]	−5.72	57[g]
2-aminothiazole (***1a***)	−5.46[h]	58
5-bromoindole[d]	−4.57	125
5-chloroindole[d]	−4.53	125.5
3,5-dimethoxyphenol[b]	−4.35	245[f]
4-methyl-2-aminothiazole (***1b***)	−3.9[h]	515
N-methylpyrrole[i]	−3.88	155[g]
pyrrole[i]	−3.79	650[g]
indole[d]	−3.46	1110
5-methylindole[d]	−3.30	5000
1,3,5-trihydroxybenzene[b]	−3.13	1600[g]
5-methoxyindole[d]	−2.90	5260
N-methylindole[d]	−2.32	6980
1,2,5-trimethylpyrrole[j]	−0.49	4.8×10^4 [g]
3-aminothiophene[i]	−0.40[h]	7×10^4 [f]
3-(dimethylamino)thiophene[i]	+0.2[h]	1.8×10^5 [f]
3-methylaminothiophene[i]	+0.8[h]	5×10^5 [f]
3,4-diaminothiophene[k]	+ 1.5[g]	2×10^6

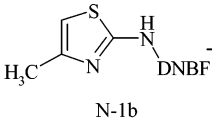
[a] The $pK_a^{H_2O}$ values refer to the C-protonation of the listed arenes or heteroarenes in aqueous solution. [b] Ref 17. [c] Ref 19a. [d] Ref 18c. [e] Ref 16. [f] Values of k_1^{DNBF} corrected for the 2-fold increase in rate caused by a transfer from 50/50 to 70/30 (v/v) H_2O/Me_2SO; see ref 18c. [g] Statistically corrected k_1^{DNBF} values have been used to draw the correlation of Figure 6. [h] The pK_a values estimated in this work through the correlation of Figure 6. [i] Ref 19c. [j] Ref 18b. [k] Ref 19b.

demonstrated that the reaction of DNBF with aniline involves the competitive formation of the nitrogen and carbon-bonded σ-adducts **N-10** and **C-10,H** according to the mechanism shown in Scheme 4.[9a,b−13] The key point in this mechanism is that the formation of the N-bonded adduct **N-10** occurs very rapidly but is reversible, while the formation of the C-bonded adduct **C-10,H** is slower but occurs irreversibly; hence, **C-10,H** (or its conjugate base **C-10** under some experimental conditions) is obtained quantitatively as the thermodynamically favored product. A kinetic study of the overall interaction in H_2O/Me_2SO mixtures and pure Me_2SO has recently been made which confirmed the proposed mechanism, while allowing a quantitative calibration of the carbon nucleophilicity of aniline through determination of the k_1^{DNBF} rate constant.[10a,16]

Based on the fact that the nitrogen basicities of **1a** ($pK_a^{H_2O} = 5.32$)[3] and **1b** ($pK_a^{H_2O} = 5.95$)[20a] are somewhat higher than that of aniline ($pK_a^{H_2O} = 4.58$),[19c] one could reasonably anticipate that these two thiazoles will exhibit a similar ambident reactivity, attacking first DNBF via one of their nitrogen centers to give a N-adduct, presumably **N-1a** and **N-1b** (vide supra for this identification), under kinetic control but affording the C-adducts **C-1a,H** (or **C-1a**) and **C-1b,H** (or **C-1b**) as the thermodynamically stable products.

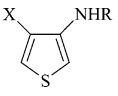


N-1a

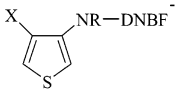


N-1b

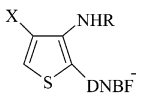
While the failure to detect the formation of **N-1a** and **N-1b** prior to that of the related C-adducts **C-1a,H** and **C-1b,H** in 70/30 (v/v) H_2O/Me_2SO can be attributed to a lack of stability of these species under the acidic conditions employed in this solvent—even the N-adduct **N-1c** which is derived from the most basic thiazole of the series does not form in the presence of 0.1 mol dm^{-3} HCl—a similar explanation cannot be invoked to account for the behavior observed in acetonitrile. In fact, the present finding that DNBF addition occurs exclusively at C-5 of **1a** and **1b** under the different experimental conditions employed in our work is reminiscent of the general reactivity pattern found for the reactions of DNBF with 3-aminothiophenes **11a**−**d**.[19] Despite the fact that these compounds have nitrogen basicities similar to those of anilines, no evidence for the formation of N-adducts of type **12** prior to that of the corresponding thermodynamically stable C-adducts **13** could be obtained.[19b,c]



11a-d



12a-d

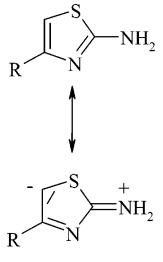


13a-d

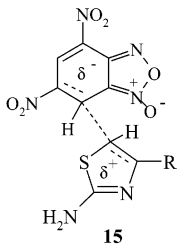
a) R = X = H
b) R = Me, X = H
c) R = H, X = NH_2
d) R = Me, X= NHMe

13c = C-8

As elaborated for the aminothiophene reactivity,[19] the exclusive formation of **C-1a** and **C-1b** in the DNBF/**1a** and DNBF/**1b** systems supports the view that the two thiazoles exhibit a noteworthy carbon nucleophilicity, reflecting a significant contribution of the enaminic structure **14** to the observed reactivity patterns. Inspection of Table 1 is revealing in this regard. With a nitrogen moiety which is 2−3 times less basic than that of **1c**, **1b** undergoes DNBF C-addition at a rate which is 2−3-fold faster than that of the N−C coupling of DNBF with **1c**. Notwithstanding the fact that the basicity data refer to aqueous solution but the kinetic data to acetonitrile solution, the above orderings are consistent with the idea that 4-methyl-2-aminothiazole, as well as the parent unsubstituted analogue **1a**, reacts more efficiently as carbon rather than nitrogen nucleophiles. Focusing on this carbon reactivity, it is of interest that the related k_1^{DNBF} rate constants increase by more than 1 order of magnitude on going from acetonitrile to 70/30 (v/v) H_2O/Me_2SO solution: $k_1^{30\%DMSO}/k_1^{ACN} = 28$ and 19.5 for **1a** and **1b**, respectively. This points to a notable influence of solvent polarity on the reactions, which is similar to that previously found on the rates of C−C coupling of DNBF with a number of indoles and can be understood in terms of the reactions proceeding through a dipolar transition state of type **15**.[18b,c] Such a transition state is expected to be more stabilized in polar aqueous solvents than in acetonitrile.

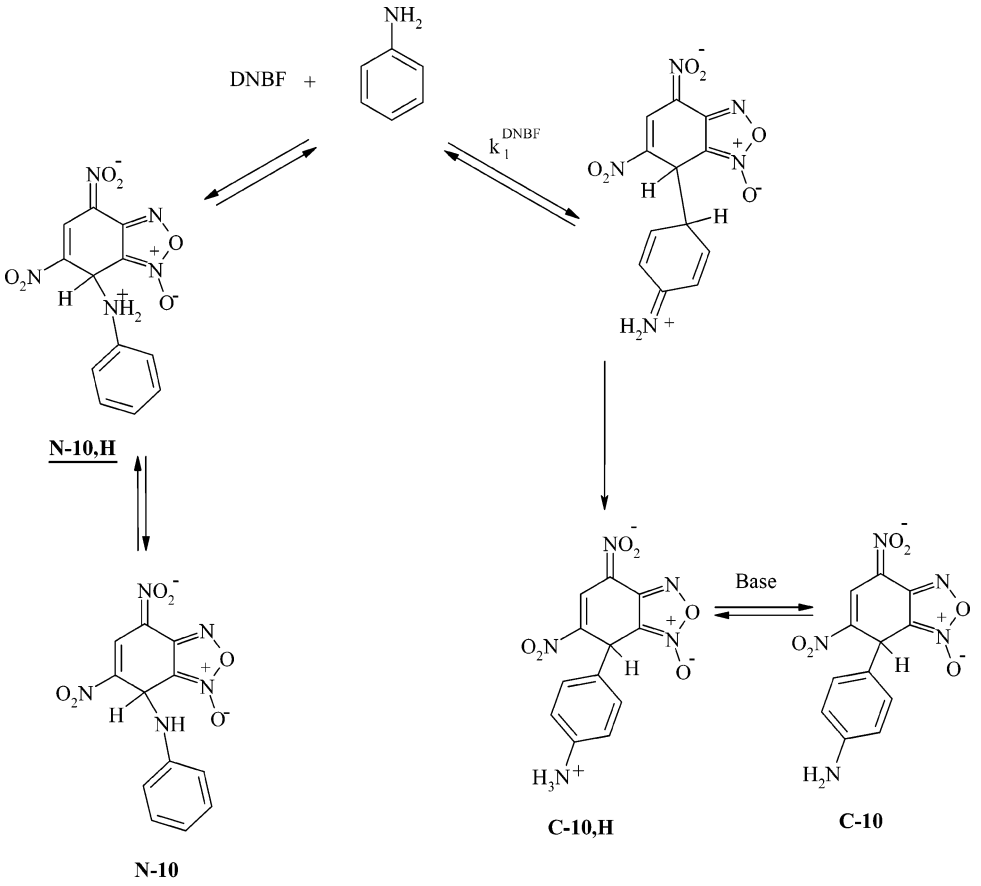


14



15

SCHEME 4



Assessing the C-Basicity of 2-Aminothiazoles. In previous studies of the coupling of DNBF with a few hydroxyl- and methoxy-substituted benzenes, 5-X-substituted indoles, and a number of pyrroles, we have pointed out that compounds with close thermodynamic C-basicities exhibit roughly similar carbon nucleophilicities.[17−19,37] Figure 6 shows that a satisfactory linear Brönsted-type relationship emerges when the log k_1^{DNBF} values measured in a given solvent are plotted versus the $pK_a^{H_2O}$ values for C-protonation of these substrates in aqueous solution. Assuming that this correlation will also fit the nucleophilic behavior of related π-excessive aromatic and heteroaromatic compounds, the plot of Figure 6 was used to derive the otherwise unaccessible $pK_a^{H_2O}$ values for C-protonation of anilines and 3-aminothiophenes from the relevant k_1^{DNBF} rate constants.[16,19b,c] The results have highlighted the totally different behavior of these similar nitrogen bases. While the carbon nucleophilicity of anilines is weak, going along with a much weaker C- than N-basicity ($\Delta pK_a \sim 10$), that of 3-aminothiophenes is very high, reflecting a C-basicity which is approaching the N-basicity domain of these substrates ($\Delta pK_a \sim 3$). Theoretical calculations have confirmed this situation which accounts for the finding that in many instances 3-aminothiophenes behave exclusively as carbon nucleophiles.[38−40]

Applying the same reasoning to the DNBF−2-aminothiazole systems, Figure 6 places the carbon nucleophilicity, and therefore the C-basicity of **1a** ($pK_a^{H_2O} \sim -5.46$) and **1b** ($pK_a^{H_2O} \sim -3.9$) at the same level as that of 1,3,5-trimethoxybenzene ($pK_a^{H_2O} \sim -5.72$)[41] and indole ($pK_a^{H_2O} \sim -3.46$).[42] This ranking clearly accounts for the finding that **1a** and **1b** are more prone—in fact by one to 2 orders of magnitude—than anilines to undergo DNBF addition at a ring carbon. In this regard, it is interesting to note that the difference between the C- and N-basicities amounts to 10 p*K* units both for **1a** and **1b**, a situation which is strictly the same as that prevailing in the case of anilines.[16] On the basis, why we failed to detect initial attack of DNBF to one of the nitrogen centers of **1a** and **1b** remains to be understood.

The positioning of **1a** and **1b** on the correlation of Figure 6 is a useful measure of the enaminic character of these compounds (structure **14**). Assessing this character as well as that of anilines and 3-aminothiophenes is also possible by referring to a general approach to nucleophilicity and electrophilicity recently developed by Mayr and co-workers.[43,44] Using a large series of diarylcarbenium ions and various π-excessive systems as reference sets for electrophiles and nucleophiles, respectively, these authors have shown that it is possible to describe the rates of a large variety of electrophile−nucleophile combinations by the three-parameter eq 10.[43−45] In this equation,

(38) Paulmier, C. *Sulfur Rep.* **1996**, *19*, 215.
(39) Outurquin, F.; Lerouge, P.; Paulmier, C. *Bull. Soc. Chim. Fr.* **1986**, *259*, 267.
(40) Bagno, A.; Terrier, F. *J. Phys. Chem. A* **2001**, *105*, 6537.
(41) Kresge, A. J.; Mylonakis, S. G.; Sato, Y.; Vitullo, V. P. *J. Am. Chem. Soc.* **1971**, *93*, 6181.
(42) Hinman, R. L.; Lang, J. *J. Am. Chem. Soc.* **1964**, *86*, 3796.
(43) (a) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938. (b) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66. (c) Mayr, H.; Patz, M.; Gotta, M. F.; Ofial, A. R. *Pure Appl. Chem.* **1998**, *70*, 1993.
(44) Mayr, H.; Ofial, A. R. *Pure Appl. Chem.* **2005**, *77*, 1807 and numerous references therein.

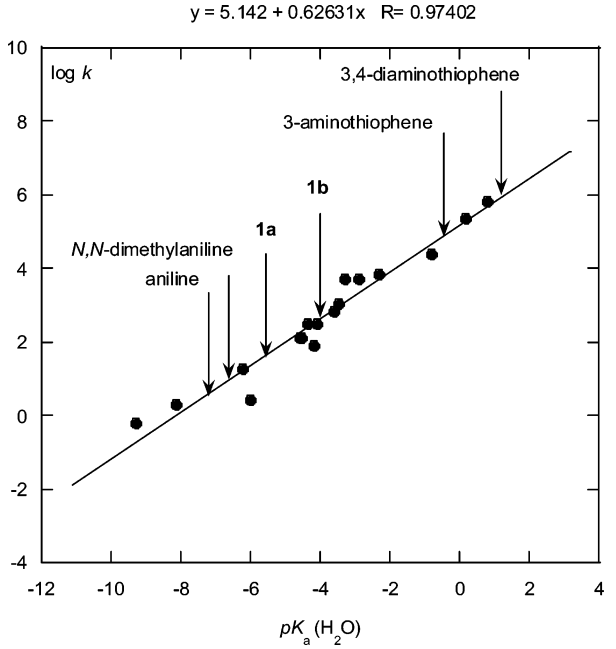


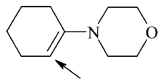
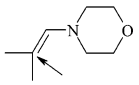
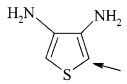
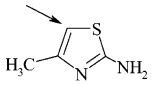
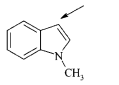
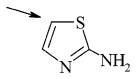
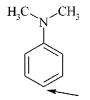
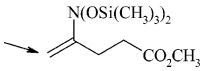
FIGURE 6. Brönsted-type relationship describing the behavior of hydroxy- and methoxy-substituted benzenes ($pK_a \sim -9$ to -3.13),[17] indoles ($pK_a \sim -6$ to -2.3),[18c] and pyrroles ($pK_a \sim -4$ to 3.8)[19c] in 70/30 (v/v) H_2O/Me_2SO. Application to the determination of pK_a values for C-protonation of anilines, aminothiazoles, and aminothiophenes (see text).

the *E* parameter measures the strength of the electrophile, while the *N* and *s* parameters characterize the sensitivity of the nucleophile.

$$\log k\,(20\ ^\circ\mathrm{C}) = s\,(N + E) \qquad (10)$$

On the basis of eq 10, general electrophilicity (*E*) and nucleophilicity (*N*) scales, each covering a reactivity range of about 25 orders of magnitude, have been defined and successfully used to assess the reactivity of many families of electrophilic or nucleophilic substrates.[43−45] Among the variety of nucleophiles studied, a number of enamines have been classified by Mayr on the *N* scale with the finding that the corresponding *s* parameter does not vary much with the enamine structure ($0.79 < s < 1.03$).[46] Thus, combining an average value of $s = 0.90$ with the *E* value recently determined for DNBF ($E = -5.2 \pm 0.3$)[47] makes it possible to approximate the *N* values for **1a** and **1b** through eq 10, in which the log *k* values refer to our kinetic measurements (k_1^{DNBF}) in acetonitrile. Table 3 gives the results obtained together with those similarly derived in this work for *N*,*N*-dimethylaniline and 3,4-diaminothiophene. Also given are the *N* values of some enamines, as derived by Mayr et al. through the accurate strategy developed by these authors to build the *N* scale.[46] In this regard, simply using the log k_1^{DNBF} values previously measured for coupling of these compounds with DNBF in acetonitrile[18c] affords *N* values which agree well with the reference values of Mayr.

TABLE 3. The Positioning of Enamine Structures on the Nucleophilicity Scale[a,b]

enamine	pK_a^{H2O}	k_1^{DNBF},[c] $dm^3\ mol^{-1}\ s^{-1}$	*N*
	7[d]	2.6×10^5[e]	11.23[f]; 11.40[g]
	5.45[d]	1.6×10^4[e]	9.90[f]; 10.04[g]
	~ 1.5[h,i]	3970	9.20[f]
	~ - 3.9[i]	26.4	6.80[f]
	-2.32[j]	13.4[e]	6.50[f]; 6.93[g]
	-3.46[j]	2.3[e]	5.61[f]; 5.80[g]
	~ -5.46[i]	2.06	5.56[f]
	~ -6.8[i]	0.05	3.8[f]; ~ 5.6[k]
	-	-	3.84[g]

[a] In each of the enaminic structures studied, the arrow indicates the site of electrophilic addition. [b] The $pK_a^{H_2O}$ values refer to the C-protonation of the listed substrates in aqueous solution. [c] The k_1^{DNBF} values for the coupling of enamine structures with DNBF ($E = -5.22$) in acetonitrile; $T = 20$ °C. [d] Ref 48. [e] Ref 47. [f] Approximate *N* values through rearrangement of eq 10 into $N = \log(k)/s - E$ with $s = 0.9$; ref 44 (see text). [g] Accurate *N* values taken from ref 46. [h] Ref 19c. [i] Values estimated from the relationship of Figure 6. [j] Ref 18c. [k] Value derived from a *N* versus σ^+_{arene} correlation; ref 49.

Notwithstanding that our *N* data are somewhat approximated, it is clear from Table 3 that the order of nucleophilicity follows roughly the order of pK_a values for C-protonation of the substrates. With a *N* value of the order of 4, *N*,*N*-dimethylaniline lies in the domain of the weakest enamines studied by Mayr. Consistent with their greater C-basicity, **1a** and **1b** exhibit *N* values in the range of 5.5−6.8, comparable to those of indole and *N*-methylindole, while 3,4-diaminothiophene ($N \sim 9$) approaches the domain of strongly enaminic structures. This positioning of the two aminothiazoles **1a** and **1b** and related substrates within the *N* scale provides an additional illustration of the essential role that the relationship of eq 10 can play in understanding organic reactivity.

Experimental Section

Materials: 2-Aminothiazole (**1a**), 4-methyl-2-aminothiazole (**1b**), and 4,5-dimethyl-2-aminothiazole (**1c**) were commercially available products which were purified as appropriate.

(45) (a) Ofial, A. R.; Ohkubo, K.; Fukuzumi, S.; Lucius, R.; Mayr, H. *J. Am. Chem. Soc.* **2003**, *125*, 10906. (b) Bug, T.; Mayr, H. *J. Am. Chem. Soc.* **2003**, *125*, 12980. (c) Minegishi, S.; Mayr, H. *J. Am. Chem. Soc.* **2003**, *125*, 286.

(46) Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem. Eur. J.* **2003**, *9*, 2209.

(47) (a) Terrier, F.; Lakhdar, S.; Boubaker, T.; Goumont, R. *J. Org. Chem.* **2005**, *70*, 6242. (b) Terrier, F.; Lakhdar, S.; Goumont, R.; Boubaker, T.; Buncel, E. *Chem. Commun.* **2004**, 2586.

(48) (a) Kuehne, M. E.; Foley, L. *J. Org. Chem.* **1965**, *30*, 4280. (b) Stamhuis, E. J.; Maas, W.; Wynberg, H. *J. Org. Chem.* **1965**, *30*, 2160.

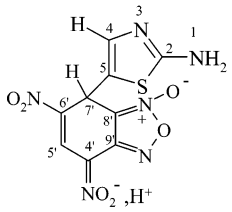
(49) Gotta, M. F.; Mayr, H *J. Org. Chem.* **1998**, *63*, 9769.

Deuteration of **1a** and **1b** at C-5 was effected as followed: to 10 mL of MeOH-d_4 was added 0.5 g of Na (0.02 mol) under argon. After completion of the reaction, 0.005 mol of the corresponding thiazole **1a** or **1b** was added to the solution. The reaction mixture was kept at room temperature for a few days. Then, the solvent was removed under vacuum, and water (100 mL) was added to the reaction mixture. The aqueous phase was extracted three times with 50 mL of dichloromethane; the organic layers were combined and washed first with 50 mL of a 2 M solution of NH_4Cl and then water (50 mL), dried over $MgSO_4$, and concentrated under vacuum at room temperature to give pale yellow solids. The deuterium incorporation at C-5 was found to be ≥98% on the basis of 300 MHz ^{1}H NMR spectra recorded in Me_2SO-d_6.

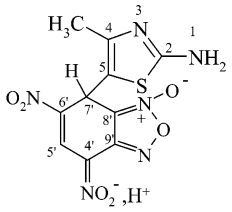
Aminothiazole Adducts: The zwitterionic C-adducts of **1a** and **1b** (i.e., **C-1a,H** and **C-1b,H** (Scheme 2)) were prepared as follows. To a solution of DNBF (0.5 g, 2.2 mmol) in 20 mL of acetonitrile was added 1 equiv of **1a** or **1b**. The reaction mixture which turned red−orange immediately was kept 10 min under stirring at room temperature. Then diethyl ether was added, resulting in the formation of a precipitate which was collected by filtration, washed with copious amounts of diethyl ether, and dried thoroughly under vacuum to give the expected zwitterionic complexes in essentially quantitative yields. Representative NMR (^{1}H, ^{13}C) and mass spectroscopy data for **C-1a,H** and **C-1b,H** are given below. Figures S6−S14 show representative ^{1}H and ^{13}C NMR spectra as well as two-dimensional correlations recorded for **C-1a,H** and **C-1b,H**.

Mixing 1 equiv of DNBF with 2 equiv of 4,5-dimethyl-2-aminothiazole **1c** and proceeding as described above, the N-adduct **N-1c** was readily isolated as a 4,5-dimethyl-2-thiazolium salt (i.e., **N-1c;1c,H**$^+$). NMR (^{1}H, ^{13}C) and mass spectroscopy data for this salt are given below. Figures S15−S20 show representative ^{1}H and ^{13}C NMR spectra recorded in Me_2SO-d_6. As emphasized in the result section, ^{1}H−^{15}N correlations based on long-range coupling leave no doubt as to the σ-complexation taking place at the exocyclic amino group of **1c**.

As with most of DNBF σ-adducts isolated so far, the crystals obtained for **C-1a−b,H** and **N-1c;1c,H**$^+$ were not found to melt prior to decomposition (explosion). In addition, attempts to obtained satisfactory elemental analysis of these species have failed, making it important to emphasize that their dissolution in Me_2SO-d_6 gave NMR spectra identical to those recorded in the in situ generation of these adducts in this solvent. As elaborated further in the results section, the available analytical data are in full accord with the proposed structures.



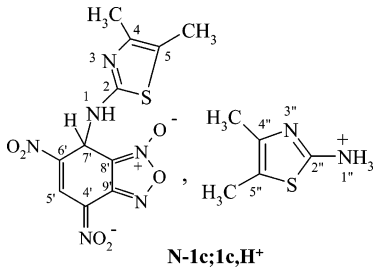
C-1a,H



C-1b,H

C-1a,H: orange solid; yield 92%; MS *m*/*z* (ESI) 325 (M−H)$^+$. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 5.60 (s, 1H, $H_{7'}$), 7.25 (s, 1H, H_4), 8.64 (s, 1H, $H_{5'}$). ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 32.3 ($C_{7'}$), 110.5 ($C_{4'}$), 112.3 ($C_{8'}$), 119.7 (C_5), 123.8 ($C_{6'}$), 125.2 (C_4), 131.8 ($C_{5'}$), 148.3 ($C_{9'}$), 169.6 (C_2).

C-1b,H: red solid; yield 88%; MS *m*/*z* (ESI) 339 (M−H)$^+$. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 2.20 (s, 3H, CH_3), 5.74 (s, 1H, $H_{7'}$), 8.64 (s, 1H, $H_{5'}$). ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 12.3 (CH_3), 31.1 ($C_{7'}$), 109.2 ($C_{4'}$), 112.0 (C_5), 112.9 ($C_{8'}$), 124.0 ($C_{6'}$), 130.8 ($C_{5'}$), 135.7 (C_4), 147.7 ($C_{9'}$), 167.4 (C_2).



N-1c;1c,H$^+$

N-1c;1c,H$^+$: red solid; yield 95%; MS *m*/*z* (FAB$^-$) 354 (**N-1c**), (FAB$^+$) 129 (**1c,H**$^+$). ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 1.90 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 6.00 (s, 1H, $H_{7'}$), 8.64 (s, 1H, $H_{5'}$). ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 10.3 (CH_3), 10.5 (CH_3), 11.7 (CH_3), 13.8 (CH_3), 46.1 ($C_{7'}$), 110.4 ($C_{4'}$), 111.8 ($C_{8'}$), 112.1 ($C_{5''}$), 112.4 (C_5), 123.5 ($C_{6'}$), 131.8 ($C_{5'}$), 132.6 ($C_{4''}$), 139.9 (C_4), 149.2 ($C_{9'}$), 162.7 (C_2), 166.9 ($C_{2''}$).

Kinetic Measurements: Most of the interactions studied in this work were kinetically followed by the stopped flow technique. Measurements were performed on a stopped flow spectrophotometer, the cell compartment of which was maintained at 20 ± 0.5 °C. A conventional HP8453 spectrophotometer was also used to follow the slowest processes. All kinetic runs were carried out in triplicate under pseudo first-order conditions with a DNBF concentration of ca. 3×10^{-5} mol dm^{-3} and a nucleophile **1a−c** concentration in the range of 10^{-3} to 0.1 mol dm^{-3}. 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 λ_{max} of the resulting adducts (e.g., 470−480 nm for the DNBF adducts **C1a−b** and **N-1c;1c,H**$^+$) or the decrease in the absorbance of the parent electrophile substrate (e.g., λ_{max} = 415 nm for DNBF) as a function of time.

Supporting Information Available: Oscilloscope pictures showing the unique relaxation process in the various electrophile−nucleophile combinations studies (Figures S1−S3 on pages S2−S4). Spectral data (^{1}H and ^{13}C NMR and mass spectroscopy) for adduct formation (Table S1, Figures S6−S20 on pages S8−S22). This material is available free of charge via the Internet at http://pubs.acs.org.

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