CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200700669

Evidence for the Intermediacy of Wheland–Meisenheimer Complexes in S_EAr Reactions of Aminothiazoles with 4,6-Dinitrobenzofuroxan

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Abstract: Reactions of DNBF with a series of 2-aminothiazoles (**1a–f**) to afford thermodynamically stable *C*-bonded σ-adducts have been investigated in acetonitrile. A most significant finding emerged on recording NMR spectra immediately after mixing of equimolar amounts of DNBF and the unsubstituted 2-aminothiazole (**1a**) in Me_2SO: namely, that the formation of **9a** is preceded by that of a short-lived intermediate species **X**. From the ^1H NMR parameters characterizing this intermediate, as well as the dependence of its lifetime on the experimental conditions—the presence of excess DNBF over **1a** increases the lifetime of **X** while an excess of base (**1a**) accelerates its conversion into **9a**—it is convincingly demonstrated that the structure of **X** combines the presence of a positively charged Wheland complex moiety (with regard to the thiazole ring) with that of a negatively charged Meisenheimer complex moiety (with regard to the benzofuroxan system). So far, only one intermediate of this type (noted WM) has been successfully characterized, in the reactions of DNBF with 1,3,5-tris(*N*,*N*-dialkylamino)benzenes. Among the key features supporting the intermediacy of **X** along the reaction coordinate leading to **9a** is the fact that the reactions of DNBF with **1a** in the presence of an alcohol (MeOH, EtOH, *n*PrOH) produce new adducts arising from the addition of an alcohol molecule to the thiazole moiety of WM-**1a**. Reflecting the presence of three chiral centres, these species are formed as mixtures of several diastereomers that could all be characterized in their racemic forms in ethanol. These findings generalize the previous report on the formation of Wheland–Meisenheimer carbon–carbon complexes in homocyclic series.

Keywords: aromatic substitution · heterocycles · reaction mechanisms · reactive intermediates · zwitterionic Wheland complexes

Introduction

Reflecting the tautomeric equilibrium shown in Scheme 1, as well as the potential contributions of the various resonance structures depicted in this scheme, 2-aminothiazoles are very versatile nucleophiles, being susceptible to electrophilic attack at each of the two nitrogen centres, as well as at the ring carbon C-5.[1] Importantly, most 2-aminothiazole derivatives exist largely in the amino aromatic form A: for example, $K_T = 4.67 \times 10^{-5}$ for the unsubstituted 2-aminothiazole (R = R′ = H).[2a] It is only when strongly electron-withdrawing groups are bonded to the exocyclic nitrogen that the B form can contribute markedly to the reactivity.[2]

The ambident nitrogen reactivity of 2-aminothiazoles towards activated aryl halides is nicely illustrated in Scheme 2. As the most basic centre of the A form, the ring aza nitrogen of 2-aminothiazole (**1a**) is the preferred reactive site in the nucleophilic aromatic substitution of 2,4-dinitrofluorobenzene (DNFB, path a).[1a,3] Because a second and much faster reaction occurs at the imino nitrogen of the monosubstituted product **2a**, the diadduct **4a** is subsequently 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 centre is sterically hindered by the presence of an alkyl substituent at C-4, such as in **1b** ($R = CH_3$), the reaction takes place first at the amino nitrogen to give **3b** (path b).[3] In this instance, the

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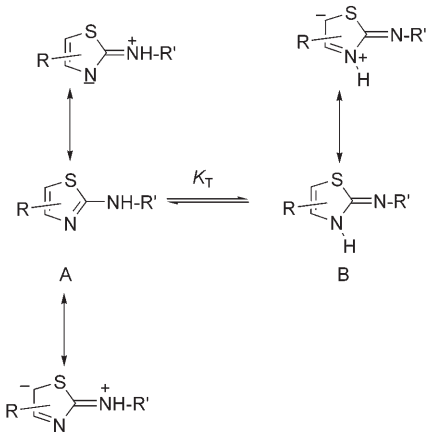
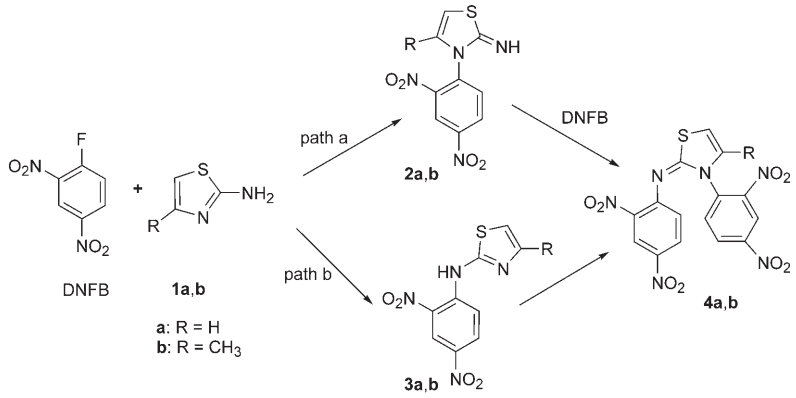


Scheme 1. Tautomeric equilibria of 2-aminothiazoles.



Scheme 2. Reactivity of 2-aminothiazoles towards activated aryl halides.

rate of reaction is low and the diadduct **4b** is obtained in low yield.

Steric hindrance around the two nitrogen centres also plays a major role in determining the carbon versus nitrogen reactivity of 2-aminothiazoles. The reaction between picryl chloride and 4-methyl-*N*-benzylaminothiazole to afford exclusively a *C*-substitution product is a prototype example.[4]

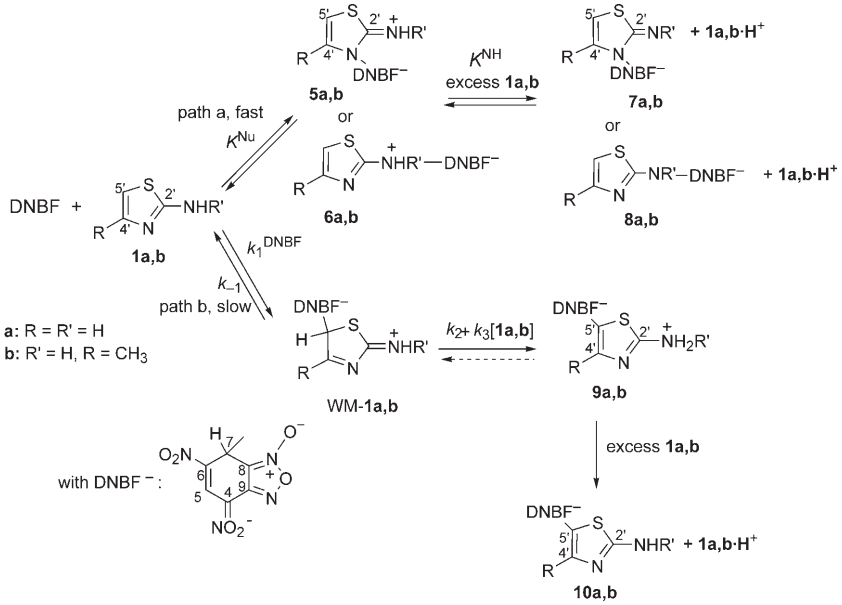
Also important in driving the coupling of 2-aminothiazoles with various electrophiles is the role of the pH. As an example, 2-aminothiazole (**1a**) undergoes the addition of aromatic aldehydes at the exocyclic amino nitrogen in neutral media.[5] In contrast, the ring carbon C-5 becomes the preferred reaction site in moderately acidic media where *N*-protonation of **1a** is essentially complete, thereby rendering the nitrogen pathway very difficult.[6]

Recently, a comprehensive kinetic study of the reactions of a superelectrophilic heterocycle—4,6-dinitrobenzofuroxan (DNBF)—with 2-aminothiazole (**1a**) and 4-methyl-2-aminothiazole (**1b**) in acetonitrile has been made by stopped-flow spectrophotometry.[7] The results revealed the exclusive formation of the *C*-bonded adducts **10a** and **10b** according to path b in Scheme 3.

DNBF

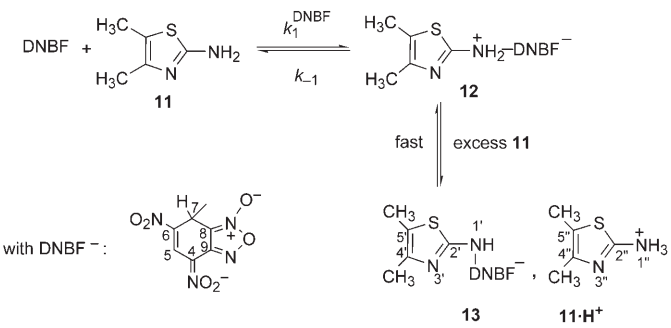
With a 3×10^{-5} M concentration of DNBF and a large excess (10^{-3}–10^{-1} M) of the basic aminothiazole reagent, the nucleophilic addition step (k_1) was found to be rate-limiting with no observed base catalysis and no detection of the Wheland–Meisenheimer intermediate adducts WM-**1a** or WM-**1b**, which are initially formed along the reaction coordinates. From previous discussions of how the presence of substituents at the 4- and/or 5-positions of 2-aminothiazoles influence the ambident reactivity of these substrates (e.g., see Scheme 2),[1,3] the formation of the adducts **7a** and **8b** could be expected to occur prior to that of the related *C*-adducts **10a** and **10b**, respectively.

It is notable that no evidence for a process corresponding to path a in Scheme 3 could be obtained. In fact, it was only



Scheme 3. Reactions between 2-aminothiazole derivatives and DNBF.

when both the 4′- and the 5′-positions of the thiazole ring were substituted—by methyl groups, for example—that a *N*-adduct, namely **13** in Scheme 4, could be detected.



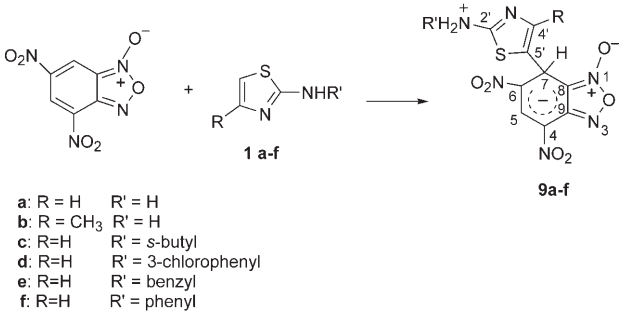
Scheme 4. Reaction between thiazole derivative **11** and DNBF.

Recently[8] we have reported evidence of the formation of Wheland–Meisenheimer (WM) adducts, which have been characterized and studied by ^{1}H and ^{13}C NMR spectroscopy, between DNBF and 1,3,5-tris-(*N*,*N*-dialkylamino)benzenes. Aiming at a better understanding of the σ-complexation process shown in Scheme 3, we have now carried out a detailed NMR structural study of the reaction between DNBF and 2-aminothiazole (**1a**) under various experimental conditions: that is, with equimolar amounts of the two reagents, with excess DNBF or excess **1a**, in acetonitrile and in [D_6]DMSO. A number of NMR spectroscopic investigations involving other 2-aminothiazoles (**1b–f**) have also been made.

As will be seen, two significant conclusions emerge from the results obtained: 1) the zwitterionic C-bonded adducts **9** (or their conjugate bases **10**) are obtained in all systems because they are the thermodynamically more stable products of the reactions, and 2) the formation of these complexes proceeds through the intermediacy of the Wheland–Meisenheimer adducts WM-**1**, as demonstrated by a successful NMR characterization of this species in the DNBF/**1a** system.

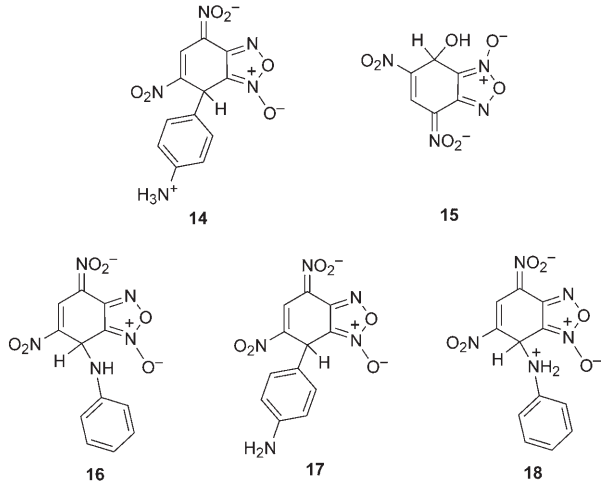
Results and Discussion

Mixing of equimolar amounts of compounds **1a–f** and DNBF on a preparative scale in acetonitrile resulted in the precipitation of orange-red solids that were readily collected by filtration. These solids were dissolved in [D_6]DMSO and characterized by ^{1}H and ^{13}C NMR spectroscopy. The related spectral data support the quantitative formation of the stable zwitterionic *C*-bonded adducts **9a–f** (Scheme 5). The zwitterionic character of the σ-complexes agreed with mass spectroscopy data (*m*/*z*: 325 $[M-H]^+$ for **9a**, for example). Representative ^{1}H and ^{13}C NMR parameters are summarized in Tables S1 and Table S2, respectively (Supporting Information). To be noted is that the adducts **9a–f** are formally the products of S_EAr substitution of the 2-aminothiazole ring.



Scheme 5. σ-Complexes obtained from the reactions between DNBF and 2-aminothiazoles **1a–f**.

Major diagnostic NMR features for structures **9a–f** are as follows: a) in accord with the sp^2–sp^3 rehybridization resulting from the complexation of the DNBF moiety, there is a strong upfield shift of the H_7 and C_7 resonances of the DNBF moiety (from 9.04 and 120.8 ppm, respectively, for DNBF, to 5.59–5.74 and 31.1–31.9 ppm, respectively, for **9a–f** adducts), these variations being very similar to those found for many C-bonded DNBF adducts,[9] such as the aniline adduct **14**,[10a,11] b) in agreement with previous observations showing that the chemical shifts of the H_5 proton and the C_5 carbon located between the two NO_2 groups of the negatively charged DNBF moiety depend very little on the nature of the C-bonded structure,[12] the related resonances for **9a–f** are essentially the same ($\delta H_5 = 8.62$–8.64 ppm, $\delta C_5 = 130.6$–131.3 ppm) and close to those found for σ-adducts such as **14**,[10–12] c) there is a significant low-field shift of the resonances of the $C_{5'}$ carbon of the thiazole ring ($\Delta\delta \approx 13$ ppm) upon substitution of **1a–f** by DNBF (this deshielding is the reflection of the fact that the negatively charged DNBF structure exerts a notable $-I$ effect, which has been quantified in comparison of the pK_a values of water (15.74) and of the OH group of the adduct **15** (11.45) in aqueous solution[13]), and d) the chemical shifts of the signals related to $H_{4'}$ in the thiazole moieties of **9a–f** are downfield with respect to the starting 2-aminothiazole derivative, as expected when a positive charge is introduced in the thiazole ring (in line with this finding, deprotonation of **9a–f** by addition of

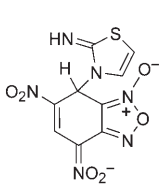


an excess of the parent aminothiazole produced (see Table S1, Supporting Information) for the adducts **10a** and **10b**, appreciable shifts of some especially sensitive resonances to high field).

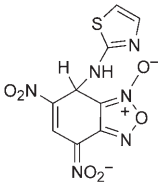
A most significant finding emerged when ^1H NMR spectra were recorded immediately after the mixing of **1a** and DNBF in equimolar amounts in [D_6]DMSO. In this instance, the spectra revealed the presence of a transient set of signals consisting of two singlets at $\delta = 5.65$ and 8.68 ppm, two doublets ($J = 4.9$ Hz) at 7.08 and 7.45 ppm and a broad singlet at 6.37 ppm. These signals disappeared after a few minutes, suggesting the formation of an intermediate species **X**, which rapidly afforded **9a**, as evidenced by the final NMR spectra, which show exclusively the resonances corresponding to this adduct.

Interestingly, carrying out the experiments with excess DNBF (DNBF/**1a** ratio $\approx$1.5:1) has the effect of increasing the lifetime of **X**. In contrast, an excess of the parent 2-aminothiazole was found to accelerate the conversion of **X** into a mixture of **9a** and **10a**. This feature is consistent with a base-catalysed step. Because of the short lifetime of **X**, ^{13}C NMR spectra could not be recorded.

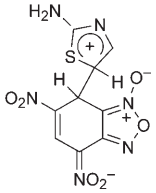
What the structure of **X** may be is of particular interest, as no such intermediate was detected in previous studies of the S_EAr substitution of a variety of π-excessive heteroaromatics (for example, pyrroles, thiophenes, indoles) by DNBF,[10b,c,14–16] the unique exception being that reported in ref. [8]. As a first major piece of information, there are the two singlets at 5.65 and 8.68 ppm, which can only be understood in terms of the presence of a negatively charged moiety of a DNBF σ-adduct and not of the initial formation of a π-complex between the DNBF acceptor molecule and the 2-aminothiazole donor molecule.[17] Thus, we are reasonably left with **X** being one of the two possible *N*-bonded adducts **7a** and **8a** or the Wheland–Meisenheimer adduct WM-**1a**. For consistency with Scheme 2, which shows the aza nitrogen of **1a** as the preferred site of electrophilic attack by DNFB, the following discussion will assume for simplicity that the formation of the endocyclic adduct **7a** is preferred relative to that of the exocyclic adduct **8a** (see below). Should the reverse situation prevail, it will not affect the forthcoming discussion.



7a



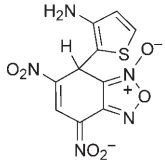
8a



WM-**1a**

X as a *N*-bonded adduct? The assumption of the initial formation of **7a** implies that the overall interaction proceeds as described in Scheme 3, in which a nitrogen adduct is formed in a rapid equilibrium while the formation of the stable *C*-bonded adduct **9a** (or **10a**) is slower but irreversible. Interestingly, this situation is the same as that discussed in detail by Buncel, Strauss et al. for the interaction of DNBF with aniline.[10a] In this instance, the initial and reversible formation of the *N*-adduct **16** takes place under kinetic control. Carbon attack then follows, with proton loss from the corresponding undetected Meisenheimer–Wheland adduct to afford the thermodynamically stable *C*-adduct **14** (or **17**) in a practically irreversible process. A key feature of the two interactions, however, is that *N*-attack leads initially to an unstable zwitterionic species—that is, **5a** or **18** (K^{Nu} step)—which must be deprotonated (K^{NH} step) in order for the product—that is, **7a** or **16**—to be formed in observable quantity. Hence, the formation, and therefore detection, of this *N*-adduct can be either favourable or unfavourable, depending on the base (nucleophile) concentration. When carrying out experiments with equimolar amounts of 2-aminothiazole (**1a**, or aniline[10a]), the overall reaction to give **7a** (or **16**), would be expected to be unfavourable, as deprotonation of the zwitterionic precursors **5a** (or **18**) would require at least an one extra equivalent of the base reagent.[18] As a matter of fact, it was only on carrying out NMR experiments with at least 2 equivalents of aniline that the short-lived *N*-adduct **16** of aniline could be characterized by ^1H NMR.[10a,11]

With regard to the DNBF/2-aminothiazole system, a significant difference is that the carrying out of a kinetic study of the interaction under the most favourable conditions for initial formation of the *N*-adduct **7a**—that is, at least a 60-fold excess of **1a**—has not allowed the detection of this species. Instead, oscilloscope traces obtained by stopped-flow spectrophotometry showed a unique relaxation process corresponding to the direct formation of the *C*-adduct **10a**.[7] A similar situation was found to prevail in the interaction of DNBF with a number of 3-aminothiophenes,[9,10c] with two possible factors accounting for this failure to trap the expected *N*-adducts. The first is that, despite similar nitrogen basicities, aniline, 2-aminothiazole and 3-aminothiophene have different enaminic characters and therefore different carbon nucleophilicities, the reactivity sequence being aniline < 2-aminothiazole < 3-aminothiophene.[9,10] The second and perhaps less plausible explanation is that the extent to which the base reagent catalyses the proton loss from the WM zwitterionic adduct, thereby accelerating its irreversible conversion into the related *C*-adducts—that is, **10a**, **17** and **19**—is greater in the aminothiazole and aminothiophene systems than in the aniline system.



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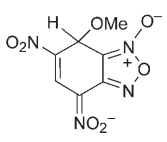

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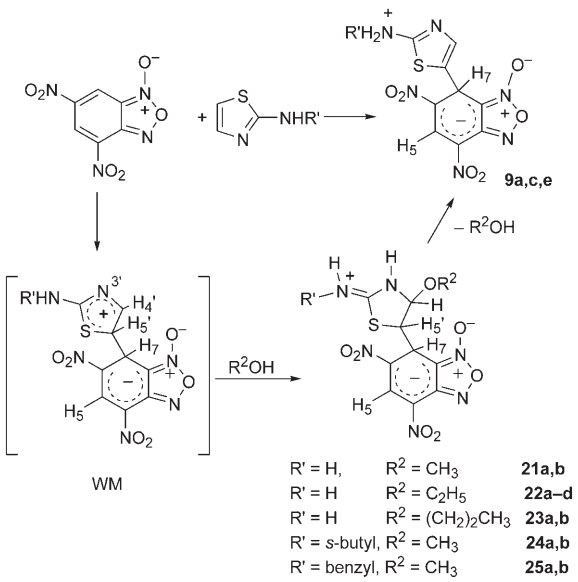
Overall, the experimental conditions employed in the NMR investigation of the DNBF/2-aminothiazole interaction are much less favourable for the initial formation of the *N*-adduct than those employed in the previous kinetic study carried out by stopped-flow spectrophotometry.[7] It follows that the kinetic failure to detect *N*-adduct formation makes it difficult to assign one of the two structures **7a** or **8a** to the short-lived **X** species detected by ^{1}H NMR. Also, it is difficult to reconcile the finding of a H_7 resonance at 5.65 ppm with a *N*-adduct structure. As elaborated in many reviews,[12,19] the evidence is that the resonance of a ring proton bonded at the sp^3 carbon of a σ-adduct, here H_7, is sensitive to the nature of the atom or group bonded to that carbon, being more and more shielded with decreasing electronegativity of the attached atom: that is, according to the sequence O < N ≈ S < C. For a DNBF structure, δH_7 commonly lies in the 5.2–5.7 ppm range for *C*-bonded adducts (see Table S1 in the Supporting Information) but in the 6.0–6.4 ppm range for *N*- and *O*-bonded adducts: $\delta H_7 =$ 6.08 ppm for the aniline adduct **16**, for example, or 6.00 ppm for the aminothiazole adduct **13** or 6.02 ppm for the methoxide adduct **20**. On grounds of analogy, a H_7 resonance at ≥6 ppm and not at 5.65 ppm should characterize the **7a** or **8a** structure.

X as a Wheland–Meisenheimer intermediate WM-1? **X** may be identified as the Wheland–Meisenheimer intermediate WM-**1a**; in fact, the H_7 resonance at 5.65 ppm is fully consistent with a C–C coupling of the two DNBF and 2-aminothiazole partners. Further support for WM-**1a** is provided by the observation that the formation of **X** is accompanied by a low-field shift of the two $H_{4'}$ and $H_{5'}$ resonances of the aminothiazole moiety: $\delta H_{4'(5')} = 7.45$ ppm, $\delta H_{5'(4')} = 7.08$ ppm ($J =$ 4.9 Hz), as compared with $\delta H_{4'} = 7.02$ ppm and $\delta H_{5'} =$ 6.64 ppm for **1a**. In principle, the sp^2–sp^3 rehybridization occurring at $C_{5'}$ must induce a shielding of $H_{5'}$. That this is not the case can be understood because this effect is overcome by the addition of the strong $-I$ effect exerted by the positively charged thiazolium ring and the negatively charged DNBF structure.[7] Obviously, the deshielding of $H_{4'}$ must be primarily the result of the $-I$ effect of the thiazolium ring of WM-**1a**. Also, the observation that the lifetime of **X** decreases with increasing [**1a**]/[DNBF] ratio is consistent with the deprotonation step of WM-**1a** to give **9a** being susceptible to base catalysis. With a very large excess of **1a**, this pathway is so fast that the formation of **9a** is governed by rate-determining nucleophilic addition of **1a** to DNBF with no accumulation of WM-**1a**, which was actually undetected in previous kinetic experiments.

An experiment supporting the hypothesis that **X** is WM-**1a** was performed when the reaction of DNBF with **1a** was carried out at room temperature in methanol. In this instance, a reddish solid precipitated and was readily collected and identified as the adduct **21** (Scheme 6). Because of the chirality of the three tetrahedral carbons $C_{4'}$, $C_{5'}$ and C_7, **21** might have been obtained as a mixture of several diastereomers (in their racemic forms) but only two predominant species, numbered as **21a** and **21b** in Scheme 6, were detected and fully characterized by ^{1}H and ^{13}C NMR (see Table S3 in the Supporting Information and the Experimental Section).



Scheme 6. Reactions between 2-aminothiazoles and DNBF carried out in alcohol.

Among other notable features in the spectral data for compounds **21**–**25** are: 1) the presence of two resonances at $\delta = 8.71$ (8.61) ppm and 5.51 (5.67) ppm, which are typical of a negatively charged DNBF moiety, 2) the presence of three NH signals, consistent with the exocyclic NH_2 bearing a positive charge, resulting in two non-equivalent protons,[20] and 3) the loss of resonance in the five-membered ring, which accounts for $H_{4'}$ and $H_{5'}$ appearing at higher field in **21** than in the parent aminothiazole **1a**. Importantly, the $H_{5'}$ resonance of the thiazole moiety remains unaffected in the ^{1}H NMR spectra recorded after the reaction of DNBF with **1a** was carried out in CD_3OD. This clearly rules out the possibility that the adduct **21** derives from the addition of methanol to the $C_{4'}$=$C_{5'}$ double bond of the thermodynamically stable *C*-adduct **10a**. Instead, this leaves no doubt that **21** is the result of the addition of MeOH to the $N_{3'}$–$H_{4'}$ fragment of the thiazole ring of the Wheland–Meisenheimer intermediate WM-**1a**.

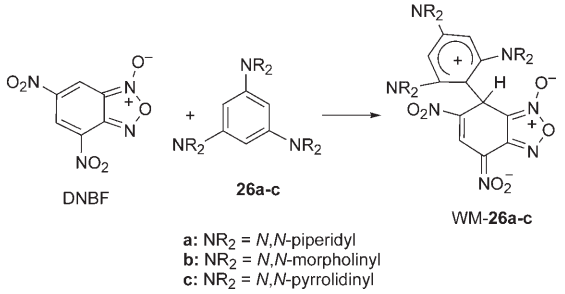
Last noted is that the solution of adducts **21** are not stable, showing the release of methanol with formation of the stable complex **9a** after less than 1 h.

Experiments carried out with the DNBF/**1a** system in ethanol and *n*-propanol similarly afforded the adducts **22** and **23**, in these instances with NMR characterization of four diastereomers (**22a–d**) and two diastereomers (**23a** and **23b**), respectively. Also characterized were two of the possible diastereomers expected for the reactions of DNBF with 2-(*N*-*sec*-butyl)aminothiazole **1c** (that is, **24a** and **24b**) or 2-(*N*-benzyl)aminothiazole **1e** (that is, **25a** and **25b**). All ^{1}H and ^{13}C NMR data pertaining to the various diastereomers identified in the above interactions are collected in Table S3

in the Supporting Information and the Experimental Section. The alcohol addition pathway described in Scheme 6 is somewhat reminiscent of that previously observed in the halogenation of 2-aminothiazole.[21]

Conclusion

The characterization of adducts **21**–**25** is a significant result as it obviously adds to the evidence obtained that the Wheland–Meisenheimer complex WM-**1** is the key intermediate in the S_EAr substitution of 2-aminothiazole by DNBF to give the *C*-adduct **9a** (**10a**) as the stable product of the reactions. It remains the case that the most important finding of this work is the successful characterization of WM-**1a** by NMR. While it has long been postulated that S_NAr–S_EAr couplings between electron-rich and electron-deficient aromatics or heteroaromatics must involve the initial formation of a Wheland–Meisenheimer complex,[22–24] only one example in which such an intermediate had a lifetime significantly sufficient to be observed spectroscopically has so far been reported[8]. Interestingly, this example deals with the reactivity of DNBF–-a superelectrophilic structure—towards supernucleophilic 1,3,5-tris-(*N*,*N*-dialkylamino)benzenes **26a–c** as shown in Scheme 7.[8] In this instance, the adducts WM-**26a–c** were fairly stable, allowing detailed ^{1}H and ^{13}C NMR characterization. In the present DNBF/**1a** system, the 2-aminothiazole reagent has much less enaminic character than the trisubstituted benzenes **26a–c**, as evidenced by the pK_a values pertaining to the *C*-protonation of these species in aqueous solution: pK_a −5.45 for **1a**[7] and pK_a 9.62 for **26c**.[25]



Scheme 7. The first examples of Wheland–Meisenheimer (WM-**26**) carbon–carbon adducts.[8]

The Wheland moiety of WM-**1a** is therefore less stable than that of WM-**26**, accounting for its more rapid conversion into the related *C*-adduct **10a**. The findings reported in this paper generalize the previous report on the formation of WM-**26a–c** carbon-carbon complexes in homocyclic series. The fact that WM-**1a** was successfully identified by NMR suggests that similar adducts deriving from the interaction of DNBF with enamines of the same strength as **1a**, such as indoles, could be also identified under appropriate experimental conditions.

Experimental Section

General remarks: NMR spectra were recorded on Varian Gemini, Mercury, or Inova spectrometers operating at 300, 400 or 600 MHz (for ^{1}H NMR) or 75.45, 100.56 or 150.80 MHz (for ^{13}C NMR). Signal multiplicities were established by DEPT experiments. The structures of some compounds were also elucidated by performing NOE experiments. Chemical shifts were referenced to the solvent ($\delta = 2.49$ and 39.5 ppm for [D$_6$]DMSO, $\delta = 3.31$ and 49.0 ppm for CD_3OD, $\delta = 2.0$ and 0.3 ppm for CD_3CN). ESI-MS spectra were recorded with a WATERS 2Q 4000 instrument.

Zwitterionic C-adducts 9a–f: A 2-aminothiazole derivative (**1a–f**, 0.14 mmol in 2 mL of CH_3CN) was added at −30 °C to a solution of DNBF (0.14 mmol in 2 mL of CH_3CN). A red-orange colour immediately developed and, after about 20 minutes, an orange solid precipitated and was collected by filtration. These solids, obtained in essentially quantitative yields, were analysed by ^{1}H and ^{13}C NMR (Tables S1 and S2 in the Supporting Information) and mass spectroscopy. The collected data are in full agreement with structures **9a–f**. As with most DNBF σ-adducts isolated so far, the solids obtained here were not found to melt prior to decomposition (explosion). In addition, attempts to obtain satisfactory elemental analysis of these species failed. Mass data for complexes **9a–f** are as follows:

[[7-(2-Ammonio-[1.3]thiazol-5-yl)-6-nitro-1-oxido-benzo[2.1.3]oxadiazol-4(7*H*)-ylidene](oxido)amino]oxidanide (9a): MS (70 eV): *m*/*z*: 325 [*M*−H]$^+$, 324, 308, 276, 250, 228, 186, 60; ES$^-$: *m*/*z*: 325 [*M*−H]$^-$.

[[7-(2-Ammonio-4-methyl-[1.3]thiazol-5-yl)-6-nitro-1-oxido-benzo-[2.1.3]oxadiazol-4(7*H*)-ylidene](oxido)amino]oxidanide(9b): ES$^-$: *m*/*z*: 339 [*M*−H]$^-$.

[[7-[2-(*sec*-Butylammonio)-[1.3]thiazol-5-yl]-6-nitro-1-oxido-benzo-[2.1.3]oxadiazol-4(7*H*)-ylidene](oxido)amino]oxidanide (9c): ES$^+$: *m*/*z*: 383 [*M*+H]$^+$; ES$^-$: *m*/*z*: 381 [*M*−H]$^-$.

[[7-{2-[(3-Chlorophenyl)ammonio]-[1.3]thiazol-5-yl}-6-nitro-1-oxido-benzo[2.1.3]oxadiazol-4(7*H*)-ylidene](oxido)amino]oxidanide (9d): ES$^-$: *m*/*z*: 435 [*M*−H]$^-$.

[[7-[2-(Benzylammonio)-[1.3]thiazol-5-yl]-6-nitro-1-oxido-benzo-[2.1.3]oxadiazol-4(7*H*)-ylidene](oxido)amino]oxidanide (9e): ES$^-$: *m*/*z*: 415 [*M*−H]$^-$.

[[6-Nitro-1-oxido-7-[2-(phenylammonio)-[1.3]thiazol-5-yl]-benzo-[2.1.3]oxadiazol-4(7*H*)-ylidene](oxido)amino]oxidanide (9f): ES$^+$: *m*/*z*: 403 [*M*+H]$^+$; ES$^-$: *m*/*z*: 401 [*M*−H]$^-$.

Adducts 21–25: DNBF (0.2 mmol) was added at 25 °C to a solution of the 2-aminothiazole derivative **1a** (or **1c** or **1e**, 0.2 mmol), dissolved in alcohol (methanol, ethanol or *n*-propanol, 2 mL). After about 20 min an orange solid had precipitated; this solid was collected by filtration and analysed by ^{1}H and ^{13}C NMR spectroscopy. In this manner, it was found that the solids isolated from the reactions of DNBF with **1a** in methanol or ethanol or *n*-propanol each corresponded to the exclusive formation of one of the possible diastereomers in its racemic form (**21a**, **22a** and **23a**). In contrast, the solids isolated from the reactions of DNBF with **1c** and **1e** each consisted of a mixture of two diastereomeric forms (**24a**/**24b** and **25a**/**25b**). In all cases, the remaining mother liquor was concentrated under reduced pressure to give crude materials, which were also characterized by NMR. This has revealed the formation of the additional diastereomers listed in Table S3 in the Supporting Information. For DNBF/**1a** reactions, these are: **21b** in methanol, **22b**, **22c** and **22d** [with **22c** and **22d** being present only in low amounts (≈7%)] in ethanol, and **23b** in *n*-propanol. With time, all the above adducts are quantitatively converted into the *C*-bonded adducts **9a**, **9c**, or **9e**. Because of the limited lifetimes of all these adducts, the corresponding ^{13}C NMR data could be recorded only for the major diastereoisomers.

^{1}H NMR data are reported in Table S3 in the Supporting Information. Additional data are as follows.

[[7-(2-Iminio-4-methoxy-[1,3]thiazolidin-5-yl)-6-nitro-1-oxido-benzo-[2.1.3]oxadiazol-4(7*H*)-ylidene](oxido)amino]oxidanide (21a): ^{13}C NMR (150 MHz, [D$_6$]DMSO, 25 °C): $\delta = 36.8$ (CH), 55.0 (OCH_3), 56.1 (CH),

92.8 (CH), 111.2, 111.8, 120.8, 134.2 (CH), 148.8, 173.1 ppm; ES^+: m/z: 359 $[M+H]^+$; ES^-: m/z: 357 $[M-H]^-$. Compound **21b**: ^{13}C NMR (150 MHz, $[D_6]$DMSO, 25 °C): $\delta = 37.7$ (CH), 55.0 (OCH_3), 57.9 (CH), 92.5 (CH), 110.6, 111.1, 123.0, 132.9 (CH), 150.2, 172.7 ppm.

[[7-(4-Ethoxy-2-iminio-[1,3]thiazolidin-5-yl)-6-nitro-1-oxido-benzo-[2.1.3]oxadiazol-4(7*H*)-ylidene](oxido)amino]oxidanide (22a): ^{13}C NMR (75.45 MHz, $[D_6]$DMSO, 25 °C): $\delta = 14.9$, 36.8 (CH), 56.5 (CH), 63.1 (OCH_2), 91.5 (CH), 111.2, 111.9, 120.9, 134.2 (CH), 148.8, 172.9 ppm; ES^-: m/z: 371 $[M-H]^-$.

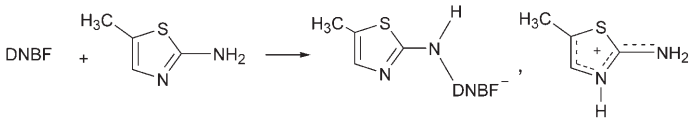
[[7-(2-Iminio-4-propoxy-[1,3]thiazolidin-5-yl)-6-nitro-1-oxido-benzo-[2.1.3]oxadiazol-4(7*H*)-ylidene](oxido)amino]oxidanide (23a): ^{13}C NMR (150 MHz, $[D_6]$DMSO, 25 °C): $\delta = 10.3$ (CH_3), 22.2 (CH_2), 36.8 (CH), 56.4 (CH), 69.1 (OCH_2), 91.7 (CH), 111.1, 111.8, 120.9, 134.1 (CH), 149.0, 173.0 ppm; ES^-: m/z: 385 $[M-H]^-$.

[[7-[2-(*sec*-Butyliminio)-4-methoxy-[1,3]thiazolidin-5-yl]-6-nitro-1-oxido-benzo[2.1.3]oxadiazol-4(7*H*)-ylidene](oxido)amino]oxidanide (24a): ^{13}C NMR (150 MHz, $[D_6]$DMSO, 25 °C): $\delta = 9.4$ (CH_3), 18.9 (CH_3), 28.1 (CH_2), 36.7 (CH), 55.1 (OCH_3) 53.7 (CH), 55.7 (CH), 92.6 (CH), 109.7, 111.3, 123.4, 134.4 (CH), 148.9, 169.2 ppm. Compound **24b**: ^{13}C NMR (150 MHz, $[D_6]$DMSO, 25 °C): $\delta = 10.1$ (CH_3), 19.6 (CH_3), 27.9 (CH_2), 36.8 (CH), 55.0 (OCH_3) 53.4 (CH), 55.7 (CH), 92.5 (CH), 109.7, 111.8, 123.4, 134.3 (CH), 148.9, 169.3 ppm.

[[7-[(2*E*)-2-(Benzyliminio)-4-methoxy-[1,3]thiazolidin-5-yl]-6-nitro-1-oxido-benzo[2.1.3]oxadiazol-4(7*H*)-ylidene](oxido)amino]oxidanide (25a): ^{13}C NMR (100 MHz, $[D_6]$DMSO, 25 °C): $\delta = 36.8$ (CH), 48.3 (CH_2), 55.0 (OCH_3), 55.9 (CH), 92.9 (CH), 111.4, 111.9, 120.7, 127.4 (CH), 128.1 (CH), 128.8 (CH), 134.4 (CH), 135.0, 148.9, 170.7 ppm.

Formation of the WM-1a complex: When a solution of **1a** in $[D_6]$DMSO (0.07 mmol in 0.5 mL) was directly added at 25 °C to a solution of DNBF in $[D_6]$DMSO (0.11 mmol in 0.5 mL) in an NMR tube at 25 °C, the ^1H NMR spectrum (300 MHz) of the resulting solution showed the appearance of new signals, ascribed to compound WM-**1a**: $\delta = 5.65$ (s, 1H), 6.37 (br s, 2H), 7.08 (d, $J = 4.87$ Hz, 1H), 7.45 (d, $J = 4.87$ Hz, 1H), 8.68 ppm (s, 1H). After less than five minutes a spectrum containing exclusively the signals of compound **9a** was recorded.

5-Methyl-1,3-thiazol-2-aminium [[7-[(5-methyl-[1,3]thiazol-2-yl)amino]-6-nitro-1-oxido-benzo[2.1.3]oxadiazol-4(7H)-ylidene]-(oxido)amino]oxidanide (28, 27·H$^+$): 5-Methyl-2-aminothiazole **27** (0.14 mmol in 2 mL of CH_3CN) was added at −30 °C to a solution of



27 28 27·H$^+$

DNBF (0.14 mmol in 2 mL of CH_3CN). A red-orange colour immediately developed and after about 20 minutes, an orange solid precipitated. This solid was collected by filtration as a salt (the counter ion being the protonated 5-methylaminothiazole (**27·H$^+$**)), and the mother liquor contained unreacted DNBF. The ^1H NMR spectral data for the solid, dissolved in $[D_6]$DMSO, are in agreement both with structure **28** and a structure in which the DNBF moiety is linked to the endocyclic thiazole nitrogen, discrimination between these two possibilities on the basis of simple ^1H NMR spectral data being a hard problem. Even if some considerations from previous kinetic data[3] indicate that the latter could be the kinetically favoured isomer, NOE experiments agree with structure **28** (with protonated **27** as counter ion). Recently,[7] ^{15}N–^1H correlation carried out on the analogous 4,5-dimethylaminothiazole showed that DNBF is also linked at the exocyclic amino nitrogen in that case.

Compound 28·27H$^+$: ^1H NMR (400 MHz, $[D_6]$DMSO, 25 °C): $\delta = 2.21$ (d, $J = 1.46$ Hz, 3H), 2.23 (d, $J = 1.28$ Hz, 3H), 6.19 (s, 1H), 6.96 (br s, 1H), 7.02 (q, $J = 1.46$ Hz, 1H), 8.66 ppm (s, 1H); ^{13}C NMR (100 MHz, $[D_6]$DMSO, 25 °C): $\delta = 11.6$ (CH_3), 11.7 (CH_3), 47.3 (CH), 110.2, 111.3, 120.1, 120.5, 122.0, 122.8 (CH, two overlapping signals), 131.9 (CH), 148.5, 166.6, 169.2 ppm; ES^+: m/z: 339 $(M+H)^+$; ES^-: m/z: 115 $[M-H]^-$.

Acknowledgements

This work was supported by the funds for a fellowship to the memory of Alessandro Zucchelli and by ALMA MATER STUDIORUM—Università di Bologna (ex-60 % MIUR). The Versailles contributors are grateful for the support of this research by the CNRS and the Ministry of Research.

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Received: May 3, 2007
Published online: September 17, 2007

