The versatile electrophilic reactivity of 4,6-dinitrobenzo[d]isoxazole-3-carbonitrile

Betty Cottyn,[a] Alexei Starosotnikov,[b] Dominique Vichard,[a] Régis Goumont,[a] Svyatoslav Shevelev*[b] and François Terrier*[a]

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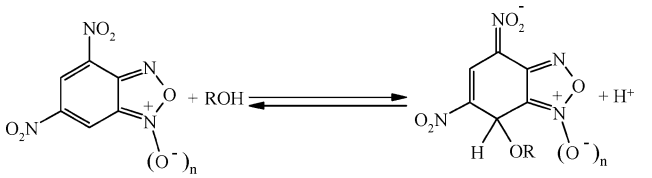
The interaction of 4,6-dinitrobenzo[d]isoxazole-3-carbonitrile (**5a**) with methoxide ion has been kinetically investigated in methanol and a 20:80 (v/v) MeOH-Me_2SO mixture. In methanol, stopped-flow experiments have revealed that a monomethoxyl σ-adduct (**5a-Me**) is first formed, resulting from a fast MeO^- addition at the unsubstituted 7-carbon. Rate and equilibrium constants for this σ-complexation process could be determined, allowing a ranking of **5a** within the pK_a scale established for Meisenheimer electrophiles in methanol. With a pK_a value of 13.50, the electrophilicity of **5a** falls in the range of 1,3,6,8-tetranitronaphthalene, 2,4-dinitrothiophene or 4-nitrobenzofuroxan. This corresponds to a two-pK_a units increase in electrophilicity from that of TNB, the common reference in σ-complex chemistry but it is notably below that of so-called superelectrophilic molecules like 4,6-dinitrobenzofuroxan. In addition to its ease of σ-complexation, **5a** is found to undergo a slow but thermodynamically favourable addition of MeO^- to the cyano group bonded to the isoxazole ring, leading to a complete conversion of the adduct **5a-Me** into a dinitroimidate **6**. The reactivity of **6** could be kinetically assessed. Going to 80% Me_2SO still afforded initially the adduct **5a-Me** but this anionic species undergoes addition of a second molecule of MeO^- to the CN group, giving a dianion whose structure is unprecedented in the literature. Combining the above results with synthetic observations showing that **5a** can readily contribute to S_NAr reactions under appropriate experimental conditions emphasizes the multifaceted electrophilic reactivity of this electron-deficient heterocycle.

Introduction

Much interest has recently been paid to the design of aromatic and heteroaromatic electron-deficient structures exhibiting a high reactivity in nucleophilic aromatic substitutions and related σ-complex formation processes.[1–13] Annelation of a nitro-substituted phenyl ring by intrinsically electron-withdrawing five-membered rings such as a furazan or a furoxan or a triazole ring has proved to be a nice entry to a variety of electron-deficient heteroaromatic structures which are considerably more electrophilic than 1,3,5-trinitrobenzene (TNB), the conventional aromatic electrophile in σ-complex chemistry.[3–14] As an illustration, the pK_a values for formation of the hydroxyl adducts **1-H** and **2-H** of 4,6-dinitrobenzofuroxan (DNBF, **1**) and 4,6-dinitrobenzofurazan (DNBZ, **2**) according to eq. 1 are 3.75 and 3.92, respectively, at 25 °C in aqueous solution.[2,9] This compares with a pK_a value of 13.43 for formation of the analogous adduct **3-H** of TNB (**3**).[14] Use of dilute alkali hydroxide solutions is in fact necessary to achieve the formation of **3-H** in aqueous solution (eq. 2). A similar situation prevails when comparing the formation of the related methoxy adducts **1-Me**, **2-Me** and **3-Me** in methanol.[1,2]



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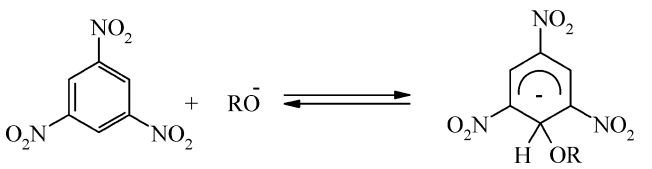
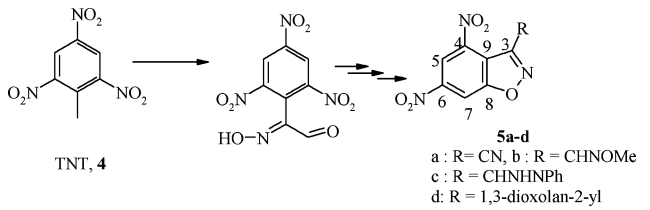


(2)

While being comparable to TNB in terms of the electron-deficiency of its trinitrophenyl ring, and therefore of the susceptibility of this ring to undergo nucleophilic addition and substitution processes, 2,4,6-trinitrotoluene (TNT,**4**), has an activated methyl group which is prone to ionization and oxidation.[1,14–16] Taking advantage of this versatile behaviour, Shevelev and coworkers have successfully used TNT as a starting material to develop efficient

[a]*Institut Lavoisier, UMR CNRS 8180, University of Versailles-Saint-Quentin-en-Yvelines, 45, Avenue des Etats-Unis, 78035, Versailles Cedex, France*
[b]*N.D.Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47, Leninsky prosp., 119992, Moscow, Russian Federation*

synthetic routes to a number of so far unknown electron-deficient heterocyclic substrates. In particular, a series of 3-R-substituted-4,6-dinitrobenzo[d]isoxazole derivatives (**5a-d**) has been described (eq. 3).[17–19]



(3)

Viewing compounds **5** as deriving from the annelation of a dinitrophenyl ring by an isoxazole ring, it was of interest to assess the intrinsic electrophilic character of these new structures by comparison with that of DNBF and TNB as well as other representative nitroactivated aromatics or heteroaromatics. For this purpose, we have selected 4,6-dinitrobenzo[d]isoxazole-3-carbonitrile **5a** as a reference substrate and carried out a comprehensive kinetic analysis of the reactions of this compound with methoxide ion in methanol and a 20–80 (v/v) MeOH-Me_2SO mixture. In this paper, we report on our finding that **5a** is actually a very versatile electrophile, being not only prone to undergo σ-complex formation at its unsubstituted 7-position but also prone to suffer S_NAr substitution of its 4-nitro group as well as nucleophilic addition to its exocyclic CN group. To be noted is that a low solubility of **5a** precluded a similar study in water.

Results

Reactions in methanol

Addition of dilute sodium methoxide solutions (2×10^{-3}–1.5×10^{-2} moldm^{-3}) to a solution of **5a** (λ_{max} = 245 nm; [**5a**] ≈ 5×10^{-5} moldm^{-3}) in methanol resulted in the immediate and essentially complete formation of an orange species, X, exhibiting an intense absorption maximum at λ = 480 nm (Fig. 1). Rapid acidification of the resulting solutions by methanesulfonic acid led to a full recovery of **5a**. This showed that the formation of X is reversible, suggesting that we were dealing with a σ-complexation process. Firm identification of X as being the σ-adduct **5a-Me** was

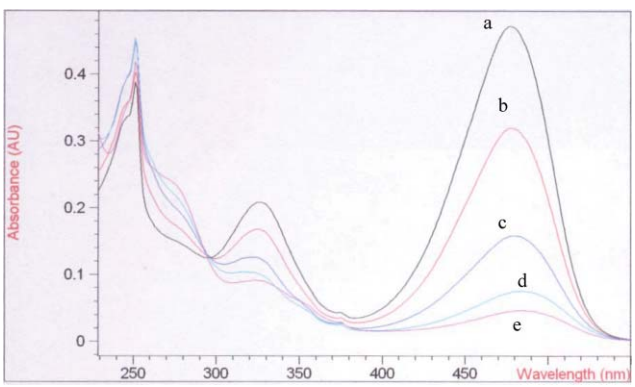
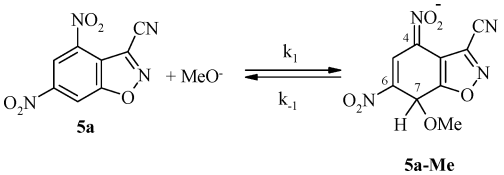


Fig. 1 UV-Visible absorption spectra illustrating the slow conversion of the σ-adduct **5a-Me** into the dinitroimidate **6** in methanol: a) t = 0; b) t = 1 min, c) t = 2 min, d) t = 6 min; e) t = 16 min.

obtained from a ^1H and ^{13}C NMR investigation of the reaction in Me_2SO-d_6 (see Experimental section).



(4)

The stopped-flow technique was used to investigate the kinetics of the approach to equilibrium (4), following the appearance of the adduct **5a-Me** at 480 nm, a wavelength where the parent molecule **5a** has a negligible absorption in methanol. All experiments were carried out under first-order conditions at T = 25 °C with at least a 40-fold excess of the methoxide ion reagent ([MeO^-] = 2×10^{-3}–2×10^{-2} moldm^{-3}) over the substrate concentration (≈ 5×10^{-5} moldm^{-3}). Fig. 2 shows an oscilloscope picture illustrating the unique relaxation process corresponding to the formation of **5a-Me**. Under the experimental conditions employed, the general expression for the observed first-order rate constant, k_{obsd}, for the approach to equilibrium (4) at a given MeO^- concentration is simply given by eq. 5.

$$k_{obsd} = k_1 [MeO^-] + k_{-1} \quad (5)$$

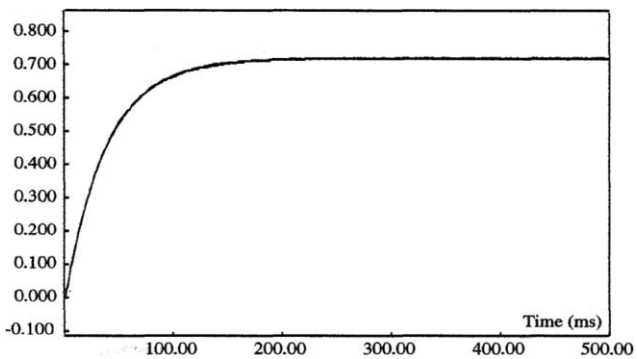


Fig. 2 Oscilloscope trace showing the unique relaxation process associated with the formation of the σ-adduct **5a-Me** at a given MeO^- concentration in methanol ([MeO^-] = 2×10^{-3} moldm^{-3}).

In accordance with eq. 5, an excellent straight line was obtained in plotting the measured k_{obsd} values *versus* the methoxide ion concentration (Fig. 3). Determination of the second-order rate constant k_1 for formation of **5a-Me** and the first-order rate constant k_{-1} for the decomposition of this adduct was straightforward from the slope and intercept of this line, respectively. We thus obtained: k_1 = 10460 dm^{3}mol^{-1}s^{-1}, k_{-1} = 6.77 s^{-1}. Combining these two rate constants leads to the equilibrium constant for eq. 4: $K_1 = k_1/k_{-1}$ = 1545 dm^3 mol^{-1}. This corresponds to a pK_a^{MeOH} value of 13.50.

Interestingly the adduct **5a-Me** is not a stable species under the experimental conditions required for its formation. As illustrated by the group of UV-Visible absorption spectra shown in Fig. 1, **5a-Me** undergoes a slow decomposition to afford a colorless species, Y, which is characterized by an absorption maximum at λ = 250 nm. The presence in Fig. 1 of a well- defined isobestic point at 295 nm showed that this decomposition was a clean process, in agreement with the finding that it is associated with a unique relaxation time at the various methoxide concentrations

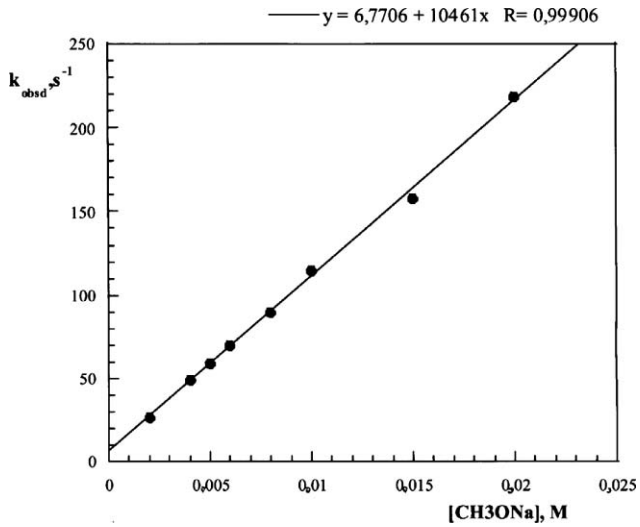


Fig. 3 Effect of methoxide ion concentration on the observed rate constant k_{obsd} for formation of the σ-adduct **5a-Me** at 25 °C in methanol.

studied. The corresponding first-order rate constant k'_{obs} for the formation of Y, as derived from the time dependence of the observed absorption changes, was found to be independent of the methoxide ion concentration (Fig. 4). This kinetic behaviour is noteworthy since it suggests that the formation of Y is the result of a concurrent MeO^- addition to the parent molecule **5a** (vide infra).

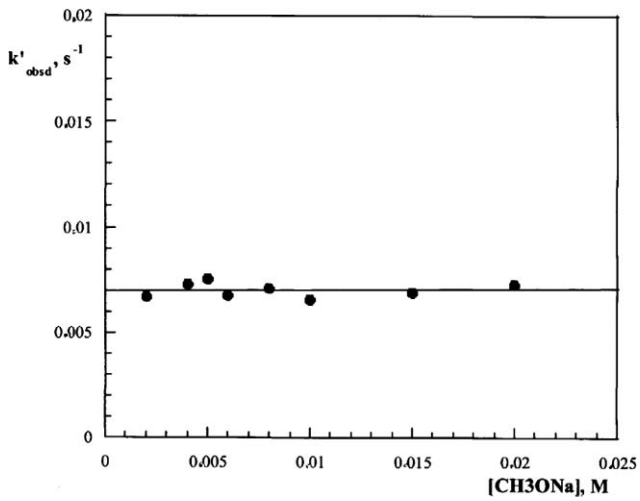
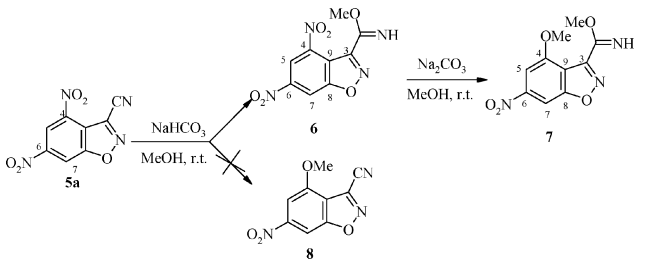


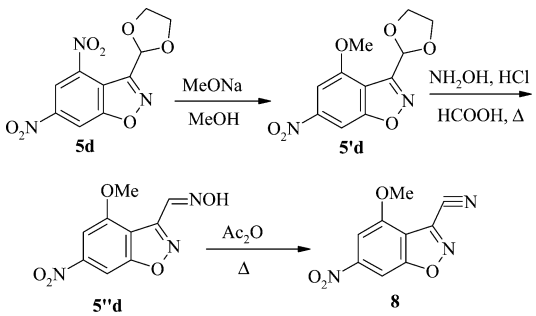
Fig. 4 Plot showing lack of effect of the MeO^- concentration on the observed rate constant k'_{obsd} for the conversion of **5a-Me** into **6** in methanol.

A structural investigation of the reactivity of **5a** with MeO^- has been made to identify the Y species. The results are summarized in Scheme 1. Upon dissolution of **5a** in a sodium bicarbonate solution at room temperature and acidification of the resulting solution after a few minutes, the dinitroimidate **6** resulting from MeO^- addition to the exocyclic CN group was quantitatively obtained. Carrying out the interaction under more basic conditions, namely sodium carbonate solutions, afforded the 4-methoxyimidate **7** arising from a S_NAr substitution of the 4-nitro group of **6** (see discussion). In none of the above experiments, which have included



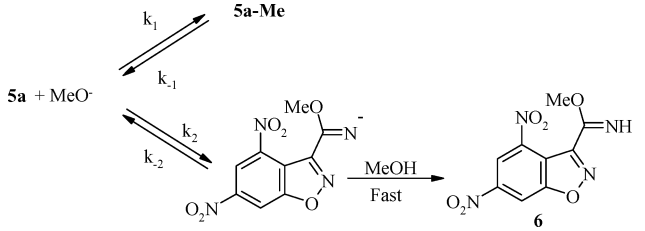
Scheme 1

a ^1H monitoring of the conversion of **5a** into **6** and **7**, the formation of the 4-methoxy-6-nitro carbonitrile **8** was detected. For an unambiguous structural understanding of the reactivity of **5a**, compound **8** was prepared and characterized as depicted in Scheme 2. ^1H and ^{13}C NMR data as well as mass spectroscopy, UV-Visible and elemental analysis data for compounds **6–8** are given, together with a detailed report of the synthetic procedures, in the Experimental Section.



Scheme 2

As will be elaborated further in the discussion, the above information leaves little doubt that Y is the dinitrocarboxyimidate **6**. As a major spectral diagnostic feature, there is the close similarity between the UV-Visible spectrum obtained with a pure sample of **6** and the one obtained at completion of the conversion of **5a-Me** into **6** (λ_{max} = 250 nm; see Fig. 1). Instead, compounds **7** and **8** exhibit an absorption maximum at a higher wavelength, namely 273 nm and 269 nm, respectively. On this basis, the conversion of **5a-Me** into **6** in dilute MeO^- solutions can be kinetically described by the two competitive reactions depicted in Scheme 3 which in fact consists of two well-separated steps. The first step is the previously studied fast equilibration between **5a** and **5a-Me**, with the observed first-order rate constant given by eq. 5. The second step is the slower equilibrium formation of the imidate **6** from the parent molecule **5a** which is considered to be in instantaneous equilibrium with the initially formed σ-adduct



Scheme 3

5a-Me. As previously shown for many competitive interactions of this type, the pertinent expression for the corresponding first-order rate constant k'_{obsd} is given by eq. 6:[4b,20]

$$k'_{obsd} = k_{-2} + (k_2[MeO^-])/(1 + K_1[MeO^-]) \quad (6)$$

From this equation, k'_{obsd} is expected to depend curvilinearly on the methoxide concentration, reaching a plateau at base concentrations where there is a complete initial formation of **5a-Me**. Obviously, the plateau observed in Fig. 4 shows that this limiting situation holds at all MeO^- concentrations studied, so that eq. 6 reduces to eq. 7. Neglecting k_{-2} (**6** is totally formed under our experimental conditions), the maximum value of k'_{obsd} is given by eq. 8. Combining the value of $k'_{obsd,max}$ (7×10^{-3} s^{-1}) with that of the equilibrium constant K_1 (1545 dm^3mol^{-1}) affords $k_2 = 10.81$ $dm^3mol^{-1}s^{-1}$.

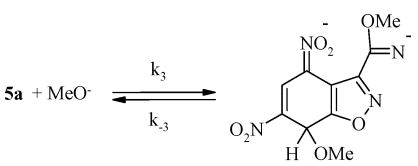
$$k'_{obsd,max} = k_{-2} + k_2/K_1 \quad (7)$$

$$k'_{obsd,max} = k_2/K_1 \quad (8)$$

Reactions in a 20:80 (v/v) MeOH-Me_2SO mixture

The reaction of **5a** with dilute sodium methoxide solutions (10^{-3}–1.5×10^{-2} $moldm^{-3}$) consisted of two steps in 80% Me_2SO. The first is associated with the complete formation of an orange species whose UV-Visible spectrum is strictly identical to the one recorded upon dissolution of a pure sample of the adduct **5a-Me** (vide supra) in the same solvent mixture. Contrasting with the situation in methanol, the formation of **5a-Me** is so fast in 80% Me_2SO that it appears instantaneous on the stopped-flow time scale. This precludes measurements of the related rate constants, k_{obsd}, for the observed process.

In a second step, **5a-Me** disappears in a few minutes to give rise quantitatively to a new and also strongly colored species, Z (λ_{max}= 470 nm). As shown in Fig. 5, the recorded absorption changes at a given MeO^- concentration are characterized by the presence of a well-defined isobestic point at λ = 460nm. This indicates that the conversion of **5a-Me** to Z is a clean process, in accord with the finding that the interaction is associated with a unique relaxation time at each of the various methoxide concentrations studied. Importantly, the measured first-order rate constant, k''_{obsd}, for the formation of Z is found to increase linearly with increasing MeO^- concentration (Fig. 6).This implies that the formation of Z does not occur *via* an isomerisation reaction (see discussion) but involves, instead, the addition of a second mole of MeO^- to **5a-Me**, as described in equation 9. The fact that the visible absorption of Z is rather similar to that of **5a-Me** supports the idea that the σ-complexation of the six-membered ring is retained on going to Z. Combining this experimental feature with the susceptibility of the cyano group to undergo MeO^- addition makes it reasonable to identify Z as being the diadduct **9**. A firm identification of **9** has been successful by ^1H NMR (see Experimental).



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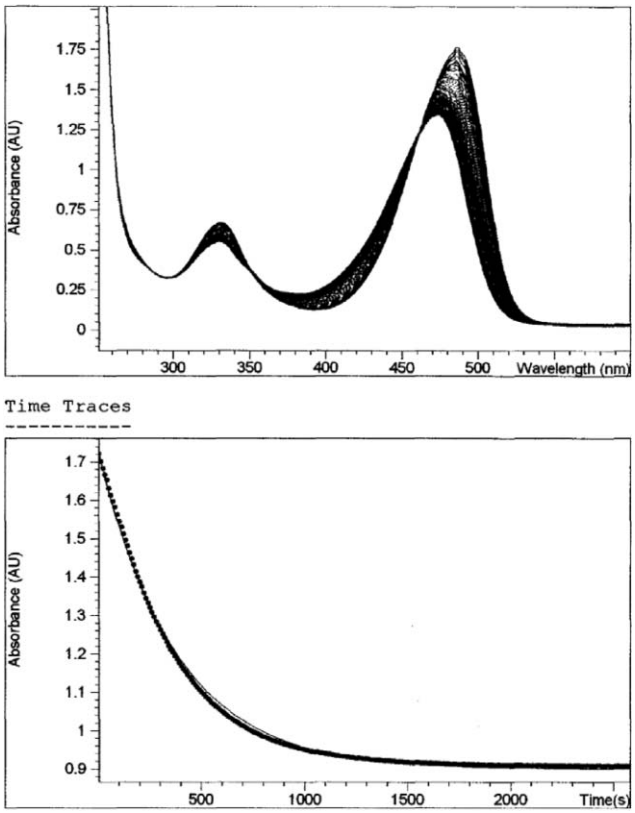


Fig. 5 UV-Visible absorption spectra associated with the conversion of **5a-Me** into the dianion **9** in 20–80 (v/v) MeOH-Me_2SO.

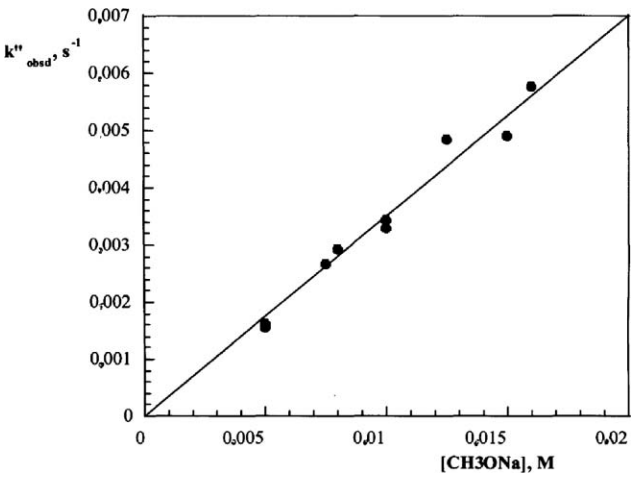


Fig. 6 Plot showing the linear dependence of the observed rate constant k''_{obsd} for formation of the dianion **9** on the MeO^- concentration in 20–80 (v/v) MeOH-Me_2SO.

Based on equation 9, the observed rate constant k''_{obsd} for formation of **9** is given by eq. 10, accounting for its linear dependence on the MeO^- concentration. Determination of the second-order rate constant k_3 from Fig. 6 was straightforward: $k_3 = 0.36$ $dm^3mol^{-1}s^{-1}$.Reflecting the complete formation of **9** in the range of methoxide concentrations studied, the intercept of the line is negligible, preventing a meaningful determination of the rate constant k_{-3}.

$$k''_{obs} = k_3[MeO^-] + k_{-3} \quad (10)$$

Discussion

Our study of substrate **5a**, representing a model for a new family of electron-deficient heteroaromatic compounds has revealed a number of features which highlight a multifaceted electrophilic behaviour. In addition to a high capability of **5a** to undergo σ-complexation at the unsubstituted activated 7-position of the phenyl ring, the cyano group bonded to the isoxazole ring appears to be very sensitive to methoxide ion addition. This thermodynamically favored process in methanol does not prevent **5a** behaving as an S_NAr substrate, undergoing a slow but regioselective displacement of the 4-nitro group by MeO^-. Interestingly, going from methanol to 20–80 (v/v) MeOH-Me_2SO, results in the preferred addition of this nucleophile to the CN group of the initially formed σ-adduct **5a-Me**.

σ-Complexation and electrophilicity of 5a

The kinetic and thermodynamic parameters for formation and decomposition of the σ-adduct **5a-Me** derived from the isoxazole **5a** are obviously the appropriate references for assessing the electrophilic character of this heterocyclic structure in methanol. For this purpose, relevant rate and equilibrium constants are compared in Table 1 with previously reported data for a number of methoxy σ-adducts, covering a domain of thermodynamic reactivity of 12 pK_a units in this solvent. These structures are identified in Chart 1 together with those of the parent substrates. The pK_a values listed in Table 1 have been calculated as $pK_a = pK_s - \log K_1$ with pK_s being the ionic product of methanol (16.70 at 25 °C).[21,22]

Table 1 Rate and equilibrium constants for formation and decomposition of the adduct **5a-Me** in methanol. Comparison with some related methoxy σ-adducts[a]

Adduct	k_1 in $dm^3mol^{-1}s^{-1}$	k_{-1} in s^{-1}	K_1 in dm^3mol^{-1}	pK_a^{MeOH}
2-Me[b]	9.3×10^5	2×10^{-5}	4.65×10^{10}	6.05
1-Me[b]	1.9×10^6	8.89×10^{-5}	2.1×10^{10}	6.46
15-Me[c]	3.9×10^5	0.011	3.5×10^7	9.12
18-Me[d]	27.7	4.8×10^{-4}	5.8×10^4	11.93
10-Me[e]	28.5	3.35×10^{-3}	8500	12.77
16-Me[f]	2.32×10^4	<3	>7700	<12.8
11-Me[e]	6	2.04×10^{-3}	2940	13.23
5a-Me[g]	10460	6.63	1580	13.50
17-Me[d]	14.9	1.75×10^{-2}	850	13.77
12-Me[h]	2460	35.5	69.5	14.85
3-Me[i]	7050	305	23.1	15.33
13-Me[j,k]	—	—	1.9 (1)	16.4 (16.7)
14-Me[k]	—	—	0.012	18.62

[a] T = 25 °C unless otherwise stated; see Chart 1 for the structural identification of the adducts and related parent substrates. [b] T = 20 °C, ref. 29. [c] T = 20 °C, ref. 28. [d] ref. 29. [e] ref. 20. [f] ref. 27. [g] this work. [h] ref. 24. [i] ref. 14. [j] ref. 25. [k] ref. 25.

Table 1 reveals that the electrophilicity of **5a** (pK_a = 13.50) is markedly greater than that of all 1-X-3,5-dinitrobenzenes studied. These include 3,5-dinitropyridine (**12**; pK_a = 14.85);[23,24] TNB (**3**; pK_a = 15.33)[14] as well as 3,5-dinitrobenzonitrile (**13**; pK_a = 16.4)[25] and 3,5-dinitrobenzotrifluoride (**14**; pK_a = 18.62).[25] In fact, the pK_a value of **5a** falls in the range of the pK_a values for complexation of 2,4-dinitrothiophene (**17**; pK_a = 13.77),[26] 4-nitrobenzofurazan (**11-Me**; pK_a= 13.23),[20] 1,3,6,8-tetranitronaphthalene (**16**; pK_a = 12.82)[27] and 4-nitrobenzofuroxan (**10**; pK_a = 12.77).[20] While this corresponds to a notable increase in electrophilicity from that of TNB (~ 2 pK units), the common reference electrophile in σ-complex chemistry, it is below that of 2,4-dinitroselenophene

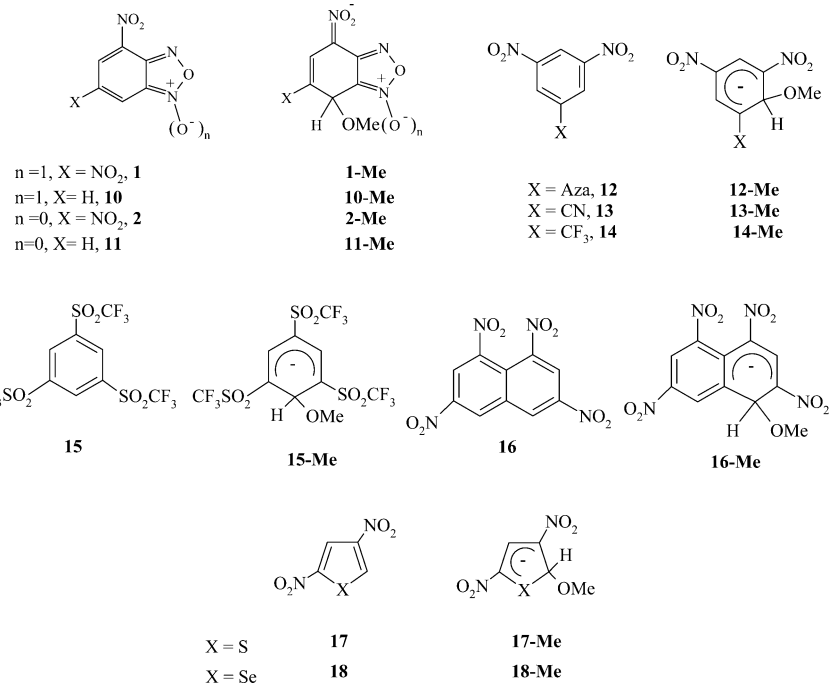
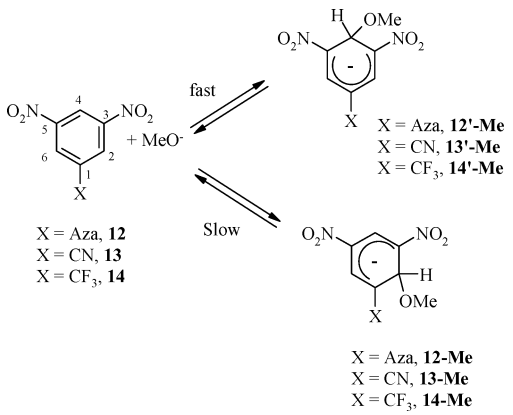


Chart 1 Structures and numbering of Meisenheimer electrophiles and related methoxy σ-adducts.

(**18**; pK_a = 11.93)[26] as well as of 1,3,5-tris(trifluromethanesulfonyl)benzene (**15**; pK_a = 9.12)[28] and rather far (about 7 pK units) from being comparable to that of the DNBF (**1**; pK_a = 6.46) and DNBZ (**2**; pK_a = 6.05) molecules.[2b] The three latter compounds have been accorded superelectrophilic properties on the basis of an effective contribution of the solvent to the σ-complexation process.[29] In this regard, recent work has shown that the methanol pathway plays a negligible role in the formation of all adducts with $pK_a^{MeOH} > 10–11$.[28a] This makes it possible to use this value as an index to define the frontier between superelectrophilicity and normal-electrophilicity in σ-complexation processes in methanol. On this ground, **5a** must be classified as a stronger electrophile than TNB within the group of normal electrophiles but certainly not as a superelectrophilic heteroaromatic.

Analysis of the contribution of the k_1 and k_{-1} rate constants to the K_1 (or pK_a) values for formation of **5a-Me** is difficult since there is no evident relationship between these kinetic and thermodynamic parameters within the group of electrophiles listed in Table 1. For example,**5a-Me** shows high rates of formation and decomposition as compared with the similarly stable adducts **11-Me** and **17-Me** which are characterized by much lower k_1 and k_{-1} values. A significant finding, however, is that the rate constant of formation of **5a-Me** is essentially the same as that for formation of the TNB adduct **3-Me**. Accordingly, the stronger thermodynamic electrophilicity of **5a** is the result of a much lower rate of decomposition of **5a-Me** than of **3-Me**. This implies that the five-membered isoxazole ring of **5a** contributes more efficiently than the *ortho*-nitro group of TNB to the resonance stabilization of the negative charge of the adduct.

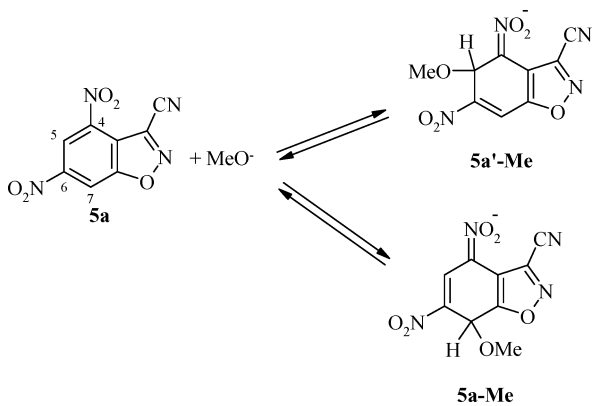
Regarding the electrophilicity of **5a**, the observed lack of reactivity of the 5-position with MeO^- is noteworthy. In the benzene series, *meta*-dinitrosubstituted rings having two non-equivalent activated unsubstituted positions behave in general as ambident Meisenheimer electrophiles.[1] The reactions of MeO^- with 1-X-3,5-dinitrobenzenes **12–14** (X = aza, CN, CF_3) are illustrative of this behaviour (Scheme 4).[23–25] In these instances, MeO^- addition takes place under kinetic control at the 4-position *para* to the X substituent, affording the adducts **12′-Me**, **13′-Me** and **14′-Me** which subsequently rearrange to the 2-methoxy isomers,*i.e.***12-Me**, **13-Me** and **14-Me**. Because a *para*-NO_2 group is especially effective in stabilizing anionic σ-adducts,[1,23] these latter complexes are the thermodynamically stable products of the interactions. In fact, **12–14-Me** are the sole



Scheme 4

species observable in methanol and it is only in carrying out the interactions in the presence of a dipolar aprotic cosolvent known to stabilize delocalized negative charges, *e.g.* Me_2SO, that the isomeric adducts **12′–14′-Me** are stable enough to be initially detected.[24,25]

On the above grounds, one might have expected a similar ambident reactivity of **5a** toward MeO^- in 80% Me_2SO, with the two steps of the interaction corresponding to the formation of the 5-methoxy adduct **5a′-Me** followed by the rearrangement of this species into **5a-Me** (Scheme 5).The experimental evidence, however, is that the first step corresponds to the direct formation of **5a-Me** which is the adduct benefiting from the powerful stabilization by a *para*-NO_2 group. This makes it difficult to reverse the course of the interaction in viewing the second step as the isomerisation of **5a-Me** into **5a′-Me**. On the other hand, should the competitive interaction depicted in Scheme 5 prevail, the measured rate constant for the isomerisation step should depend curvilinearly and not linearly, as it is observed, on the MeO^- concentration (Fig. 6). It thus appears that the presence of the isoxazole moiety induces strong variations in the relative reactivities of the 5- and 7-positions of **5a**. In this regard, we thank a referee for suggesting that the absence of methoxide adduct formation in position-5 of **5a** may be the reflection of disturbed symmetry of the aromatic ring in **5a** as compared with benzene.



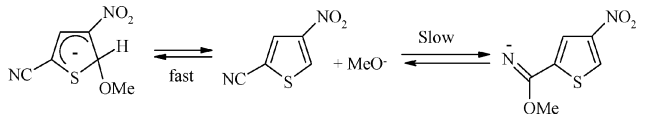
Scheme 5

Reactivity at the cyano group

A major feature of the reactivity of **5a** in dilute methanolic sodium methoxide solutions is that the initially formed σ-adduct **5a-Me** undergoes a subsequent and complete conversion into the dinitroimidate **6**. This compound is therefore the thermodynamically stable product of the competitive interaction depicted in Scheme 3, at least in this solvent. Importantly, the experimental evidence is also that **6** is directly and quantitatively formed upon dissolution of **5a** in sodium bicarbonate or sodium carbonate buffer solutions whose pH is too low to allow for even a partial initial formation of **5a-Me**. Due to this full conversion of **5a** into **6**, only a subsequent and very slow S_NAr displacement of the 4-nitro group of **6** to give the methoxyimidate **7** is observed, as emphasized in Scheme 1.

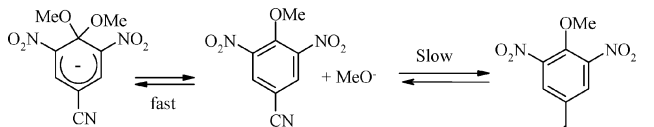
For a meaningful evaluation of how the facile formation of **6** is indicative of a high electron-deficient character of the parent carbonitrile **5a**, it is first to be noted that methoxide addition at a cyano group is a known process, including in the context of σ-adduct formation and S_NAr substitutions. Thus, Miller

and Bolton have reported a competition between methoxy-dechlorination or -defluorination S_NAr processes and reversible addition of MeO^- to the CN group in reactions of this nucleophile with *ortho*- and *para*-chloronitrobenzonitriles or polyfluorobenzonitriles.[30] Also, the reaction of MeO^- with 2-cyano-4 nitrothiophene **19** proceeds according to equation 11 where the formation of the stable thiophenecarboximidate **20** is preceded by the fastest formation of the σ-adduct **19-Me**.[26,30] In a similar way, Crampton and coworkers have found that the reaction of MeO^- with 4-cyano-2,6-dinitroanisole **21** to give the *gem*-dimethoxy complex **21-Me** is followed by a slower methanolysis of the ring-cyano substituent to give the imidoester **22** (equation 12).[31] Interestingly, the rate constant k_2 pertaining to the attack of MeO^- at the CN group could be measured: $k_2 = 0.26\ dm^3mol^{-1}s^{-1}$ for **21**. This value can be compared with the rate constant k_1 for MeO^- addition at the methoxy-bearing carbon of **21**: $k = 2.4\ dm^3mol^{-1}s^{-1}$.[31]



19-Me **19** **20**

(11)



21-Me **21** **22**

(12)

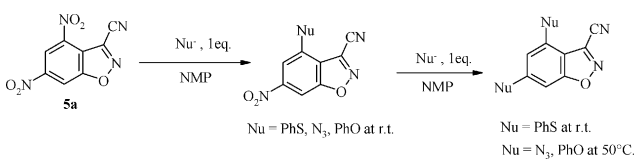
In the present study of the reactivity of **5a**, the k_2 rate constant measured for formation of the dinitroimidate **6** is $10.81\ dm^3mol^{-1}s^{-1}$, *i.e.*methoxide addition to the CN group of the isoxazole ring of **5a** is 42 times faster than to the CN group of **21**. Compared to the other substrates, the susceptibility of **5a** to undergo MeO^- addition to the CN group is enhanced. This is obviously consistent with its strong electrophilicity in σ-adduct formation.

In as much as the isomerisation of **5a-Me** into the dinitroimidate **6** is largely favored in methanol, the preference for the formation of the diadduct **9** in 20–80 (v/v) MeOH-Me_2SO calls for discussion. In fact, this major change in the reactivity pattern can be readily understood in terms of solvent effects. In pure methanol, hydrogen-bonding solvation is known to be very efficient in stabilizing oxyanionic structures with a localized negative charge such as carboxylate, phenoxide or, here, imidate structures.[32,33] Contrasting with this situation, polarizable negative charges such as those of σ-adducts, are not prone to hydrogen bonding.[23] Accordingly, the initially formed adduct **5a-Me** is less thermodynamically stable than **6** in methanol, accounting for the isomerisation observed in this solvent. On the other hand, going to Me_2SO-rich solvents has the effect to strongly decrease the hydrogen-bonding stabilization of localized negative charges while the polarizable negative charge of the cyclohexadienate moiety of σ-adducts is subject to better stabilization by the dipolar aprotic solvent.[23,32,33] On this ground, one might have expected a complete reversal in the stabilities of **5a-Me** and **6** on going to 20–80 (v/v) MeOH-Me_2SO, resulting in the unique formation of the former species in this solvent. However, the favourable thermodynamics of formation of the diadduct **9** can be understood because the lack of stabilization of the imidate functionality is here overcompensated by the enormous gain in stability of the attached cyclohexadienyl moiety. Numerous studies have shown that the equilibrium constants measuring the ease of σ-complexation of nitroactivated substrates with MeO^- increase by about 5 orders of magnitude on going from MeOH to 80% Me_2SO.[34]

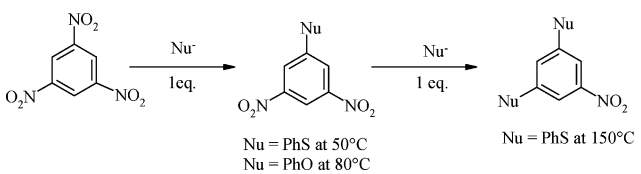
At this point, it is perhaps worthy to relate the above solvent effects to the failure to follow kinetically the initial formation of the adduct **5a-Me** in 80% Me_2SO. From the many studies devoted to σ-complexation, it has emerged the finding that the effect of adding Me_2SO to methanolic solutions is to increase the stability of all σ-adducts to a rather similar extent.[1,34] Importantly, the similar changes in K_1 are the result of similar increases in the rate constants for formation (k_1) and similar decreases in the rate constants for decomposition (k_{-1}) of the adducts. Thus the 10^5 increase in K_1 which characterizes the transfer MeOH-80% Me_2SO goes approximately with a 300-fold increase in k_1 and a 300-fold decrease in k_{-1}.[34] Based on these figures, the estimated parameters for the σ-complexation of **5a** in 80% Me_2SO are the following: $K_1 \approx 10^8\ dm^3mol^{-1}$; $k_1 \approx 3 \times 10^6\ dm^3mol^{-1}s^{-1}$; $k_{-1} \approx 0.02\ s^{-1}$. At the lowest MeO^- concentration which can be used without using buffer solutions, *i.e.* $[MeO^-] = 5 \times 10^{-4}\ moldm^{-3}$, these estimates lead to a k_{obs} value of $1.5 \times 10^3\ s^{-1}$, a value which is much beyond the upper limit for measurable rates by the stopped-flow technique.

S_NAr reactivity of 5a

Some synthetic investigations are fully consistent with the above demonstration that **5a** is a stronger electrophile than TNB. As an example, **5a** reacts readily with thiophenoxide anion (PhS^-) at room temperature in N-methylpyrrolidone (NMP) to afford the S_NAr products arising from the successive displacements of the 4-NO_2 and 6-NO_2 groups (Scheme 6).[35] In the same solvent, the temperature must be raised to 50 °C to achieve the S_NAr displacement of a first NO_2 group and to 150 °C to complete the substitution of a second NO_2 group of TNB (Scheme 7).[36,37] Similarly, the substitutions of the NO_2 groups of **5a** by phenoxide (PhO^-) and azide (N_3^-) anions take place under much smoother experimental conditions than the displacements of the NO_2 groups of TNB.[35,36] These results are qualitatively in accord with the

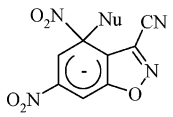


Scheme 6

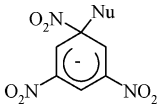


Scheme 7

conclusion that the 3-cyanoisoxazole fragment of **5a** exerts a greater stabilizing effect on the intermediate *ipso*-complex, *e.g.* **23**, thereby favoring the related S_NAr displacement, than does a *meta*-NO_2 group on the analogous *ipso*-adduct, *e.g.* **24**, of TNB.[1] To be noted is that the regioselectivity observed in substituting first the 4-NO_2 group of **5a** by soft nucleophiles (PhS^-, PhO^-, N_3^-) is reminiscent of previous findings by Stirling in studies of substitutions of various polynitroaromatics by a variety of thiolate nucleophiles.[38]



23



24

In the present study, no evidence for S_NAr displacement of the NO_2 groups of **5a** by MeO^- has been found in the time scale of our kinetic experiments in methanol and 20:80 (v/v) MeOH-Me_2SO. As shown in Scheme 1, the formation of the imidate **6** is in fact followed by a slow S_NAr substitution of the 4-NO_2 group of this compound at room temperature. So far, no S_NAr substitution of the 4-NO_2 group of **5a** to give the 4-methoxy-6-nitrocarbonitrile **8** has been observed. However, it is noteworthy that the 4-NO_2 group of the isoxazoles **5b-5d**, which do not undergo initial MeO^- addition to the exocyclic group, is prone to a selective S_NAr substitution by MeO^- at room temperature in methanol. This shows that these compounds also have a notable electrophilic character.[17–19]

Experimental

General

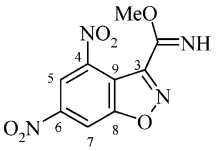
Melting points were determined on a Reichert-type microscope and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are reported in ppm (J values in Hertz) relative to internal Me_4Si. The peaks are characterized by s (singlet), bs (broad singlet). Mass spectra (CI, NH_3) were obtained using a NERMAG R10–10C spectrometer equipped with a quadrupole and mass spectra (EI, 70eV) using a Kratos MS-30 spectrometer.

Kinetic measurements

Measurements were performed on an Applied-Photophysics SX-18MV stopped-flow spectrophotometer, the cell compartment of which was maintained at 25 ± 0.1 °C. A conventional HP8453 UV-visible spectrophotometer was also used to follow the slowest processes. All kinetic runs were carried out in triplicate under pseudo first order conditions with an electrophile (**5a**) concentration of ca. 3×10^{-5} moldm^{-3} and a base concentration in the range 10^{-3}–0.1 moldm^{-3}. In a given experiment, the rates were found to be reproducible to ± 2–3%.

Materials

4,6-Dinitrobenzo[d]isoxazole-3-carbonitrile **5a** was available from a previously reported synthetic work by some of us.[17,19] Dilute sodium methoxide solutions in methanol and 20:80 (v/v) MeOH-Me_2SO were prepared as previously described, using solvent purified according to reported procedures.[24,26,28,34]



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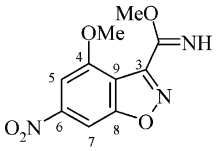


7

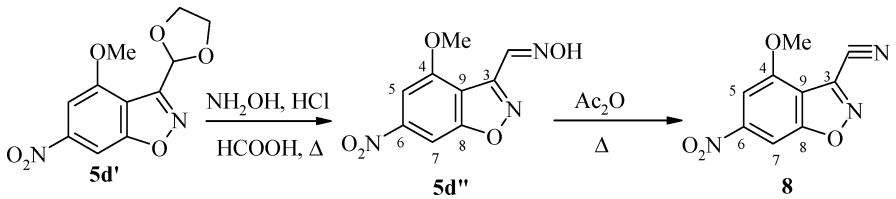
4,6-Dinitrobenzo[d]isoxazole-3-carboximidic acid methyl ester 6. **6** was obtained on mixing 0.234 g (1 mmol) of **5a** with 0.1 g (1.2 mmol) of $NaHCO_3$ in 10 ml of methanol. After 24 hours stirring at room temperature, the solvent was evaporated to dryness, affording a white solid which was very unstable in air. However, an immediate dissolution of this solid in Me_2SO-d_6 has allowed a firm ^1H NMR characterization of **6**. The UV visible absorption spectrum of this dinitroimidate could be also recorded.

6: white solid, unstable. ^1H NMR (Me_2SO-d_6, δ): 3.85 (s, 3H, OCH_3), 8.85 (s, 1H, H_5), 9.40 (bs, 1H, NH), 9.60 (s, 1H, H_7); UV-visible : λ_{max} (MeOH) = 218, 249 nm.

4-Methoxy-6-nitrobenzo[d]isoxazole-3-carboximidic acid methyl ester 7. **7** was prepared on mixing 0.234 g (0.1 mmol) of **5a** with 0.138 g (1 mmol) of K_2CO_3 in 10 ml of methanol. After 1 hour stirring at room temperature, 50 ml of water were added to the reaction mixture which was then acidified at pH = 2. This caused the precipitation of white crystals which were collected by filtration, washed with water and dried over P_2O_5. All analytical data confirmed the formation of **7** (yield 82%).

7: white solid, yield 82%; mp 187–8 °C; MS (CI, NH_3^+): 252 [MH^+]; ^1H NMR (Me_2SO-d_6, δ): 3.87 (s, 3H, OCH_3), 4.09 (s, 3H, $C(N{=}H)OCH_3$), 7.71 (s, 1H, H_5), 8.39 (s, 1H, H_7), 9.68 (bs, 1H, NH); ^{13}C NMR (Me_2SO-d_6, δ): 53.4, 57.4 (OCH_3), 99.2 (C_7), 100.6 (C_5), 113.5 (C_6), 150.7 (C_9), 151.2 (C_3), 153.8 (C_4), 157.1 (C_{10}), 163.2 (C_8); UV-visible: λ_{max} (MeOH) = 217, 273, 342 nm. Anal. Calcd for $C_{10}H_9N_3O_5$: C. 47.81%; H. 3.61%; N. 16.73%; found, C. 47.47%; H. 3.45%; N. 16.34%.

4-Methoxy-6-nitrobenzo[d]isoxazole-3-carbonitrile 8. was obtained in two steps as follows. In a first step, 0.40 g (5.6 mmol) of NH_2OH, HCl were added to a solution of 1.06 g (4 mmol) of 3-(1,3-dioxolan-2-yl)-4-methoxy-6-nitrobenzo[d]isoxazole **5d′** in 25 ml of formic acid. After refluxing the reaction mixture for 5 h (monitoring by TLC), water was added, inducing the precipitation of a white solid which was collected by filtration and recrystallized in ethanol. All spectroscopic data and elemental analysis data indicated the formation of the oxime **5d″** (yield 37%).



5d' **5d"** **8**

5d″: white solid, yield 37%; mp 160–1 °C; MS (EI): 237 [$M^{+\bullet}$]; ^{1}H NMR (Me_2SO-d_6, δ): 4.15 (s, 3H, OCH_3), 7.80 (s, 1H, H_5), 8.55 (s, 1H, H_7); Anal. Calcd for $C_9H_7N_3O_5$: C. 45.58%; H. 2.97%; N. 17.72%; found, C. 45.29%; H. 2.85%; N. 17.48%.

In a second step, a sample of **5d″** (0.22 g) was dissolved in 6 ml of acetic anhydride. Refluxing the solution for 15 hours (monitoring by TLC) and pouring it in water caused the precipitation of a white solid which was collected by filtration and recrystallized in ethanol. All analytical data are consistent with the formation of **8** (yield 93%).

8: white solid, yield 93%; mp 170–2 °C; MS (EI): 219 [$M^{+\bullet}$], 173 [$M - NO_2]^{+\bullet}$; ^{1}H NMR (Me_2SO-d_6, δ): 4.15 (s, 3H, OCH_3), 7.80 (s, 1H, H_5), 8.55 (s, 1H, H_7); ^{13}C NMR (Me_2SO-d_6, δ): 57.7 (OCH_3), 99.7 (C_7), 101.5 (C_5), 109.3 (CN), 114.8 (C_9), 134.42 (C_3), 151.5 (C_6), 153.4 (C_4), 163.6 (C_8); UV-visible: λ_{max} (MeOH) = 219, 269, 342 nm. Anal. Calcd for $C_9H_5N_3O_4$: C. 49.32%; H. 2.30%; N. 19.17%; found, C. 49.29%; H. 2.45%; N. 19.44%.

σ-Adducts 5a-Me and 9. the 7-methoxy adduct **5a-Me** was obtained quantitatively as a sodium salt upon treatment of **5a** by one equivalent of MeONa in methanol. After stirring the resulting solution for 5 minutes at room temperature, and evaporating the solvent, **5aMe**, $\mathbf{Na^+}$ was obtained as reddish crystals. As with most alkali salts of anionic σ-adducts so far obtained, these solids did not melt prior to decomposition (explosion) and attempts to obtained satisfactory elemental analysis have been unsuccessful. However, **5aMe** could be characterized by ^{1}H and ^{13}C NMR as well as mass spectroscopy. The data, given below, do not call for much comment since they agree well with the proposed structure for **5aMe**. Reflecting the change in hybridization from sp^2 to sp^3 brought about at the 7-position by the σ-complexation, the H_7 and C_7 resonances move strongly to highfield.[1,13] Loss of aromaticity and increased negative charge in the carbocyclic ring also cause the signal for H_5 proton to be shifted upfield on formation of **5aMe**, but to a much lesser extent than the signal for H_7 proton.[1,13] As shown in Fig. 1, the visible spectrum of **5aMe** in methanol exhibits a strong absorption maximum at λ = 480 nm, a wavelength typical for σ-complexation of *meta*-dinitroactivated arene and hetarene rings.[13]

Attempts to isolate the 7-methoxy dianionic adduct **9** as a disodium salt have failed because of a lack of stability of this species. Evidence for structure **9** has therefore come from in situ experiments, recording ^{1}H NMR spectra immediately after addition of one equivalent of MeONa to a Me_2SO-d_6 solution of the isolated monoanionic adduct **5aMe**, $\mathbf{Na^+}$. These spectra showed unambiguously that the H_5 and H_7 resonances of the AX system typical of **5aMe** are retained with, however, a slight upfield shift, as expected from the presence of a second negative charge at the remote imidate functionality. Because of overlap with the resonance of MeOH, the chemical shifts of the methoxy groups at C_7 and C_3 could not be ascribed.

5aMe, Na^+: red solid, yield 90%; mp: 160 °C (dec.); MS (ESI): 265 ($M - Na^+$). ^{1}H NMR (Me_2SO-d_6, δ): 3.18 (s, 3H, OCH_3), 6.23 (s, 1H, H_7), 8.56 (s, 1H, H_5); ^{13}C NMR (Me_2SO-d_6, δ): 56.2 (OCH_3), 68.3 (C_7), 111.90 (C_9), 112.3 (C_4), 112.4 (CN), 113.3 (C_8), 125.2 (C_6), 127.9 (C_5), 164.2 (C_3); UV-visible: λ_{max} (MeOH) = 480 nm.

9 (not isolated in the solid state): ^{1}H NMR (Me_2SO-d_6, δ): 6.17 (s, 1H, H_7), 8.50 (s, 1H, H_5); UV-visible: λ_{max} (20:80 (v/v) MeOH-Me_2SO) = 470 nm.

Acknowledgements

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