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An extremely highly electrophilic heteroaromatic structure: 4,6-dinitrotetrazolo[1,5-*a*]pyridine †

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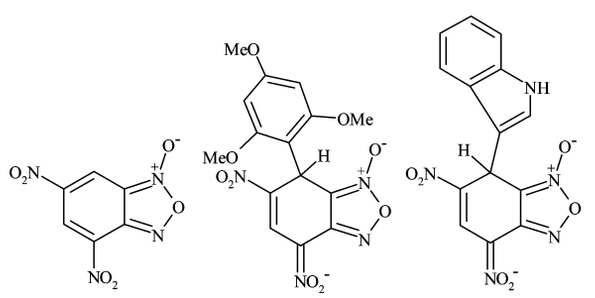
A detailed thermodynamic and kinetic investigation of the reactions of 4,6-dinitrotetrazolo[1,5-*a*]pyridine (DNTP) with water and methanol has been made in the corresponding solvents. In aqueous solution, covalent addition of water to DNTP occurs with the exclusive formation of an anionic hydroxy σ-complex **C-4a** which is half-formed in a 0.4 M HCl solution ($pK_a^{\sigma} = 0.4$). This corresponds to a 3 p*K*-units jump in thermodynamic stability from the most stable hydroxy σ-complex known so far, *i.e.* the hydroxy adduct **C-3a** of 4,6-dinitrobenzofuroxan (DNBF). DNTP forms similarly a very stable methoxy σ-complex **C-4b** in methanol ($pK_a^{\sigma} = 2.64$). Interestingly, the addition of methanol to DNTP also results in the partial formation of a neutral carbinolamine-type adduct (**C-5b**) at low pH. Rate and equilibrium constants pertaining to most of the reaction pathways involved in the interactions have been determined. In particular, the following rate constants $k_1^{H_2O}$ and k_1^{MeOH} for formation of **C-4a** and **C-4b** have been measured: $k_1^{H_2O} = 1.93\ s^{-1}$; $k_1^{MeOH} = 3.50\ s^{-1}$, to be compared with $k_1^{H_2O} = 0.035\ s^{-1}$; $k_1^{MeOH} = 0.030\ s^{-1}$ for σ-complexation of DNBF under similar experimental conditions. Altogether, the results obtained reveal that DNTP is a considerably more powerful electrophile than DNBF, the common reference as to whether an electron-deficient aromatic or heteroaromatic substrate may be accorded superelectrophilic properties in addition or substitution processes.

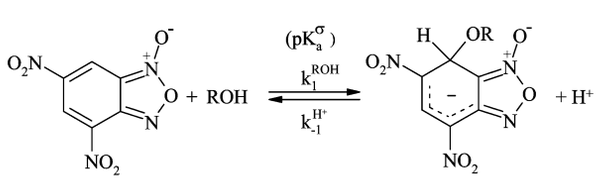
Introduction

In the last two decades, much evidence has been accumulated that nitro-2,1,3-benzoxadiazoles and related 1-oxide derivatives, commonly referred to as nitrobenzofurazans and nitrobenzofuroxans, respectively, represent a class of electron-deficient heteroaromatic compounds that show an exalted reactivity in covalent nucleophilic and substitution processes.[1–10] As an illustration of this behaviour, 4,6-dinitrobenzofuroxan (DNBF)—the reference compound in this family—reacts very readily with such extremely weak carbon nucleophiles as benzenoid aromatics or π-excessive heteroaromatics with large negative pK_a values, *e.g.* 1,3,5-trimethoxybenzene (p$K_a = -5.72$) or indole (p$K_a = -3.46$).[3c,11] The resulting stable anionic C-bonded σ-adducts, *e.g.* **1** and **2**, are formally the products of S_EAr substitution of the benzene or hetarene ring. From kinetic studies of these reactions, it has been shown that DNBF is more electrophilic than the *p*-nitrobenzenediazonium cation.[3c] This superelectrophilic behaviour has led to many analytical applications, with in particular a facile assessment of so far unknown C-basicities, such as those of anilines or aminothiophenes.[5,9,12]

A crucial step for the development of the chemistry of nitrobenzofuroxans has been the recent discovery that the nitro-substituted carbocyclic ring can be involved in a variety of Diels–Alder type reactions, acting as a dienophile, a heterodiene or a carbodiene depending upon the reaction partners and the experimental conditions at hand.[13–16] Besides the potentiality of this versatile behaviour in terms of new synthetic approaches in heterocyclic chemistry, the results obtained have revealed the existence of a significant relationship between superelectrophilicity and pericyclic reactivity.[17] In other words, the compounds which are the most prone to undergo σ-complexation, as measured by the pK_a values for water addition, are also those which exhibit the greatest pericyclic reactivity. With a pK_a^{σ} value of 3.75 for formation of the hydroxy σ-adduct **C-3a**,[3a] DNBF has been ranked as the compound exhibiting the most versatile reactivity in the benzofuroxan family.[17]



DNBF **1** **2**



DNBF **C-3a** (R = H) **C-3b** (R = Me) (1)

The above results led us to search for related heterocyclic structures which might behave similarly to, or even surpass, the DNBF molecule in terms of electrophilicity and Diels–Alder reactivity. In this context, we are prompted to report on a neutral polyazaheteroaromatic structure, namely 4,6-dinitrotetrazolo-[1,5-*a*]pyridine (DNTP)‡ that we have identified as being by far the most electrophilic neutral heterocycle known to date.

† Electronic supplementary information (ESI) available: Fig. S1 Effect of pH on the ionization of the OH group of **C-4a** to give the diadduct **D-4a** in aqueous solution. See http://www.rsc.org/suppdata/ob/b3/b306437a/

‡ The IUPAC name for DNTP is 6,8-dinitrotetrazolo[1,5-*a*]pyridine.

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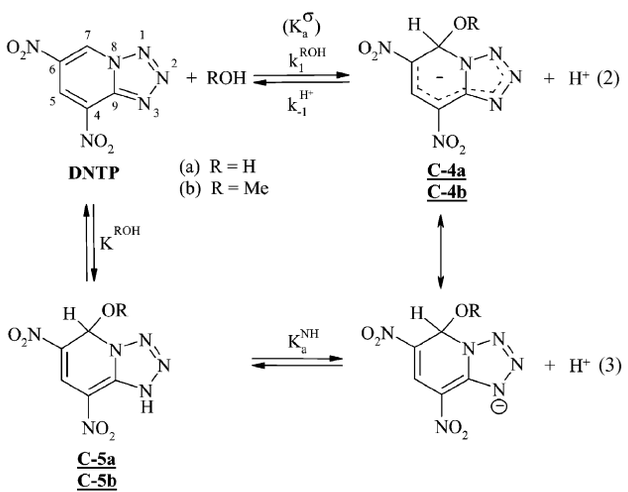
Results

σ-Complexation in aqueous solution

DNTP exists essentially in the form of the σ-adduct **C-4a** (λ_{max} = 457 nm, ε = 21700 mol^{-1} dm^3 cm^{-1}) in the absence of any added base in aqueous solution. It is only in going to a 0.4 mol dm^{-3} HCl solution that half-conversion of **C-4a** to DNTP (λ_{max} = 300 nm in acetic acid) could be achieved, corresponding to a pK_a^{σ} value of 0.4 ± 0.05 for reaction (2) in water. A kinetic study of the approach of equilibrium (2) has been carried out by mixing an aqueous solution of **C-4a** (~3 × 10^{-5} mol dm^{-3}) with HCl solutions in the concentration range 0.03–0.5 M, keeping the ionic strength constant at I = 0.5 mol dm^{-3} with KCl. From the straight line, shown in Fig. 1, which describes the variations of the observed first-order rate constant k_{obsd} with the H$^+$ concentration [eqn. (4)], the following values of the rate constants $k_1^{H_2O}$ and $k_{-1}^{H^+}$ were readily obtained: $k_1^{H_2O}$ = 1.93 s^{-1}; $k_{-1}^{H^+}$ = 3.87 mol^{-1} dm^3 s^{-1}. Combining these two values leads to a pK_a^{σ} value of 0.3, in satisfactory agreement with the value determined at no constant ionic strength.



Scheme 1

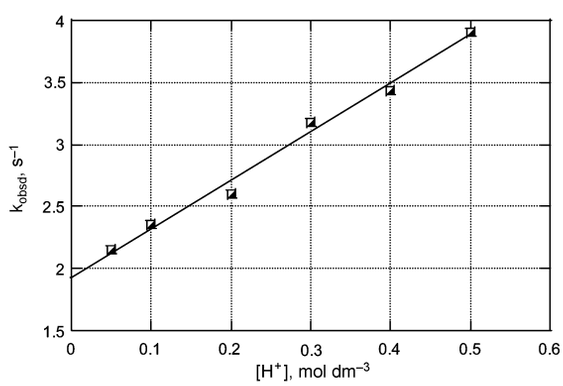


Fig. 1 Influence of the H$^+$ concentration on the observed first-order rate constant, k_{obsd}, for the interconversion of DNTP and the adduct **C-4a** in aqueous solution; T = 25 °C, I = 0.5 mol dm^{-3}.

$$k_{obsd} = k_1^{H_2O} + k_{-1}^{H^+}[H^+] \quad (4)$$

As shown in Fig. 2, pH-dependent and reversible changes in the absorption of **C-4a** occurred in the pH-range of 7.5–10.5. As will be elaborated further in the discussion, these variations are consistent with the ionisation of the OH group of **C-4a** to give the dianion **D-4a** (λ_{max} = 435 nm, ε = 10900 mol^{-1} dm^3 cm^{-1}) according to eqn. 5. The p$K_a'^{\sigma}$ value for interconversion of these two species, as determined according to a standard spectrophotometric study of the pH dependence of the spectral changes is equal to 8.78 ± 0.05 (Fig. S1 †).

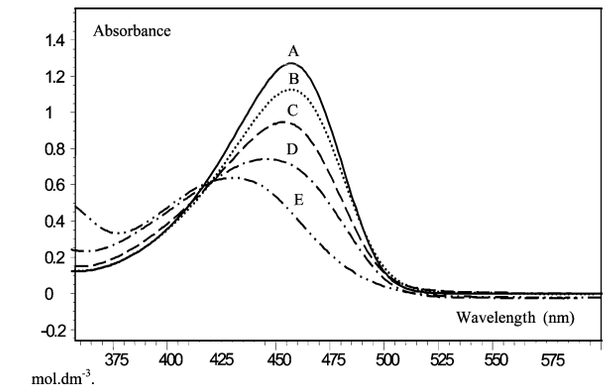
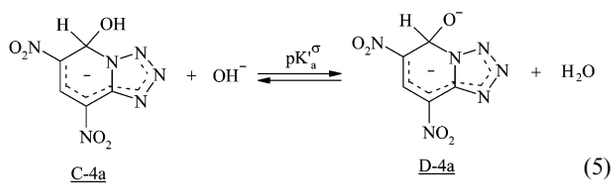


Fig. 2 Absorption spectra illustrating the ionization of the hydroxy group of the adduct **C-4a** in aqueous solution (A); pH = 8.21 (B); pH = 8.70 (C); pH = 9.00 (D) and 10.13 (E).



(5)

σ-Complexation in methanolic solution

In contrast with the situation in aqueous solution, the σ-complexation of DNTP to give the adduct **C-4b** (λ_{max} = 445 nm, ε = 25800 mol^{-1} dm^3 cm^{-1}) cannot be described by a simple equilibrium of type (2) in methanol. Instead, the experimental evidence is consistent with Scheme 1 where the complexation proceeds from DNTP in equilibrium with the neutral carbinolamine-type adduct **C-5b**. As a matter of fact, stopped-flow experiments revealed that mixing a solution of **C-4b** (~3 × 10^{-5} mol dm^{-3}) with methanesulfonic acid solutions (10^{-3}–0.20 mol dm^{-3}) resulted in the instantaneous and pH dependent formation of a new species which is completely formed for H$^+$ concentrations ≥ 0.03 mol dm^{-3}. Fig. 3 shows the UV-visible spectra of the adduct **C-4b** and the new species (λ_{max} = 410 nm, ε = 18330 mol^{-1} dm^3 cm^{-1}) that we assume to be **C-5b** (*vide infra*). This conjugate acid of **C-4b** is also the product of covalent addition of methanol to DNTP. From the pH dependence of the observed instantaneous spectral changes at 410 nm,

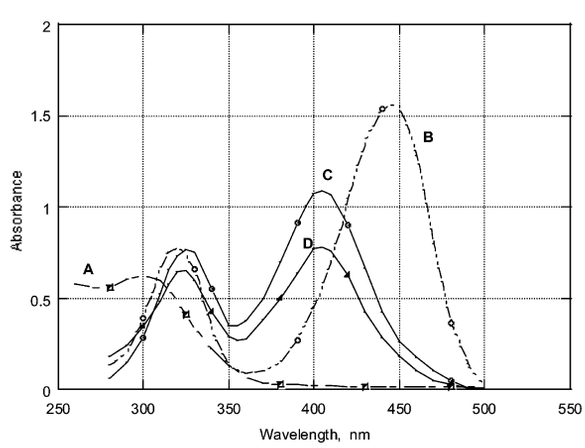


Fig. 3 UV-visible spectra of: (A) the pure DNTP molecule in acetic acid; (B) the pure σ-adduct **C-4b** in methanol; (C) the pure carbinolamine-type adduct **C-5b** at pH = 1.3 in methanol; (D) the mixture of the DNTP and **C-5b** species at final equilibrium and pH = 1.3 in methanol.

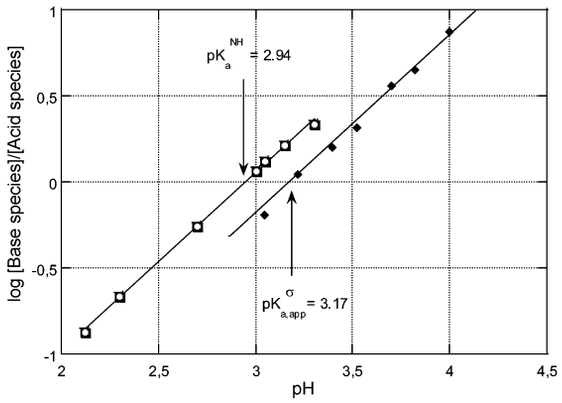


Fig. 4 Effect of pH on the ionization of the NH acid **C-5b** to give the adduct **C-4b** ($pK_a^{NH} = 2.94$) and on the overall formation of this base species from a low pH equilibrium mixture of the two parent neutral acid forms, *i.e.* DNTP and **C-5b**, $pK_a^{app.} = 3.17$ [see eqn. (6)] in methanol. $T = 25$ °C.

the pK value for this acid–base process was readily obtained (Fig. 4): $pK_a^{NH} = 2.94 \pm 0.05$.

At all pH studied, the instantaneous formation of **C-5b** was followed by a partial conversion to the parent DNTP molecule. Fig. 3 also shows the UV-visible spectrum recorded at final equilibrium after complete disappearance of the adduct **C-4b** in a 0.05 mol dm^{-3} CH_3SO_3H solution. Based on the residual absorption at 410 nm, where the original DNTP structure does not absorb, the composition of the final reaction mixture could be calculated as consisting of 65% of **C-5b** and 35% of DNTP, *i.e.* the equilibrium constant $K^{\mathbf{MeOH}}$ for formation of the carbinolamine derivative **C-5b** from DNTP is equal to *ca.* 2. Increasing the H^+ concentration up to 0.20 mol dm^{-3} had no effect on the composition of the final solutions, as expected.

Based on Scheme 1, the σ-complexation of DNTP to give **C-4b** can be viewed as the sum of the equilibria pertaining to the covalent addition of methanol to give **C-5b** ($K^{\mathbf{MeOH}}$) and the ionization of the NH group of this conjugate acid of **C-4b** (K_a^{NH}). This implies the relationship $K_a^{\sigma} = K_a^{NH} \times K^{\mathbf{MeOH}}$, allowing the calculation of the pK_a^{σ} value from the above estimates of pK_a^{NH} and $K^{\mathbf{MeOH}}$, *i.e.* $pK_a^{\sigma} = 2.64$.

Interestingly, the validity of this pK_a^{σ} value could be controlled as follows. Since **C-4b** absorbs considerably more than DNTP and **C-5b** at 450–460 nm, we could carry out a direct investigation of the formation of this σ-adduct in the pH range 2–4. From the observed absorbance variations at 460 nm obtained at equilibrium as a function of pH, an excellent straight line with unit slope fitting eqn. (6) was obtained (Fig. 4) with the related apparent acidity constant $K_{a,app.}^{\sigma}$ being defined by eqn. (7): $pK_{a,app.}^{\sigma} = 3.17$. This value is in satisfactory agreement with the $pK_{a,app.}^{\sigma}$ value that one can derive from eqn. (7) by using the above estimates of K_a^{σ} and $K^{\mathbf{MeOH}}$, *i.e.* 3.12.

$$\log \frac{[\mathbf{C\text{-}4b}]}{[\mathrm{DNTP}] + [\mathbf{C\text{-}5b}]} = \mathrm{pH} - pK_{a,app}^{\sigma} \qquad (6)$$

$$K_{a,app} = \frac{[\mathbf{C\text{-}4b}][H^+]}{[\mathrm{DNTP}] + [\mathbf{C\text{-}5b}]} = \frac{K_a^{\sigma}}{1 + K^{\mathrm{MeOH}}} \qquad (7)$$

Starting from a mixture of the two neutral structures at pH = 2.5, the formation of the adduct **C-4b** could be kinetically studied in the pH range 4–11, using a set of appropriate carboxylic acid (trichloroacetic acid, dichloroacetic acid, chloroacetic acid, 3-chlorobenzoic acid and benzoic acid) and phenol (2,4,6-trichlorophenol and 2,6-dichlorophenol) buffers.[18] No buffer catalysis of this process by the buffer base component was observed under the experimental conditions employed, *i.e.* total buffer concentration ≤4.10^{-2} mol dm^{-3}. Also, changing the pH of the initial mixture of the reactants to 2.3 and 2.7 did not affect the rates measured at the various final pH. Thus, we obtained the right part of the pH rate profile of Fig. 5 which is obviously consistent with $k_{\mathbf{obsd}}$ being given by eqn. (8). The rate constants k_1^{MeOH} and $k_2^{MeO^-}$ which refer to the formation of **C-4b** through methanol [eqn. (2)] and methoxide ion [eqn. (9)] attacks on DNTP were readily determined from the plateau and the straight line of slope +1 which prevail at pH ≤ 8 and pH ≥ 9, respectively: $k_1^{MeOH} = 3.5$ s^{-1} and $k_2^{MeO^-} = 6.30 \times 10^7$ mol^{-1} dm^3 s^{-1}. From a standard treatment combining these rate constants with the pK_a^{σ} value determined above for reaction (2) and the ionic product of methanol ($pK_s = 16.7$ at 25 °C),[19] the rate constants $k_{-1}^{H^+}$ and k_{-2} for the H^+ catalyzed and non-catalyzed decomposition pathways of **C-4b** were also derived: $k_{-1}^{H^+} = 1520$ mol^{-1} dm^3 s^{-1}; $k_{-2} = 5.5 \times 10^{-7}$ s^{-1}.

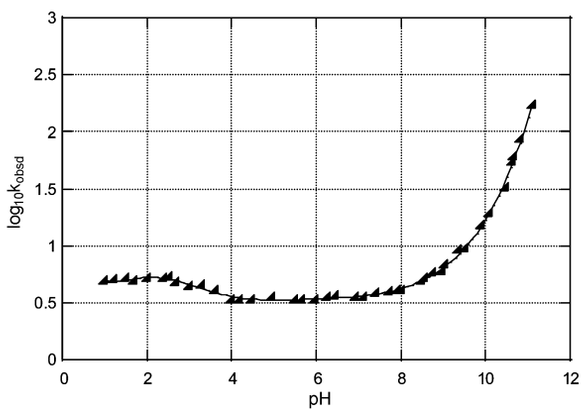


Fig. 5 pH dependence of $k_{\mathbf{obsd}}$ (s^{-1}) for formation and decomposition of the adduct **C-4b** in methanol; $T = 25$ °C.

$$k_{obsd} = k_1^{MeOH} + k_2^{MeO^-}[MeO^-] \qquad (8)$$

$$\mathrm{DNTP} + MeO^- \underset{k_{-2}}{\overset{k_2^{MeO^-}}{\rightleftharpoons}} \mathbf{C\text{-}4b} \qquad (9)$$

The kinetics of the decomposition of **C-4b** were studied in the pH range 1.3–3.3 by mixing a methanolic solution of this adduct with appropriate methanesulfonic acid solutions. As discussed above, the process consists of two steps, namely an instantaneous pH-dependent protonation of **C-4b** at N-3 to give partially or totally **C-5b** followed by a subsequent slow and partial conversion to the neutral DNTP structure. The dependence of the rate constant $k_{\mathbf{obsd}}$ measured for this process is shown in the left part of Fig. 5. As can be seen, $k_{\mathbf{obsd}}$ is rapidly subject to a levelling effect with the appearance of a plateau at pH ≤ 2. Very importantly the presence of the plateau implies that we are actually dealing with the recovery of DNTP through the H^+ catalyzed decomposition of **C-4b** according to eqn. (10).[20] Thus, $k_{\mathbf{obsd}}$ is given by eqn. (11) which reduces to eqn. (12) at the lowest H^+ concentrations where we have $[H^+] >> K_a^{NH}$. From the plateau ($k_{obsd}^{max} = 5.7$ s^{-1}), the value of $k_{-1}^{H^+}$ could be derived using the known values of k_1^{MeOH} and K_a^{NH}. We thus obtain: $k_{-1}^{H^+} = 1900$ mol^{-1} dm^3 s^{-1}. This is in satisfactory agreement with the value determined above from the study of the formation of **C-4b**.

$$\mathbf{C\text{-}5b} \underset{}{\overset{K_a^{NH}}{\rightleftharpoons}} \mathbf{C\text{-}4b} + H^+ \underset{k_1^{MeOH}}{\overset{k_{-1}^{H^+}}{\rightleftharpoons}} \mathrm{DNTP} + \mathrm{MeOH} \qquad (10)$$

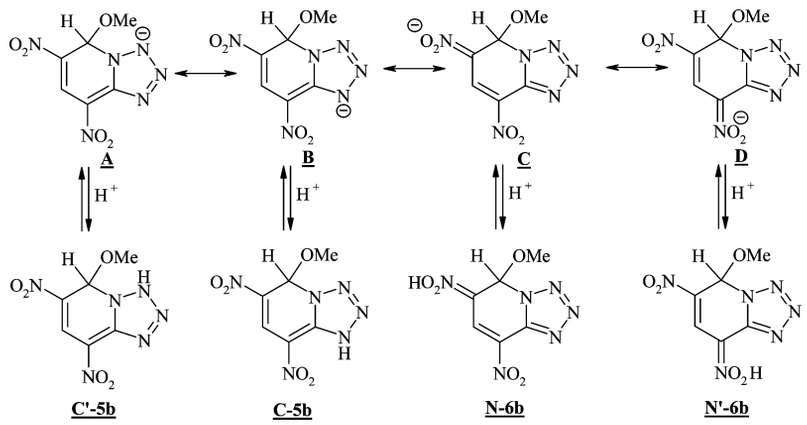
$$k_{obsd} = k_1^{MeOH} + \frac{k_{-1}^{H^+} K_a^{NH} [H^+]}{K_a^{NH} + [H^+]} \qquad (11)$$

$$k_{obsd}^{max} = k_1^{MeOH} + k_{-1}^{H^+} K_a^{NH} \qquad (12)$$

Table 1 Kinetic and thermodynamic data for formation and decomposition of hydroxy and methoxy σ-adducts and relevant pseudobases in aqueous or methanolic solution[a]

Adduct or pseudobase	Solvent	pK_a^{σ}	$pK_a'^{\sigma}$	k_1^{ROH}/s^{-1}	$k_{-1}^{H^+}/mol^{-1}\ dm^3\ s^{-1}$	$k_2^{RO^-}/mol^{-1}\ dm^3\ s^{-1}$	k_{-2}/s^{-1}
C-3a[b]	H_2O	3.75	11.80	0.0345	146	33500	2.5×10^{-6}
C-3b[c]	MeOH	6.46	—	0.03	4.68×10^4	1.87×10^6	8.9×10^{-5}
C-4a[d]	H_2O	0.3	8.78	1.93	3.87	—	—
C-4b[d]	MeOH	2.64	—	3.50	1520 (1900)	6.3×10^7	5.5×10^{-7}
C-7a[e]	H_2O	6.70	—	1.13×10^{-3}	4215	392	1.96×10^{-5}
C-8a[f]	H_2O	13.43	—	—	—	37.5	9.8
C-8b[f]	MeOH	15.33	—	—	—	7050	305
C-9[g]	H_2O	4.76	—	2.60	1.5×10^5	3.1×10^5	1.8×10^{-4}
C-10[h]	H_2O	5.11	11.15[i]	1.04	1.3×10^5	8.8×10^6	0.011
C-11[i]	H_2O	5.41	11.75[i]	11	2.90×10^6	3.80×10^7	0.097

[a] $T = 25°$ C unless otherwise stated. [b] Ref. 3*a* [c] Ref. 3*b* at 20 °C. [d] This work. [e] Ref. 31. [f] Ref. 32. [g] Ref. 33, $k_1^{H_2O}$ and $k_2^{OH^-}$ at 23 °C; $k_{-1}^{H^+}$and k_{-2} at 26 °C. [h] Ref. 34*a*. [i] Ref. 34*c*.



Scheme 2

The whole kinetic and thermodynamic data pertaining to the various pathways of the σ-complexation of DNTP in aqueous and methanolic solution are summarized in Table 1. For comparison, data for some relevant systems are also included.

Discussion

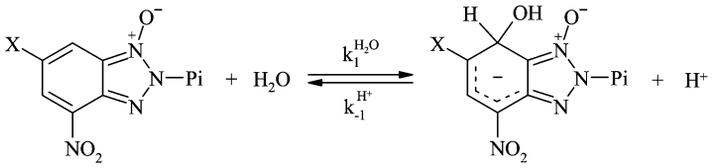
The results described above have revealed that the dinitrotetrazolopyridine DNTP has a remarkable tendency to undergo covalent addition of a methanol molecule with either formation of a neutral carbinolamine-type adduct **C-5b** at low pH or complete formation of an anionic σ-adduct (**C-4b**) at pH ≥ 4 in this solvent. In contrast, water addition is found to afford exclusively the σ-adduct **C-4a** in aqueous solution. The significance of this behaviour for ranking DNTP on the scale of superelectrophilic heteroaromatics is now considered in detail. Prior to this discussion, we will comment on the various features which have led to the attribution of structure **C-5b** to the conjugate acid of **C-4b**. Also justified will be the non observation of a similar acid–base process in water.

The nature of the conjugate acid of C-4b

In view of the resonance structures **A**–**D** (Scheme 2), fast protonation of the adduct **C-4b** could in principle take place either at a nitrogen atom of the annelated ring to give the carbinolamine **C-5b** (as postulated in Scheme 1) or **C′-5b**, or at an oxygen atom of the two nitro groups to give the nitronic acid **N-6b** or **N′-6b**. Because of the reduced capability of a furoxan ring relative to a tetrazolo ring to accommodate part of the negative charge of an anionic σ-adduct, protonation of the NO_2 groups is expected to be more difficult in **C-4b** than in the DNBF analogue **C-3b**. The experimental evidence being that **C-3b** does not undergo appreciable protonation at low pH in methanol,[3b] the formation of the nitronic acids **N-6b** and **N′-6b** from **C-4b** is not a realistic situation. We are therefore left with a protonation process at the nitrogen atoms of the annelated ring, a situation which is in agreement with the results of *ab initio* calculations carried out at the STO 3-21G level.[21] As can be seen in Fig. 6, which shows the optimized geometry and charge densities for **C-4b**, these calculations favour the presence of a notable negative charge at the N-3 nitrogen atom, thus supporting the assignment of structure **C-5b** to the conjugate acid of **C-4b**.

Very importantly, the formation of **C-5b** could be confirmed by ^{1}H NMR in Me_2SO solution. Dissolution of a sample of **C-4b**, isolated as a potassium salt (see Experimental section), in this solvent followed by acidification by methanesulfonic acid (1 mol dm^{-3}) resulted in the formation of two sets of signals in a 1 : 2 ratio assignable, respectively, to the DNTP structure (δH_5 = 9.41; δH_7 = 10.87; see Experimental section) and the neutral adduct **C-5b** (δH_5 = 8.77; δH_7 = 7.32, δ_{OMe} = 3.32). These latter figures correspond to a move to low-field of the resonances of H_5, H_7 and the OMe group, on going from the anionic adduct **C-4b** (δH_5 = 8.72; δH_7 = 7.06, δ_{OMe} = 3.18) to **C-5b**, as expected.

Regarding the absence of the formation of the related hydrate **C-5a** in aqueous solution, it can be understood with reference to previous comparative studies of covalent addition of water and methanol to some aza- and polyaza-aromatics or to carbonyl groups.[22–30] In most of these systems, the equilibrium constant for methanol addition (K^{MeOH}) was found to be greater than that for water addition (K^{H_2O}) by a factor of 15–20.[22,24,25,29] Assuming that a similar solvent effect prevails in the case of DNTP, a K^{H_2O} value of about 0.05–0.1 can be estimated for formation of **C-5a**. On the other hand, it is well-known that the effect of a transfer from methanol to water is to increase the acidity of oxygen and nitrogen acids by 2.5–3 pK_a units.[18,30] In view of the similar environment of the NH group in **C-5a** and **C-5b**, a rather low pK_a^{NH} value would thus be associated with the equilibrium **C-5a**–**C-4a** in aqueous solution (pK_a^{NH} ~ 0–0.5). Altogether, the above figures account well for



7a X = NO_2 **C-7a**
7b X = H **C-7b**

(13)

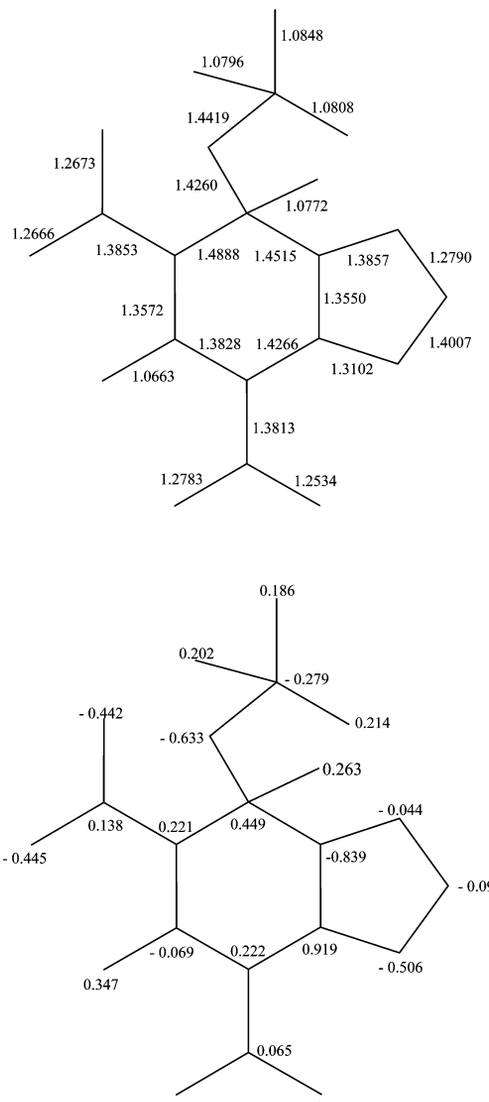
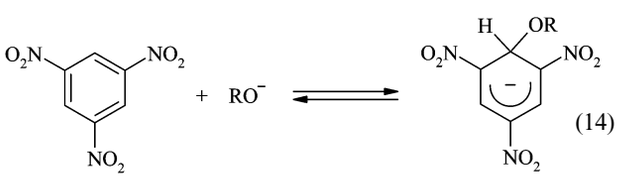


Fig. 6 Optimized geometry and charge densities for the adduct **C-4b**, as provided by *ab initio* calculations at the STO 3-21 G level.

the non-observation of the hydrate **C-5a** under our experimental conditions.

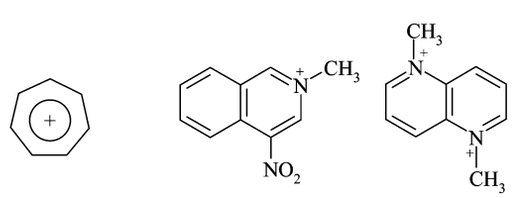
The superelectrophilic behaviour of DNTP

Thermodynamic studies. The high susceptibility of electron-deficient aromatic or heteroaromatic substrates to σ-complexation through water attack has commonly been the major criterion as to whether they may be accorded superelectrophilic properties. In this respect, Table 1 reveals that the pK_a^{σ} value for conversion of DNTP into the hydroxy adduct **C-4a** is 0.4, as compared with pK_a^{σ} values of 3.75 and 6.70 for a similar complexation of DNBF to give **C-3a** [eqn. (1)][3a] and 2-picryl-4,6-dinitrobenzotriazole 1-oxide **7a** to give **C-7a** [eqn. (13)],[31] respectively. This makes DNTP by far the most electrophilic neutral heterocycle known to date with a considerable increase in electrophilic character of 13 pK_a units from that of 1,3,5-trinitrobenzene (TNB).[32] This common reference substrate in σ-complex chemistry only reacts with the strong oxygen base hydroxide ion to give the adduct **C-8a** according to eqn. (14).[32] Significantly, the thermodynamic susceptibility of DNTP to water attack is markedly greater than that of positively charged structures such as the tropylium cation **9** (pK_a = 4.76), or the isoquinolinium or naphthyridinium cations **10** (pK_a = 5.11) or **11** (pK_a = 5.41) to give the corresponding pseudobases **C-9**, **C-10** and **C-11**.[33,34]

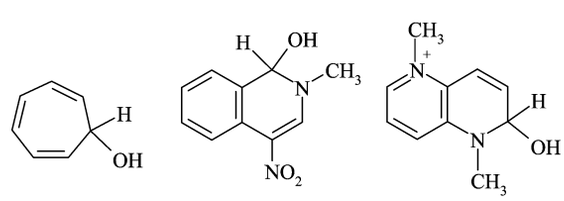


TNB R = H R = Me **C-8a** **C-8b**

(14)



9 **10** **11**



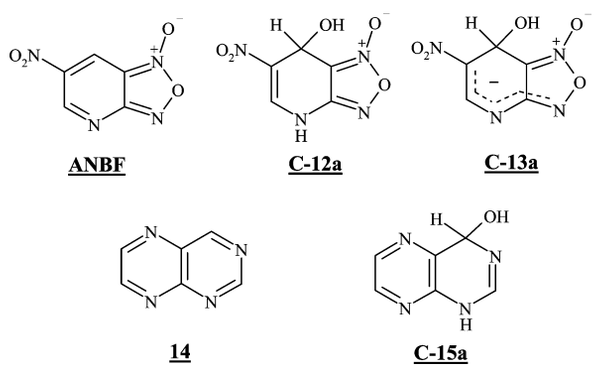
C-9 **C-10** **C-11**

Going from water to methanol reduces the ease of σ-complexation of DNTP by 2.3 units (pK_a^{σ} = 2.64). This solvent effect is essentially the same as that found in comparison of the formation of hydroxy and methoxy adducts derived from other electrophilic substrates, including DNBF and TNB (see Table 1).[1] Accordingly, DNTP exhibits the same acidity differences with respect to these reference compounds in water and methanol.

The exceptional electron-deficient character of the DNTP structure is also demonstrated by the low $pK_a^{'}$ value measured for ionization of the OH group of **C-4a** in aqueous solution [$pK_a^{'\sigma}$ = 8.78 for eqn. (5)]. That the spectral changes shown in Fig. 2 actually deal with the formation of the dianion **D-4a** according to eqn. (5) is supported by the fact that a similar ionization process has been identified at high pH with other structures, such as the DNBF σ-adduct **C-3a** ($pK_a^{'\sigma}$ = 11.80)[3a] or a number of pseudobases derived from quaternary ammonium heterocycles, *e.g.* $pK_a^{'\sigma}$ = 11.15 for **C-10**.[34] Also consistent with the occurrence of eqn. (5) in aqueous solution is that no similar spectral changes take place in basic media in methanol where no ionization of the OCH_3 group of the adducts, *e.g.* **C-3b** and **C-4b**, can be envisioned. Here we note that $pK_a^{'\sigma}$ decreases by 3.5 units on going from **C-3a** to **C-4a**. Based on the pK_a value for ionization of water (pK_a = 15.74),[35] the activating inductive *–I* effect exerted by the negatively charged DNTP

structure of **C-4a** amounts to ~7 pK_a units. Referring as usual to the benzene series, this effect is very impressive since a 2,4,6-trinitrocyclohexadienyl moiety like that of the TNB adduct **C-8a** is reported to exert an activating effect of only 1.5 pK unit on an acidic fragment covalently bound to the sp^3 carbon.[36–38]

Another manifestation of the activation provided by the parent DNTP structure is the rather high acidity of the NH group of the neutral adduct **C-5b** in methanol: pK_a^{NH} = 2.94. As discussed above, this corresponds to a pK_a^{NH} value of 0–0.5 for the related hydrate **C-5a** in aqueous solution. For comparison, we have recently measured a pK_a^{NH} value of 5.79 for ionization of the very stable hydrate **C-12a** ($K^{H_2O} \geq 100$) of 4-aza-6-nitrobenzofuroxan (ANBF), a compound which affords a hydroxy-σ adduct **C-13a** of the same thermodynamic stability as the DNBF adduct **C-3a** ($pK_a^{\sigma} = 3.3$).[39] Based on these figures, going from ANBF to DNTP results in a much greater activating effect on the ionization of the NH group ($\Delta pK_a^{NH} \sim 5–5.5$) than on the overall σ-complexation process ($\Delta pK_a^{\sigma} \sim 3$). Since we have the relation $K_a^{\sigma} = K^{H_2O} K_a^{NH}$(*vide supra*), the hydration of DNTP is therefore less favored than that of ANBF by about 2.5 pK units. With an estimated K^{H_2O} of 0.05–0.1, the hydrate **C-5a** has in fact a stability which falls in the range of those measured for a number of pteridine hydrates,[40–44] *e.g.* K^{H_2O} = 0.29 for the hydrate **C-15a** of unsubstituted pteridine **14**.[40] However, because of the favourable effect of the solvent transfer, the adduct **C-5b** is the predominant neutral form of DNTP in methanol (K^{MeOH}). This is a noteworthy result since data regarding covalent addition of methanol to neutral heterocycles are very sparse in this solvent.[23]



Kinetic studies. Besides the pK_a^{σ} value, the rate constant $k_1^{H_2O}$ for water attack is a parameter which is also revealing of the degree of electrophilicity of an aromatic or heteroaromatic substrate.[1,3a] In fact, the evidence is that no water pathway is operative in the formation of hydroxy σ-adducts of p$K_a \geq 9$, a category which includes not only the reference TNB adduct **C-8a** (pK_a^{σ} = 13.43) but also σ-adducts such as those of tetranitro activated arenes like 1,2,3,5-tetranitrobenzene (pK_a^{σ} = 9.62) or 1,3,6,8-tetranitronaphthalene (pK_a^{σ} = 9.96) as well as the adduct **C-7b** of 2-(4-nitrophenyl)-4,6-dinitrobenzotriazole 1-oxide [pK_a^{σ} = 9; see eqn. (13)].[31,45,46] In the benzotriazole 1-oxide family, however, the *N*-picryl compound **7a** was found to be sufficiently electron deficient (pK_a = 6.70) to undergo predominantly covalent addition of water through a small pH range (7–8).[31] So far, the only reported remarkable situation involving neutral substrates remained the formation of the DNBF adduct **C-3a** (pK_a^{σ} = 3.75) which arises exclusively from efficient water attack on the parent molecule between pH 3 and 7.5.[3a]

In view of the above results, the observed jump to a $k_1^{H_2O}$ value of 1.93 s^{-1} on going from DNBF ($k_1^{H_2O}$ = 0.035 s^{-1}) to DNTP is a nice illustration of the powerful electrophilic character of the latter heterocycle. A similar picture emerges from a comparison of the rate constants k_1^{MeOH} associated with the formation of the adducts **C-3b** and **C-4b** through methanol attack: k_1^{MeOH} = 0.03 s^{-1} for **C-3b**; k_1^{MeOH} = 3.55 s^{-1} for **C-4b**. Thus, the $k_1^{H_2O}$ and k_1^{MeOH} for the σ-complexation of DNTP represent the highest rates ever measured for water or methanol addition at a sp^2 carbon of a neutral aromatic or heteroaromatic structure.

Interestingly, Table 1 shows that the rate constant $k_1^{H_2O}$ for DNTP falls in the domain of the $k_1^{H_2O}$ values reported for water on a number of very reactive heterocyclic cations such as **9** or **10**.[33,34] Only in the case of the doubly charged naphthyridinium cation **11**, water attack takes place more rapidly.[34a] In the three latter systems, however, the resulting pseudobases **C-9**, **C-10** and **C-11** are more prone than the adduct **C-4a** to decomposition through the H^+-catalyzed pathway ($k_{-1}^{H^+}$). As a result, not only the anionic hydroxy σ-complex of DNTP, **C-4a**, but also its DNBF analogue **C-3a**, are thermodynamically more stable than the pseudobase analogues.

Conclusion

The above results provide a quantitative demonstration that the neutral DNTP molecule ranks as one of the most powerful non-charged electrophiles known to date, being in particular more reactive than 4,6-dinitrobenzofuroxan, the standard superelectrophilic reference in σ-complexation and nucleophilic aromatic substitution processes. In view of this finding, studies are presently being developed to assess the high reactivity of DNTP, as well as of DNBF, on the "universal" nucleophilicity–electrophilicity scale recently introduced by Mayr and coworkers.[47] Also, preliminary results regarding the high reactivity of DNTP in Diels–Alder processes are very promising.

Experimental

Materials

4,6-Dinitrotetrazolo[1,5-*a*]pyridine was prepared according to the procedure reported by Lowe-Ma *et al.* (mp: 125 °C; lit.[48] 123 °C).[48] Aqueous HCl solutions were prepared from Titrisol. Methanolic solutions of methanesulfonic acid and of the various buffers employed in this solvent (see text) were prepared as reported before.[3a,b,18] All buffer solutions were made from the best available grades of reagents.

The anionic adducts **C-4a** and **C-4b** were readily prepared as potassium salts by adding slightly less that one equivalent of KOH or CH_3OK to 1 mM solutions of DNTP in 1 ml of Me_2SO at room temperature. After one hour, 10 ml of $CHCl_3$ were added and the resulting solution cooled in an ice bath. When crystals began to deposit, further addition of 5 ml $CHCl_3$ was made and the mixture kept under stirring for another one hour. After filtration, yellow–orange crystals were obtained which were washed with chloroform and then dried thoroughly under vacuum to give the potassium salts in an essentially quantitative yield.

At this point, it should be pointed out that the two salts **C-4a**, K^+ and **C-4b**, K^+ are highly explosive, making them very difficult to handle. As with a number of alkali salts of DNBF σ-adducts, the crystals obtained for these adducts were found to decompose before melting (~170–180 °C). Attempts to obtain satisfactory elemental analysis have failed. However, dissolution of the salts in Me_2SO-d_6 gave ^{1}H and ^{13}C NMR spectra identical to those recorded in the *in situ* generation of the adducts in this solvent.

NMR data for DNTP[48]**.** ^{1}H NMR (δ in ppm, Me_2SO-d_6, Me_4Si): 10.87 (d, 1H, H_5, J_{H7H5} = 1.8 Hz), 9.41 (d, 1H, H_7, J_{H7H5} = 1.8 Hz); for comparison in acetone-d_6: ^{1}H NMR (δ in ppm, Me_4Si): 10.81 (d, 1H, H_5, J_{H7H5} = 1.8 Hz), 9.42 (d, 1H, H_7, J_{H7H5} = 1.8 Hz).[48]

^{13}C NMR (δ in ppm, Me_2SO-d_6, Me_4Si): 148.86 (C_9), 139.62 (C_6), 136.06 (C_4), 132.87 (C_7) 126.54 (C_5).[48]

NMR data for C-4a. ^{1}H NMR (δ in ppm, Me_2SO-d_6, Me_4Si): 8.63 (s, 1H, H_5), 6.36 (broad signal, 1H, OH), 7.21 (s, 1H, H_7).

^{13}C NMR (δ in ppm, Me_2SO-d_6, Me_4Si): 145.78 (C_9, broad signal), 128.27 (C_5, J_{C5H5} = 165.6 Hz, J_{C5H7} = 2.3 Hz), 123.93 (C_6, J_{C6H5} = J_{C6H7} = 5.1 Hz), 108.45 (C_4, J_{C4H5} = 3.4 Hz), 75.07 (C_7, J_{C7H7} = 171.3 Hz, J_{C7H5} = 5.7 Hz).

NMR data for C-4b. ^{1}H NMR (δ in ppm, Me_2SO-d_6, Me_4Si): 8.72 (d, 1H, H_5, J_{H5H7} = 0.70 Hz), 7.06 (d, 1H, H_7, J_{H5H7} = 0.70 Hz), 3.18 (s, 3H, OCH_3).

^{13}C NMR (δ in ppm, Me_2SO-d_6, Me_4Si): 145.92 (C_9, broad signal), 128.57 (C_5, J_{C5H5} = 166.26 Hz, J_{C5H7} = 2.3 Hz), 121.163 (C_6, J_{C6H5} = J_{C6H7} = 5.7 Hz), 108.14 (C_4, J_{C4H5} = 2.9 Hz), 82.45 (C_7, J_{C7H7} = 171.8 Hz, J_{C7H5} = 5.7 Hz), 48.09 (OCH_3, J_{CH} = 139.6).

Rate measurements

Stopped-flow determinations were performed on an Applied-Photophysics spectrophotometer, the cell compartment of which was maintained at 25 ± 0.2 °C. Other kinetic runs were carried out in triplicate under pseudo-first order conditions with a substrate concentration of 2 to 3 × 10^{-5} mol dm^{-3}. All rate constants are accurate to ±3%.

Ab initio calculations

Ab initio calculations of the optimized geometry and Mulliken charges of the adduct **C-4b** have been carried out at the STO-3-21G level using Hyperchem Release 6.03 (Hypercube, 2000).

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