Dual Behavior of 4-Aza-6-nitrobenzofuroxan. A Powerful Electrophile in Hydration and σ-Complex Formation and a Potential Dienophile or Heterodiene in Diels−Alder Type Reactions

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In investigating the reactivities of aza analogues of super-electrophile 4,6-dinitrobenzofuroxan (DNBF, **1**), we have found that the nitro-substituted pyridofuroxan **2** gives a remarkably stable hydrate **3** in aqueous solution (as evidenced by the requirement of ca. 50% H_2SO_4 ($H_0 \sim -3$) for complete recovery of **2**). The equilibrium constant K_{H_2O} for hydration of **2** is estimated to be ≥ 100, being comparable only with the K_{H_2O} values reported for hydration of highly activated neutral polyazaaromatics such as 2- and 6-hydroxypteridines or 7-azapteridine. Interestingly, the NH group of **3** undergoes ionization at rather low pH ($pK_a^{NH} = 5.79$), affording an anionic hydroxy σ-adduct **4** which is thermodynamically 10^8 times more stable than the related σ-adduct of pteridine. The experimental evidence is that **4** is slightly more stable than the hydroxy σ-adduct of DNBF, indicating not only that **2** ranks among the most electrophilic heteroaromatics known to date but also than an aza group may in fact be as efficient as a nitro group in promoting σ-complex formation. **2** is also found to be a versatile Diels−Alder reagent, as a result of the low aromatic character of its six-membered ring. Upon treatment of **2** with cyclopentadiene and 2,3-dimethylbutadiene, various reactivity patterns have been observed. These led to different cycloadducts arising from normal as well as inverse electron-demand condensations involving the pyridine ring as the dienophile or the heterodiene contributor. Altogether, the results reveal major differences between the reactivity of **2** and that of DNBF, with in particular a remarkable tendency of the pyridofuroxan adducts to undergo covalent hydration, resulting in the formation of stable carbinolamines. Also noteworthy is the characterization of a diadduct which results from a Diels−Alder trapping of the o-dinitroso intermediate involved in the exchange of the 1-oxide and 3-oxide tautomers of **2**.

Introduction

The last several decades have witnessed extensive studies of the interaction of electron-deficient aromatics with nucleophiles resulting in the discovery of diverse operative pathways other than the conventional S_NAr pathway,[1] e.g., vicarious nucleophilic aromatic substitution and single electron-transfer processes,[1b,2−5] with significant structure−reactivity relationships. However, a challenging problem which has remained largely unanswered is the quantitative evaluation of aza substitution in the aromatic ring on the aforementioned processes.[6] Moreover, an additional mechanism, namely the ANRORC pathway, can now occur, adding to the complexity of such aza systems.[7−9] An interesting feature which emerges from the available data is that the overall activating effect of an aza functionality can be comparable, and in some instances even greater than that of a nitro substituent.[1b,6,10] However, despite these initially promising results, few in-depth investigations of this phenomenon have appeared over the last 25 years.

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(1) (a) Miller, J. In *Aromatic Nucleophilic Substitution*; Elsevier: Amsterdam, 1968. (b) Terrier, F. In *Nucleophilic Aromatic Displacement*; Feuer, H., Ed.; VCH: New York, 1991. (c) Buncel, E.; Crampton, M. R.; Strauss, M. J.; Terrier, F. In *Electron Deficient Aromatic and Heteroaromatic-Base Interactions. The Chemistry of Anionic Sigma-Complexes*; Elsevier: Amsterdam, 1984. (d) Nudelman, N. S. In *The Chemistry of Amino, Nitroso, Nitro and Related Groups*; Patai, S., Ed.; Supplement F2, Wiley: Chichester, 1996; Chapter 26, p 1215. (e) Buncel, E.; Dust, J. M.; Park, K. T.; Renfrow, R. A.; Strauss, M. J. In *Nucleophilicity*; Harris, J. M., McManus, S. P., Eds.; ACS Advances in Chemistry Series 215; American Chemical Society: Washington, DC, 1987; p 369. (e) Bernasconi, C. F. *M. T. P. Int. Rev. Sci. Org. Chem. Ser. 1* **1973**, *3*, 33.

(2) (a) Makosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282. (b) Makosza, M.; Wojciechowski, K. *Liebigs Ann. Chem.* **1997**, 1805. (c) Makosza, M. *Russ. Chem. Bull.* **1996**, *45*, 491. (d) Makosza, M.; Lemek, T.; Kwast, A. *Tetrahedron Lett.* **1999**, *40*, 7541. (e) Terrier, F.; Goumont, R.; Pouet, M. J.; Hallé, J. C. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1629.

(3) Chupakhin, O. N.; Charushin, V. N.; Van der Plas, H. C. In *Nucleophilic Aromatic Substitution of Hydrogen*; Academic Press: San Diego, 1994.

(4) Makosza, M.; Stalinski, K. *Chem. Eur. J.* **1997**, *3*, 2025.

(5) Paradisi, C.; Scorrano, G. *Acc. Chem. Res.* **1999**, *32*, 958.

(6) (a) Illuminati, G.; Stegel, F. *Adv. Heterocycl. Chem.* **1983**, *34*, 305. (b) Terrier, F.; Chatrousse, A. P.; Schaal, R. *J. Org. Chem.* **1972**, *37*, 3010.

(7) (a) Van der Plas, H. C. *Acc. Chem. Res.* **1978**, *11*, 462. (b) Van der Plas, H. C.; Wozniak, M.;. Van der Haak, H. J *Adv. Heterocycl. Chem.* **1983**, *33*, 96. (c) Charushin, V. N.; Van der Plas, H. C. *J. Org. Chem.* **1983**, *48*, 2667.

(8) (a) Reinheimer, J. D.; Mayle, L. L.; Dolnikowski, G. G. *J. Org. Chem.* **1980**, *45*, 3097. (b) Reinheimer, J. D.; Sourbatis, N.; Lavallée, R. L.; Goodwin, D.; Gould, G. *Can. J. Chem.* **1984**, *62*, 1120.

(9) (a) Al-Lohedan, H. A.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1283. (b) Fox, J. J.; Su, J. L.; Steinpel, I. M.; Watanabe, C. A. *J. Org. Chem.* **1982**, *47*, 1081.

(10) Terrier, F.; Chatrousse, A. P. *Bull. Soc. Chim. Fr.* **1972**, 4549.

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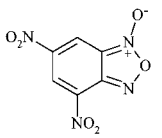
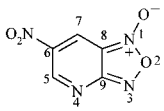
Recent work has revealed the great versatility and extremely high reactivity of nitrobenzofuroxans as reagents in nucleophilic addition and substitution processes, as a result of which the prototypical molecule, 4,6-dinitrobenzofuroxan **1**, also commonly referred to as DNBF, has been accorded super-electrophilic properties.[11−18] Interestingly, **1** has been shown to exhibit dienophilic or heterodienic behavior in Diels−Alder type reactions in several instances.[19−21] It therefore appeared to us that aza substitution in the DNBF molecule could lead to substantial changes in these reactivity patterns. In addition to a quantitative assessment of the effect of the aza functionality in covalent nucleophilic addition, it was envisaged that the Diels−Alder reactivity of **2** would give access to novel heterocyclic structures with potential pharmacological properties. Interestingly, it was found that some of the resulting Diels−Alder adducts undergo subsequent covalent hydration with formation of carbinolamine-type structures, thus adding to their potential pharmalogical properties.[22−24]



DNBF **1**



2

In the present paper we describe the results of a study of 6-nitro[2,1,3]oxadiazolo[4,5-*b*]pyridine 1-oxide **2**,[25,26] as the 4-aza-6-nitro analogue of DNBF **1**. Specifically, we have investigated the covalent hydration of **2**, which has allowed a quantitative comparison of the electrophilic character of this molecule, not only with **1** but also with that of a number of polyazaaromatic compounds.[22−27] As well, the Diels−Alder reactivity of **2** has been studied via reactions with cyclopentadiene and 2,3-dimethylbutadiene; this has led to three types of Diels−Alder adducts, namely a normal Diels−Alder adduct, a hetero Diels−Alder adduct and a di-adduct arising from a minor dinitroso tautomer of **2**.

Table 1. ^{1}H NMR Data for 2 and the Related Hydrate 3 and σ-Adduct 4 Species in Me_2SO-d_6[a]

	H_5	H_7	OH	NH
2	9.47	9.35	-	-
3	8.41	5.91	4.34	12.00
4	8.46	5.78	4.32	-

[a] δ in ppm, internal reference Me_4Si.

Table 2. ^{13}C NMR Data for 2 and the Related Hydrate 3 and σ-Adduct 4 Species in Me_2SO-d_6[a]

	C_5	C_6	C_7	C_8	C_9	coupling constants (Hz)
2	155.24	142.78	123.30	108.45	158.45	$^1J_{C5H5} = 195.54$; $^1J_{C7H7} = 187.35$; $^2J_{C8H7} = 7.63$
3	137.32	128.05	56.02	107.51	150.77	$^1J_{C5H5} = 168.87$; $^1J_{C7H7} = 159.37$; $^2J_{C8H7} = 7.63$; $^3J_{C5H7} = 2.26$; $^3J_{C7H5} = 5.09$; $^3J_{C9H5} = 9.32$

[a] δ in ppm, internal reference Me_4Si.

Results

1. Covalent Hydration of 2. ^{1}H and ^{13}C NMR spectra recorded after dissolution of a sample of **2** in Me_2SO-d_6 consisted of the resonances characteristic of the 4-aza-6-nitrobenzofuroxan structure previously described by Lowe-Ma et al.[25] (Tables 1 and 2). Major changes in the spectra occurred, however, when special care was not taken to protect the Me_2SO solution from moisture. Under these conditions, a new set of signals developed at the expense of those for **2**, consistent with partial conversion of this species to the hydrate **3** as a result of covalent addition at C-7 of adventitious water present in the solvent. Complete conversion of **2** to **3** was in fact achieved in control experiments carried out with direct addition of H_2O to the Me_2SO solution. Notable diagnostic features for structure **3** are the strong shielding of the C_7 carbon and the observation of a NH resonance in the ^{1}H spectra.

The structural evidence obtained from the NMR spectra (Tables 1 and 2) as well as the UV−visible spectra shows that **2** (λ_{max} = 390 nm in MeOH,[26] 401 nm in Me_2SO) exists in aqueous solution essentially in its hydrated form **3** (λ_{max} = 340 nm). No trace of even a minor conversion of **3** to **2** could be detected in dilute to moderately concentrated acid solutions, i.e, 10^{-3}−1 M HCl, and it is only in going to a 50:50 (w/w) H_2SO_4−H_2O mixture, where the amount of free water is strongly decreased, that complete dehydration could be achieved.[28] As shown in Figure 1, there is then reappearance of a

(11) (a) Gasco, A.; Boulton, A. J. *Adv. Heterocycl. Chem.* **1981**, *203*, 6224. (b) Ghosh, P. B. *J. Chem. Soc. (B)* **1968**, 334.
(12) (a) Terrier, F.; Millot, F.; Norris, W. P. *J. Am. Chem. Soc.* **1976**, *98*, 5883. (b) Buncel, E.; Dust, J. M.; Terrier, F. *Chem. Rev.* **1995**, *95*, 2261. (c) Terrier, F.; Chatrousse, A. P.; Soudais, Y.; Hlaibi, M. *J. Org. Chem.* **1984**, *49*, 4176. (d) Terrier, F.; Hallé, J. C.; Pouet, M. J. P.; Simonnin, M. P. *Ibid. Idem.* **1986**, *51*, 410. (e) Terrier, F.; Kizilian, E.; Hallé, J. C.; Buncel, E. *J. Am. Chem. Soc.* **1992**, *114*, 1740. (f) Terrier, F.; Pouet, M. J.; Hallé, J. C.; Hunt, S.; Jones, J. R.; Buncel, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1665.
(13) (a) Strauss, M. J.; Renfrow, R. A.; Buncel, E. *J. Am. Chem. Soc.* **1983**, *105*, 2473. (b) Buncel, E.; Renfrow, R. A.; Strauss, M. J. *J. Org. Chem.* **1987**, *52*, 488. (c) Manderville, R. A.; Buncel, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1887. (d) Buncel, E.; Manderville, R. A.; Dust, J. M. *Ibid. Idem.* **1997**, 1019.
(14) (a) Spear, R. J.; Norris, W. P.; Read, R. W. *Tetrahedron Lett.* **1983**, *24*, 1555. (b) Norris, W. P.; Spear, R. J.; Read, R. W. *Aust. J. Chem.* **1983**, *36*, 297.
(15) (a) Crampton, M. R.; Rabbitt, L. C. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1669. (b) Crampton, M. R.; Rabbitt, L. C.; Terrier, F. *Can. J. Chem.* **1999**, *77*, 639. (c) Terrier, F.; Pouet, M. J.; Gzouli, K.; Hallé, J. C.; Outurquin, F.; Paulmier, C. *Ibid. Idem.* **1998**, *76*, 937.
(16) (a) Kind, J.; Niclas, H. J. *Synth. Commun.* **1993**, *23*, 1569. (b) Niclas, H. J.; Göhrmann, B.; Gründemann, E. *Ibid. Idem.* **1991**, *21*, 909.
(17) Ghosh, P. B.; Ternai, B.; Whitehouse, M. W. *Med. Res. Rev.* **1981**, *2*, 159.
(18) (a) Evgen'yev, M. I.; Garmonov, S. Y.; Evgen'yeva, I. I.; Goryunova, S. M.; Pogorel'tsev, V. I.; Levinson, F. S. *Talanta*, **1998**, *45*, 1465. (b) Evgen'yev, M. I.; Garmonov, S. Y.; Evgen'yeva, I. I.; Gazizullina, L. S. *J. Anal. Chem.* **1998**, *53*, 571.
(19) Kresze, G.; Bathelt, H. *Tetrahedron* **1973**, *29*, 1043.
(20) (a) Vichard, D.; Hallé, J. C.; Huguet, B.; Pouet, M. J.; Riou, D.; Terrier, F. *Chem. Commun.* **1998**, 791. (b) Hallé, J. C.; Vichard, D.; Pouet, M. J.; Terrier, F. *J. Org. Chem.* **1997**, *62*, 7178. (c) Pugnaud, S.; Masure, D.; Hallé, J. C.; Chaquin, P. *J. Org. Chem.* **1997**, *62*, 8687.
(21) (a) Sepulcri, P.; Hallé, J. C.; Goumont, R.; Riou, D.; Terrier, F. *J. Org. Chem.* **1999**, *64*, 9254. (b) Sepulcri, P.; Goumont, R.; Hallé, J. C.; Marrot, J., Terrier, F. *J. Chem. Soc., Perkin Trans. 2* **2000**, 51.
(22) (a) Albert, A. *Adv. Heterocycl. Chem.* **1976**, *20*, 117. (b) Albert, A.; Armarego, W. L. F. *Ibid. Idem.* **1965**, *4*, 1. (c) Perrin, D. D. *Ibid. Idem.* **1965**, *4*, 43.
(23) Jones, W.; Wolfenden, R. *J. Am. Chem. Soc.* **1986**, *108*, 7444.
(24) Erion, M. D.; Reddy, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 3295.
(25) Lowe-Ma, C. K.; Nissan, R. A.; Wilson, W. S. *J. Org. Chem.* **1990**, *55*, 3755.
(26) Ayyangar, N. R.; Madan Kumar, S.; Srinivasan, K. V. *Synthesis* **1987**, 616.
(27) Bunting, J. W. *Adv. Heterocycl. Chem.* **1979**, *25*, 1.

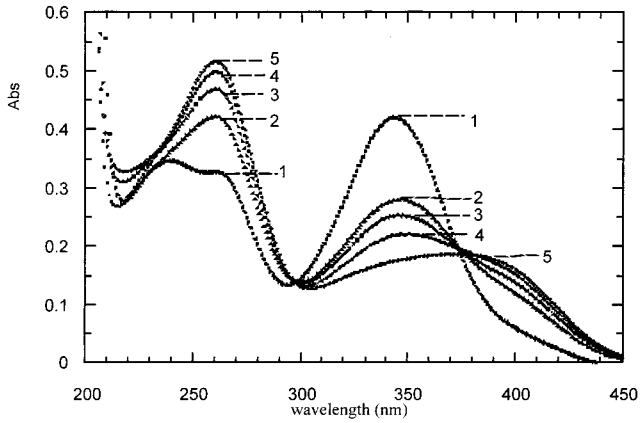
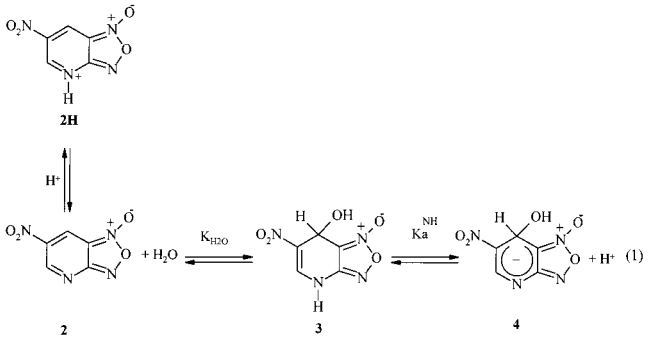


Figure 1. Effect of acidity on the UV−vis spectrum of the hydrate **3** in aqueous H_2SO_4 (in % by weight of H_2SO_4): (1) H_2SO_4 0.1 mol L^{-1}; (2) 29.81%; (3) 33.78%; (4) 41.17%; (5) 46.8%.

UV−visible spectrum which is very similar to that recorded for the unhydrated molecule in various solvents.[25] A remarkable feature of Figure 1, however, is that the set of spectra associated with the dehydration of **3** in the various $H_2O-H_2SO_4$ mixtures studied shows two relatively well-defined isobestic points, at 295 and 375 nm. Notwithstanding the fact that protonation of an azaaromatic compound is known to produce only small changes in the UV−visible spectrum,[22] the presence of the isobestic points in Figure 1 suggests that the process results only in the recovery of neutral **2** rather than of a mixture of **2** and its conjugate monocationic acid **2H**. This idea is supported by the accumulated evidence that the six-membered ring of **2** is extremely electron-deficient, thereby rendering the protonation of the pyridyl-type nitrogen very difficult, even at the lowest H_0 values involved in our experiments ($H_0 = -3.30$ in 50% H_2SO_4 by weight).[28] In fact, the ^{1}H NMR spectra recorded after direct dissolution of **2** in pure methanesulfonic acid show no evidence for formation of the cation **2H**.



Complete conversion of **3** to the yellow-colored anion **4** (λ_{max} = 393 nm) occurs according to eq 1 in 10^{-3} M aqueous sodium hydroxide solution. The pH dependence of the UV−visible spectra associated with this conversion between pH 4 and 8 is shown in Figure 2. From the absorbance changes at λ_{max} of **4**, a pK_a of 5.79 is derived for the formation of **4** from **3**. Similar changes in the

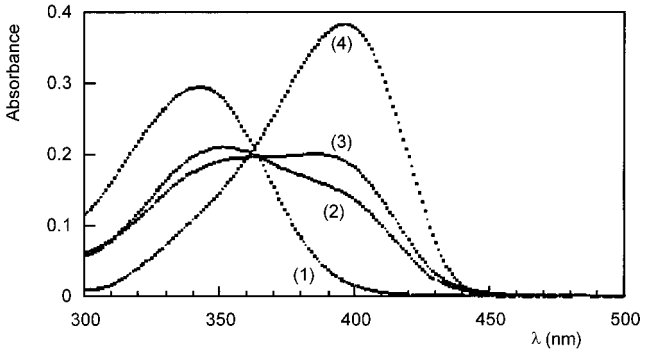


Figure 2. Effect of pH on the ionization of the hydrate **3** to the σ-adduct **4**: (1) pH = 4.3; (2) pH = 5.1; (3) pH = 6.1; (4) pH = 8.1.

electronic spectra occur in DMSO. ^{1}H and ^{13}C NMR data obtained in the presence of base in this solvent agree fully with the formation of **4**. In particular, a major feature is the absence of a NH signal in the ^{1}H spectrum of **4**.

2. Reaction of 2 with Cyclopentadiene. Treatment of **2** with a large excess of cyclopentadiene (5 equiv) in dichloromethane overnight at room temperature led, after addition of pentane, to the isolation of a yellow solid in good yield. A detailed analysis of the ^{1}H and ^{13}C NMR spectra of the product recorded in $CDCl_3$ (Tables 3 and 4) indicates that it may be formulated as one of the two cycloadducts **5a** or **5b** (in their racemic form) resulting from a regioselective and diastereoselective Normal Electron Demand Diels−Alder (NEDDA) process involving the C_6C_7 double bond of **2** as the dienophile component. Although we failed to achieve successful NOE experiments, the evidence obtained from previously characterized nitrobenzofuroxan NEDDA adducts leaves little doubt that the isolated adduct is the adduct **5a**.[21]

IR data are also in agreement with the structure of **5a** ($\nu_{C=C}$ = 1609 cm^{-1} and $\nu_{C=N}$ = 1646 cm^{-1}). Interestingly, redissolution of **5a** in Me_2SO-d_6 or Me_2CO-d_6 gave rise to the slow disappearance of the signals due to this adduct and the concomitant appearance of signals due to a new species which can be identified as the hydrate **6** resulting from reaction with adventitious water in the solvents. The main NMR features were the signals of two labile protons which could be suppressed by addition of D_2O (δ = 8.37, δ = 7.20), and the resonances of the carbon C_5 and its related proton H_5 (δ_{H5} = 5.48, δ_{C5} = 78.71) which are consistent with a sp^3 carbon. NOE experiments were very useful to discriminate between the three protons H_7, H_{10}, and H_{13} which have very close chemical shifts. Even though not totally conclusive, the finding that irradiation of H_{14} did not affect the resonance of H_7 gives some support to our above assignment of structure **5a** to the precursor adduct of **6**.

Mass spectroscopic data are also in agreement with the structures **5a** and **6**. Besides molecular peaks (m/z = 266 and 248 for **6** and **5a**, respectively), the spectra (EI) exhibit base peaks corresponding to loss of a NO_2 group (m/z = 202 for **5a**). Other daughter peaks may be explained, for example, by the loss of cyclopentadiene (m/z = 182 for **5a**) or the successive loss of NO and H_2O (m/z = 200 for **5a**).

A more complicated reactivity pattern was observed when the reaction of **2** with cyclopentadiene was initially carried out at −20 °C. In this instance, the NMR spectra revealed the presence of three compounds in a 9/9/1 ratio.

(28) (a) Hammett, L. P. In *Physical Organic Chemistry*; McGraw-Hill: New York, 1949; p 262. (b) Johnson, C. D.; Katritzky, A. R.; Shapiro, S. A. *J. Am. Chem. Soc.* **1969**, *92*, 6654. (c) Cox, R. A.; Yates, K. *Can. J. Chem.* **1983**, *61*, 2225. (d) Jorgensen, M. J.; Harter, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 878.

Table 3. ^{1}H NMR Data for the Adducts and Related Hydrates Resulting from the Reaction of 2 with Cyclopentadiene (5a, 6, 7) and 2,3-Dimethylbutadiene (11, 12)[a]

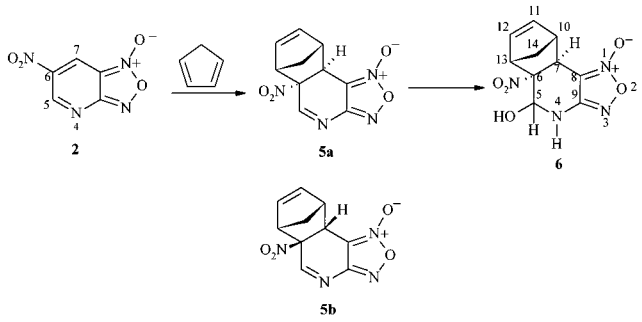
compds	H_5	H_7	H_{10a}	H_{10b}	H_{11}	H_{12}	H_{13a}	H_{13b}	H_{14a}	H_{14b}	coupling constants (Hz)
5a[b]	8.38	3.84	3.84	–	6.18	6.65	3.59	–	1.73	1.30	$^3J_{H10-H11} = 2.87$; $J_{H11-H12} = 5.55$; $^3J_{H12-H13} = 3.15$; $J_{H14a-H14b} = 10.36$
6[c]	5.48	3.66	3.56	–	6.52	6.08	3.19	–	1.67	1.51	$^3J_{H5-OH} = 3.60$; $^3J_{H10-H11} = 3.12$; $J_{H11-H12} = 5.55$; $J_{H12-H13} = 2.85$; $J_{H14a-H14b} = 9$
7[b]	8.66	4.26	4.02	–	5.92		6.17	–	2.57	1.97	$^3J_{H7-H10} = 5.58$; $J_{H14a-H14b} = 18.37$
11[b]	8.11	4.16	3.02	2.55	1.70	1.70	2.55	2.55	–	–	$^3J_{H7-H10b} = 5.60$; $J_{H10a-H10b} = 17.44$
12[c]	5.07	4.17	3.12	2.38	1.56	1.53	2.74	2.47	–	–	$^3J_{H5-OH} = 4.10$; $^3J_{H5-NH} = 3.93$; $^3J_{H7-H10b} = 6.90$; $J_{H10a-H10b} = 18.22$; $J_{H13a-H13b} = 19.03$

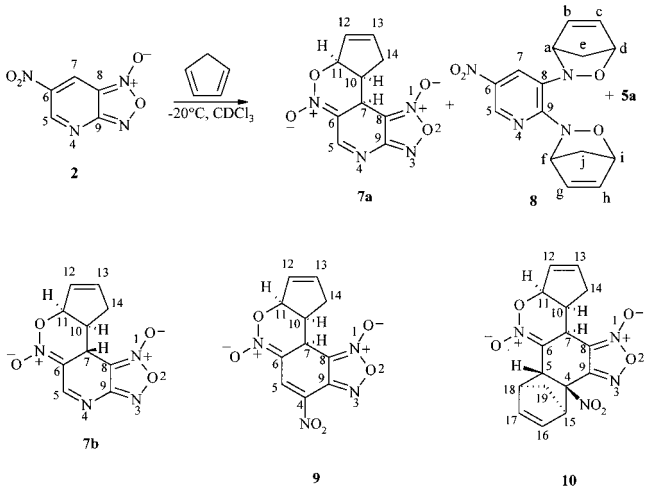
[a] δ in ppm, internal reference Me_4Si. [b] Solvent $CDCl_3$. [c] Solvent Me_2SO-d_6.

Table 4. ^{13}C NMR Data for the Adducts and Related Hydrates Resulting from the Reaction of 2 with Cyclopentadiene (5a, 6, 7) and 2,3-Dimethylbutadiene (11, 12)[a]

compounds	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}	C_{13}	C_{14}	CH_3 11	CH_3 12
5a[b]	163.77	95.26	37.41	102.19	155.80	54.03	133.20; 140.91		46.70	45.71	–	
6[c]	78.71	100.05	36.07	108.06	155.75	45.89	136.06; 139.58		50.98	46.29	–	
7[b]	155.04	119.09	31.93	102.44	150.64	37.04	93.18	126.62	141.06	34.72	–	
11[b]	166.85	87.48	31.76	102.28	154.80	27.11	125.74; 121.25		36.93	–	18.79; 18.46	
12[c]	77.75	89.39	27.07	101.15	153.44	23.86	122.79; 120.07		34.73	–	18.42; 18.10	

[a] δ in ppm, internal reference Me_4Si. [b] solvent $CDCl_3$. [c] solvent Me_2SO-d_6.





Notably, one of the two major products was identical to **5a**, and this aids in analyzing the complex NMR spectrum, allowing one to assign structures **7a** (or **7b**) and **8** to the two other products obtained in 9/1 ratio. As diagnostic features typical of the formation of the two species **5a** and **7a** (or **7b**) were the appearance of two singlets ($\delta = 8.41$ for **5a**, $\delta = 8.66$ for **7a** (or **7b**)) for H_5, a broad signal ($\delta = 3.87$), and a doublet ($\delta = 4.27$) assignable to the proton H_7 for **5a** and **7a** (or **7b**), respectively, and finally a multicoupled signal ($\delta = 4.02$) typical of the proton H_{10} in **7a** (or **7b**) (Tables 3 and 4). While it is noteworthy that the inverse electron demand Diels–Alder process leading to the latter adduct proceeds diastereoselectively, it has proved very difficult to discriminate between the two diastereomeric structures **7a** and **7b** through NOE experiments. The close analogy between the $^3J_{H7H10}$ coupling constant in the resulting structure ($^3J_{H7H10} = 5.58$ Hz) and the related DNBF monoadduct **9** ($^3J_{H7H10} = 5.9$ Hz) and diadduct **10** ($^3J_{H7H10} = 5.40$ Hz) suggest, however, that the stereochemistry shown in **7a** is favored.[21a]

As expected, raising the temperature to 0 °C led to some clarification of the spectrum due to complete conversion of the adduct **7a** into **5a** while the signals due to **8** remained unaffected.

For structure **8**, characteristic chemical shifts were observed for the aromatic protons H_5 and H_7 at 8.73 and 7.86 ppm, respectively, while the multiplets centered at 5.52, 5.45, and 5.36 ppm were assignable to the O–CH and N–CH protons deshielded by the electron-withdrawing effect of the oxygen and nitrogen atoms (NMR data of **8** are reported in the Experimental Section).

3. Reaction of 2 with 2,3-Dimethylbutadiene. When 2 equiv of 2,3-dimethylbutadiene were added to a solution of **2** in $CDCl_3$, the ^{1}H NMR spectra recorded directly after mixing of the reagents showed the disappearance of the signals due to the starting material and the concomitant appearance of new sets of signals indicating the formation of a new product. On the basis of a detailed analysis of the ^{1}H and ^{13}C NMR spectra, this product could be identified as the adduct **11**.The resonances of the various protons and carbons were unambiguously assigned by 2D (COSY 90 and HETCOR) and NOE experiments. The data are reported in Tables 3 and 4.

Interestingly, carrying out another experiment, under similar conditions, but with a longer reaction time, did not allow the isolation of **11**, but instead the hydrate **12** formed as a pale yellow solid, resulting from the reaction of **11** with adventitious water in the solvent. The structure of **12** was determined by X-ray crystallography (only one of the two crystallographic structures present in the cell is given in Figure 3) which confirmed that addition of H_2O has taken place at the C_5–N double bond.

In accordance with the structures of **11** and **12** was the observation in the ^{1}H NMR spectra of ABC systems reflecting the coupling of the two nonequivalent methylenic protons H_{10a} and H_{10b} with the H_7 proton of the

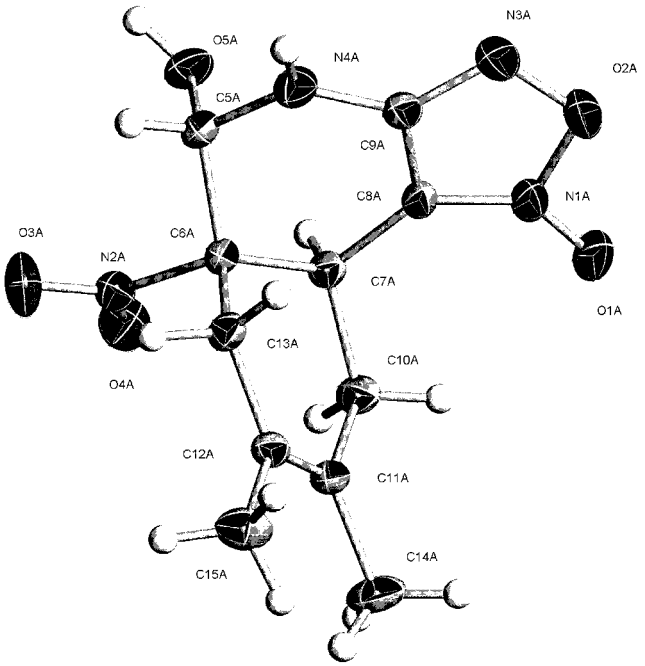
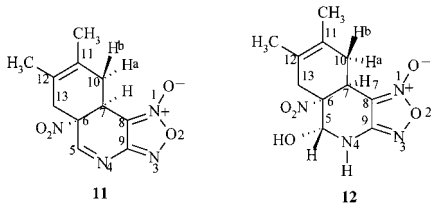


Figure 3. ORTEP view of the adduct **12**.

carbocyclic ring (**11**: $\delta_{H10a} = 2.55$, $\delta_{H10b} = 3.02$, $^3J = 5.60$ Hz; **12**: $\delta_{H10a} = 2.79$, $\delta_{H10b} = 3.22$, $^3J = 6.60$ Hz).



11 **12**

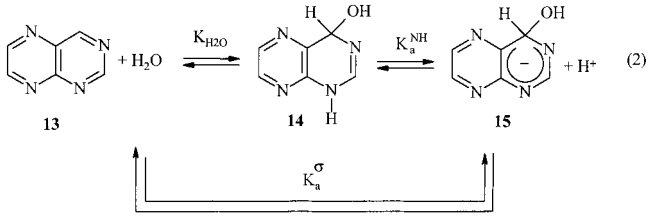
The stereochemistry assigned to **12** is in full agreement with the detailed NMR analysis. Saturation of H_7 showed a positive response with H_{10a} at 2.79 ppm; this NOE was in full accord with the distance obtained by X-ray crystallography: $d_{H7-H10a} = 2.186$ Å. A similar NOE was observed in the case of the cycloadduct **11**: saturation of H_7 showed a positive response with H_{10a} at 2.55 ppm. Mass spectroscopic data are in agreement with the structure of compound **12**. Besides molecular peaks ($m/z = 282$), the spectra (EI) exhibit base peaks corresponding to loss of a NO_2 group ($m/z = 236$). Other daughter peaks may be accounted for by the successive loss of NO and H_2O ($m/z = 234$). IR spectra are also in accord with the above structure ($\nu_{C=C} = 1609$).

Discussion

Two types of reactivity are to be discussed for our aza system, the first referring to the electrophilic nature of the molecule, and the second to its properties as a dienophile or a heterodiene undergoing Diels−Alder reactions. Such a dual behavior is reminiscent of that observed with DNBF, further emphasizing the versatile character of nitrobenzofuroxans.[11−21]

Covalent Hydration, Structure−Reactivity Correlations. The results described above reveal a remarkable case in covalent hydration of the azabenzofuroxan **2**. It is especially noteworthy that this addition process occurs with a neutral compound since covalent addition of water across −C=N− bonds occurs in general much more readily with cationic than with neutral nitrogen-containing heterocycles.[24,25,27,28] So far, only a few strongly activated neutral polyazaaromatics, e.g., 2- and 6-hydroxypteridines or 7-azapteridine, have been reported to undergo essentially complete conversion to the related neutral hydrates in aqueous solution.[22b,29−32] Interestingly, full dehydration of these species occurs at similar H_0 values (∼−3) as that of the hydrate **3** in $H_2O-H_2SO_4$ mixtures. It follows that the electrophilic character of **2** must be of the same order as, or greater than, that of the above-mentioned polyazaaromatics for which the equilibrium constants K_{H_2O} measuring the extent of hydration have been found to fall in the range 100−1000.[24,29−33]

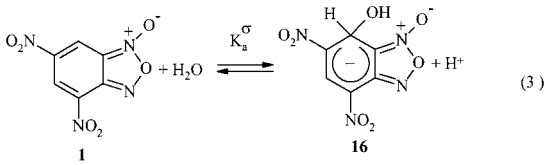
Regarding the electron-deficient nature of the pyridyl ring of **2**, comparison of the behavior of this heterocycle with that of the unsubstituted pteridine **13** is also very revealing. Although this latter compound is not fully hydrated in aqueous solution (the ratio of the hydrated neutral species **14** to the anhydrous neutral species is reported to be 0.29 at 20 °C[22c,35]), the pK_a value for the ionization of the aza group of **14** to give the anionic σ-adduct **15** according to eq 2 could be measured; $pK_a^{NH} = 11.21$.[22b,36] This value is more than 5 pK units higher than that determined in this work for the conversion of the hydrate **3** into the anionic σ-complex **4** ($pK_a^{NH} = 5.79$). Such a considerable difference in acidity of the NH group of **14** and **3** shows clearly that the azanitrobenzofuroxan structure is intrinsically more electron-withdrawing than the related tetraazanaphthalene structure, providing in particular an especially high capability of resonance delocalization of negative charge in adduct **4** over the furoxan ring and the aza and nitro substituents.



Focusing on reactivity in the benzofuroxan series, it is appropriate to compare the susceptibility to water addition for the aza molecule **2** with that of its 4,6-dinitro analogue **1**. As reported earlier,[11a,37] **1** reacts very readily

(29) Brown, D. J.; Mason, S. F. *J. Chem. Soc.* **1956**, 3443.
(30) Albert, A. *J. Chem. Soc.* **1955**, 2690.
(31) (a) Inoue, Y.; Perrin, D. D. *J. Chem. Soc.* **1962**, 2600. (b) Perrin, D. D.; Inoue, Y. *Proc. Chem. Soc.* **1960**, 342.
(32) Biffin, M. E. C.; Brown, D. J.; Sugimoto, T. *J. Chem. Soc.* (*C*) **1970**, 139.
(33) The H_0 values required for the dehydration of **3** in $H_2O-H_2SO_4$ mixtures are also closely reminiscent of those reported for the dehydration of a number of stable hydrates derived from protonated forms of heteroaromatics such as quinazoline-3-oxide, 8-nitro-1,6-naphthyridine, or 1,4,6-triazanaphthalene.[34] In these instances, K_{H_2O} values ≥ 100 have also been measured or estimated, thereby confirming the above conclusion than the related equilibrium constant for the hydration of **2** may reasonably be estimated as falling in the range 100−1000.
(34) (a) Albert, A.; Armarego, W. L. F.; Spinner, E. *J. Chem. Soc.* **1961**, 2689. (b) Armarego, W. L. F. *Ibid. Idem.* **1962**, 5030. (c) Albert, A.; Armarego, W. L. F. *Ibid. Idem.* **1963**, 4237. (d) Perrin, D. D.; Inoue, Y. *J. Phys. Chem.* **1962**, *66*, 1689. (e) Albert, A.; Armarego, W. L. F.; Spinner, E. *J. Chem. Soc.* **1961**, 5267. (f) Albert, A.; Barlin, G. B. *Ibid. Idem.* **1963**, 5156.
(35) Perrin, D. D. *J. Chem. Soc.* **1962**, 645.
(36) Albert, A.; Brown, D. J.; Wood, H. C. S. *J. Chem. Soc.* **1956**, 2066.
(37) Terrier, F. *Chem. Rev.* **1982**, *82*, 77.

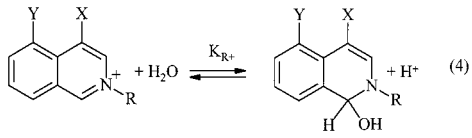
with water through an addition process according to the equilibrium shown in eq 3. A pK_a value of 3.73 was measured for formation of the resulting hydroxy σ-complex **16** at 25 °C in aqueous solution,[12a] but it is evident that the process of eq 3 does not compare directly to the reversible hydration equilibrium of **2** (eq 1). It turns out, however, that the sum of the hydration and NH-ionization reactions of **2** is equivalent to the σ-complexation process of eq 3, implying the relationship $K_a^{\sigma} = K_{H_2O} \times K_a^{NH}$, which may be also applied to the overall process for σ-complexation of pteridine in eq 2. If one therefore assumes that K_{H_2O} for **2** is in the range of 100−1000, then the pK_a value for direct formation of the anionic σ-complex **4** can be estimated as being equal to or somewhat lower than that for **1**, i.e., pK_a^2 falls in the range of 2.8−3.8. This emphasizes not only a slightly higher or similar stability of the adduct **4** relative to its DNBF analogue **16** but also a 10^8 times greater stability of the two benzofuroxan complexes relative to the pteridine model **15** (pK_a^{15} = 11.74). On the other hand, the comparison of the behavior of **1** and **2** adds to the sparse evidence that the overall activating effect of an aza functionality can in some instances be somewhat greater than that of a nitro substituent.[6,10,37,38]



(3)

1 **16**

Even though they refer to equilibria which do not correspond totally in charge type, it is worth noting that the pK_a values for formation of adducts **4** and **16** are comparable to the pK_{R+} values reported for pseudobase formation from various quaternary nitrogen heterocyclic cations.[27] Prototype examples are the isoquinolinium cations of the general structure **17** shown in eq 4 for which pK_{R+} values in the range 5.11−12.61 have been reported in aqueous solution.[27,39] The fact that **1** and **2**, i.e., two neutral species, show higher susceptibility to nucleophilic addition than the most electrophilic quinolinium cation in the series, i.e., **17a**, again emphasizes the strongly electron deficient character of the six-membered ring of the nitrobenzofuroxans. A further revealing comparison can be made with addition of H_2O to the tropylium cation for which the pK_{R+} value of 4.75 has been reported.[40]



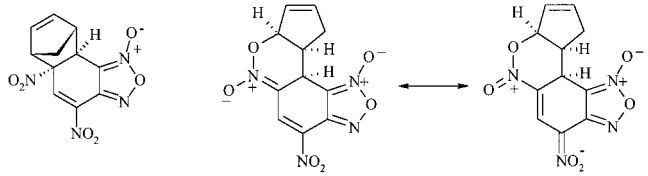
(4)

17 **18**

(a) X = NO_2, Y = H, R = Me
(b) X = H, Y = NO_2, R = Me, Et, n-Pr, sec Bu, CH_2-C_6H_5, CH_2-C_6H_4-NO_2(p), $CH_2COC_6H_5$, CN, CH_2CN

Altogether, the above results provide a clear demonstration of the efficient activation provided by an aza functionality in promoting nucleophilic processes.

Reaction of 2 with Cyclopentadiene and 2,3-Dimethylbutadiene: NEDDA and IEDDA Reactivities. Proceeding to Diels−Alder reactivity, an interesting comparison arises between the behavior of **1** and **2**. Thus, it is found that the reaction of **2** with cyclopentadiene at room temperature affords exclusively a cycloadduct arising from a normal-electron-demand Diels−Alder (NEDDA) condensation involving the nitro-activated C_6C_7 double bond as the dienophile contributor. Carrying out the same experiment at −20 °C reveals, however, the formation of adduct **7a**, this latter compound being the result of a competitive Diels−Alder reaction in which the aza molecule now acts as a heterodiene through its $O_6N_6C_6C_7$ fragment. Interestingly, this adduct becomes slowly converted to its NEDDA counterpart **5a** when the temperature is allowed to rise to 20 °C. These observations show that **7a** is the product of kinetic control while **5a** is the thermodynamically more stable product of reaction. This contrasts directly with the situation found in the case of DNBF where it is now the NEDDA adduct **19** which is formed under kinetic control and subsequently disappears to give the hetero Diels−Alder adduct **9** as the final monoadduct of the reaction.[21a] A reasonable explanation of this different behavior may be in terms of the relative capabilities of the NO_2 and aza functionalities to stabilize the inverse-electron-demand Diels−Alder (IEDDA) adduct through a −M effect, i.e., structure **9a**.[37] Interestingly, the overall behaviors of **2** and DNBF may be compared to that of nitroalkenes which are known to react as dienophiles or heterodienes depending upon the experimental conditions at hand.[41]

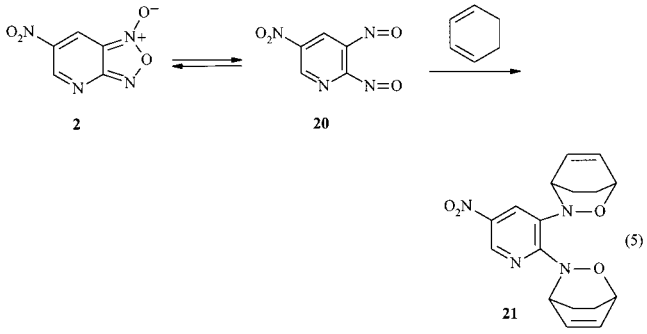


19 **9** **9a**

Also to be noted is that the reaction of **2** with cyclopentadiene at −20 °C gives rise to a minor product (∼5%) which can be identified as the bis Diels−Alder diadduct **8**. This adduct shows no decomposition on raising the temperature to room temperature and can be assigned to reaction of the ortho dinitroso tautomer **20** of **2** with the two NO groups acting as dienophiles toward the cyclopentadiene molecule.[42] Interestingly, we have recently reported that an analogous diadduct, i.e., **21**, is formed as the major product in the reaction of **2** with cyclohexadiene (eq 5).[43] This represented the first evidence of Diels−Alder trapping of a nitroso tautomer in a benzofuroxan system. Our present results therefore substantiate the intermediacy of nitroso taut-

(38) Terrier, F.; Chatrousse, A. P.; Schaal, R. *J. Chem. Res.* **1977**, *5*, 228; (M) 2413.
(39) (a) Bunting, J. W.; Meathrel, W. G. *Can. J. Chem.* **1973**, *51*, 1965. (b) *Ibid. Idem.* **1974**, *52*, 303, 966. (c) Bunting, J. W.; Norris, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 1189.
(40) Ritchie, C. D.; Fleischhauer, H. *J. Am. Chem. Soc.* **1972**, *94*, 3481.
(41) (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137 and references therein. (b) Denmark, S. E.; Hurd, S. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668. (c) Denmark, S. E.; Marcin, L. R. *Ibid. Idem.* **1997**, *62*, 1675. (d) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1998**, *63*, 6167, 6178.
(42) Boger, D. B.; S. N. Weinreb In *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987; pp 71−93.
(43) Sebban, M.; Goumont, R.; Hallé, J. C.; Marrot, J.; Terrier, F. *J. Chem. Soc., Chem. Commun.* **1999**, 1009.

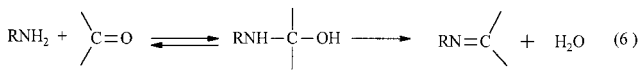
omers in the 1-oxide/3-oxide interconversion of benzofuroxans.[11a,44−47]



(5)

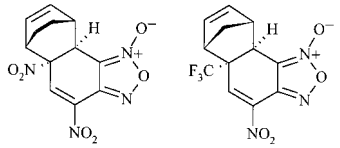
Another unique reactivity pattern of the aza molecule is our observation that the NEDDA adduct **5a** slowly (∼1 h) undergoes addition of water present adventitiously in either Me_2SO or Me_2CO solution to afford the hydrate **6**. Interestingly, a similar situation is found to occur in the reaction of **2** with 2,3-dimethylbutadiene where the sole adduct is the NEDDA adduct **11**. In this instance, **11** was firmly identified by ^1H and ^{13}C NMR but underwent facile addition of H_2O to give the hydrate **12**, as confirmed by the X-ray structure of Figure 3. The more facile hydration of **11** as compared with **5a** can readily be explained by the fact that the presence of the bridging methylene in **5a** effectively precludes approach of the water molecule from one face, as revealed by inspection of molecular models.

Our results pertaining to the hydration of the two adducts **5a** and **11** show an interesting contrast with what is commonly observed in the reversible formation of imines from the reaction of amine nucleophiles with carbonyl compounds proceeding via carbinolamine intermediates (eq 6).[48,49] In these systems, normally used for characterization of carbonyl compounds, the carbinolamine is in general an intermediate on the way to the stable imine derivatives. Viewing **5a** and **11** as imines, one might have expected formation of the hydrates **6** and **12** as analogues of carbinolamines in eq 6, being therefore thermodynamically less stable than their imine precursors. The observed reversal of the equilibrium can, however, be readily explained on the basis that the C_5N_4 double bond of **5a** and **11** is strongly activated to nucleophilic attack by the vicinal furoxan moiety. In this regard, it is noteworthy that the covalent hydrates observed in the pteridine series are among the few stable carbinolamines so far reported.[27]



(6)

As observed in the previously studied nitrobenzofuroxan systems,[20,21] it is a remarkable feature that the reaction of **2** with cyclopentadiene as well as with 2,3-dimethylbutadiene occurs with high stereospecificity. In the latter system, the X-ray-determined structure of the hydrate **12** shows conclusively that this pseudobase as well as its NEDDA precursor adduct have a cis junction between the two rings, with the hydrogen and the NO_2 groups being on the same side. Such a diastereospecificity was also firmly established in formation of the related monoadducts **22**[21a] and **23**.[21b] By analogy, it is reasonable to assume that the adduct **5a** is formed with a similar trans arrangement of the bridge and the hydrogen and NO_2 groups, although the configuration cannot be firmly defined with the presently available evidence. On the other hand, the stereochemistry of the corresponding IEDDA adduct **7a** can be reasonably suggested (vide supra) as being similar to that of other identified dihydrooxazine *N*-oxides previously studied in the DNBF series.[20a,b,21a]



Experimental Section

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. Electronic Impact mass spectra (EI, 70 eV) were obtained using a spectrometer equipped with a quadrupole. Elemental analyses were determined by the Microanalytical laboratory of the University Paris VI, France. X-ray data for adduct **12** were collected on a three-circle diffractometer equipped with a bidimensional CCD detector. All these data, together with the details of their acquisition, are given as Supporting Information (Tables S_1-S_3).[50]

Materials. 6-Nitro[2,1,3]oxadiazolo[4,5-*b*]pyridine 1-oxide **2** (mp: 95 °C, lit. 93−4 °C)[22] was prepared from the thermal decomposition of the corresponding 4,6-dinitrotetrazolo[1,5-*a*]-pyridine.[22] Cyclopentadiene, obtained from the heating of bicyclopentadiene, and commercial 2,3-dimethylbutadiene were used without further purification.

Preparation of 5a. Excess cyclopentadiene (5 mL, >10 equiv) was added to a solution of **2** (270 mg, 1.48 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The solution turned to orange, and the reaction mixture was stirred at 0 °C for 5 days. Addition of pentane resulted in the immediate formation of a precipitate which was collected by filtration and dried under vacuum. The cycloadduct **5a** was obtained quantitatively as a dark yellow solid.

Selected data for 5a: mp: 110 °C; *m/z* (EI): 248 ($M^{+\bullet}$), 202 ($M^{+\bullet} - NO_2$), 200 ($M^{+\bullet} - NO - H_2O$), 182 ($M^{+\bullet} - C_5H_6$); HRMS calcd for $C_{10}H_8N_4O_4$ ($M^{+\bullet}$) 248.05455, found *m/e* 248.05455; NMR data are collected in Tables 3 and 4.

(44) (a) Gallos, J. K.; Malamidou-Xenikaki, E. *Heterocycles* **1994**, *37*, 193. (b) Argylopoulos, N. G.; Gallos, J. K.; Nicolaides, D. N. *Tetrahedron* **1986**, *42*, 3631. (c) Bulacinski, A. B.;. Scriven, E. F. V; Suschitzky, H. *Tetrahedron Lett.* **1975**, 3577. (d) McFarland, J. W. *J. Org. Chem*. **1971**, *36*, 1842.

(45) (a) Yavari, I.; Botto, R. E.; Roberts, J. D. *J. Org. Chem*. **1978**, *43*, 2542. (b) Anet, F. A. L.; Yavari, I. *Org. Magn. Reson.* **1976**, *8*, 158. (c) Witanowski, M.; Stefaniak, L.; Biernat, S.; Webb, G. A. *Ibid. Idem.* **1980**, *14*, 365. (d) Mallory, F. B.; Manatt, S. L.; Wood, C. S. *J. Am. Chem. Soc.* **1965**, *87*, 5433.

(46) (a) Harris, R. K.; Katritzky, A. R.; Øksne, S.; Bailey, A. S.; Patterson, G. *J. Chem. Soc.* **1963**, 197. (b) Eckert, F.; Rauhut, G.; Katritzy, A. R. *J. Am. Chem. Soc.* **1999**, *121*, 6700. (c) Katritzky, A. R.; Gordeev, M. F. *Heterocycles* **1993**, *35*, 483.

(47) (a) Dunkin, I. R.; Lynch, M. A.; Boulton, A. J.; Henderson, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1178. (b) Murata, S.; Tomioka, H. *Chem. Lett.* **1992**, 57.

(48) (a) Jencks, W. P. *Prog. Phys. Org. Chem*. **1964**, *2*, 63. (b) Jencks, W. P. In *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; Chapter 10, p 463.

(49) (a) Sayer, J. M.; Pinsky, B.; Schonbrunn, A.; Washtien, W. *J. Am. Chem. Soc.* **1974**, *96*, 7998. (b) Palmer, J. L.; Jencks, W. P. *Ibid. Idem*. **1980**, *102*, 6466.

(50) All X-ray data pertaining to adduct **12** have been deposited to the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 142153.

Selected data for 8: ^{1}H NMR ($CDCl_3$, 300 MHz): 8.72 (1H, br. s, H5), 7.86 (1H, br. s, H7), 6.64 (2H, m, Hc,h), 6.17 (2H, m, Hb,g), 5.51, 5.44, 5.36 (4H, Ha,d,f,i), 1.86 (4H, m, He,j).

Preparation of 12. Excess 2,3-dimethylbutadiene (3 mL, >10 equiv) was added to a solution of **2** (450 mg, 2.47 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After 10 days, yellow crystals were collected by filtration and dried under vacuum. The hydrated cycloadduct **12** was obtained in a 80% yield.

Selected data for 12: mp: 160−165 °C; *m*/*z*: (EI) 282 ($M^{+\bullet}$), 236 ($M^{+\bullet} - NO_2$), 234 ($M^{+\bullet} - H_2O - NO$); (Anal. Found: C. 46.85; H. 4.85; N. 20.01. [$C_{11}H_{14}N_4O_5$] requires C. 46.81; H. 4.96; N. 19.86); NMR data are collected in Tables 3 and 4.

Acknowledgment. We are indebted to Dr. Didier Riou (Institut Lavoisier, Versailles) for carrying out the X-ray structure of the hydrated adduct **12**.

Supporting Information Available: Summary of crystallographic data for the monoadduct **12** (Table S1). Selected bond distances (Å) and angles (deg) for the adduct **12** (Tables S1 and S2). This material is available free of charge via the Internet at http://pubs.acs.org.

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