The remarkable effect of 7-amino substituents on the reactivity of 4-nitrobenzofurazans with nucleophiles[1]

Michael R. Crampton, Chukwuemeka Isanbor, and Thomas C. Willett

Abstract: The reactions of four 4-nitrobenzofurazans (**4a**–**4d**) substituted at the 7 position with (**a**) *N*-ethyl, (**b**) *N*-butyl, (**c**) piperidino, or (**d**) pyrrolidino groups have been examined with sulfite ions and with hydroxide ions in water–DMSO (80:20, *v*/*v*). Addition of sulfite at the 5 position gives σ adducts with equilibrium constants ca. 10^5 lower than that for the formation of the corresponding adduct from 4-nitrobenzofurazan. These reductions are attributed to the stabilization of the parent molecules **4a**–**4d** by conjugative interaction between the 4 and 7 substituents. In alkaline solution, **4a** and **4b** yield the conjugate bases while **4c** and **4d** suffer nucleophilic substitution to give 7-hydroxy-4-nitrobenzofurazan. Reactivity here is relatively high because of the iminium ion character of the substrates.

Key words: benzofurazans, σ adducts, nucleophilic reactivity, substitution.

Résumé : Opérant dans un milieu eau–DMSO (80:20, *v*/*v*), on a étudié les réactions des ions sulfites et des ions hydroxydes avec quatre 4-nitrobenzofurazanes (**4a**–**4d**) substitués en position 7 par (**a**) *N*-éthyle; (**b**) *N*-butyle; (**c**) pipéridino ou (**d**) des groupes pyrrolidino. L'addition de l'ion sulfite en position 5 conduit à des adduits σ dont les constantes d'équilibre sont 10^5 fois plus lentes que celles des formations des adduits correspondants à partir du 4-nitrobenzofurazane. On attribue ces réductions à la stabilisation des molécules parentes **4a**–**4d** par une interaction de conjugaison entre les substituants dans les positions 4 et 7. En solution alcaline, les composés **4a** et **4b** conduisent à la formation des bases conjuguées alors que les composés **4c** et **4d** subissent des réactions de substitution nucléophile qui conduisent à la formation de 7-hydroxy-4-nitrobenzofurazanes. Dans ces cas, la réactivité est relativement grande en raison du caractère d'ion iminium des substrats.

Mots clés : benzofurazanes, adduits σ, réactivité nucléophile, substitution.

[Traduit par la Rédaction]

Introduction

There is current interest in quantitatively measuring reactivity in nucleophile–electrophile combination reactions. Mayr and co-workers (1, 2) have investigated a wide-range of carbon–carbon bond forming reactions. There is also information available on the reactivities of both aromatic and heteroaromatic electron-deficient molecules with neutral and anionic nucleophiles (3, 4). Thus, Terrier, Buncel, and co-workers (5) were recently able to assign electrophilicity values (*E*) of –5.13 for 4,6-dinitrobenzofuroxan (DNBF), an excellent electrophile, and –13.10 for 1,3,5-trinitrobenzene (TNB), a weaker electrophile. These values were obtained in reactions with carbon nucleophiles in acetonitrile. The relative electrophilicities may be expected to show some dependence on the type of nucleophile and the solvent. Thus, the pK_a values (3) corresponding to the covalent reaction with water are 3.75 for DNBF and 13.43 of TNB, showing a rather larger difference than the *E* values.

In thermodynamic terms the stabilities of σ adducts formed by the reaction at the 5 position of 4-nitrobenzofurazan (**1**) are generally comparable with those of the corresponding σ adducts from TNB. However, there are significant differences depending on the nature of the nucleophile and the solvent. Thus, for the reaction with methoxide ions in methanol, values of equilibrium constants are 141 $dm^3\ mol^{-1}$ for **1** (6) and 23 $dm^3\ mol^{-1}$ for TNB (7). For reaction with aliphatic amines in dimethyl sulfoxide (DMSO), values of equilibrium constants are ca. 100 times lower for **1** than for TNB (8, 9). Interestingly, for reactions with sulfite ions (10) or hydroxide ions (11) in water, values are 10^3–10^4 times larger for **1** than for TNB. These differences may be largely due to the effects of solvation. Thus, **2** with a localized negative charge will be well-solvated by water, while **3** with a more delocalized charge will be stabilized by DMSO.

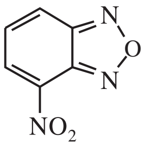

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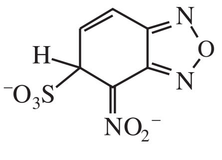
Table 1. Spectroscopic data for parent molecules, σ adducts, and products.

	^{1}H NMR data (δ)^a				UV absorbance^b	
Compound	H-5	H-6	J_{56}	Other	λ_{max} (nm)	ε (dm^3 mol^{-1} cm^{-1})
4a	8.53	6.40	8.8	9.54 (NH), 3.51 (2H), 1.28 (3H)	482	2.6×10^4
4b	8.49	6.40	8.8	9.55 (NH), 3.46 (2H), 1.65 (2H), 1.39 (2H), 0.92 (3H)	484	2.8×10^4
4c	8.44	6.64	9.4	4.16 (4H), 1.76 (6H)	510	2.6×10^4
4d	8.46	6.27	9.0	4.19 (2H), 3.69 (2H), 2.10 (4H)	502	3.0×10^4
5a	5.34	5.23	6.2	3.05 (2H), 1.15 (3H)	315	1.2×10^4
5b	5.31	5.19	6.2	2.99, 2.51 (2H), 1.61, 1.55 (2H), 1.29 (2H), 0.83 (3H)	310	1.0×10^4
5c	5.36	5.73	5.8	3.05 (2H), 2.84 (2H), 1.57 (4H), 1.46 (2H)	327	1.1×10^4
6a	7.62^c	6.42	10.5	3.58 (2H), 1.23 (3H)	393	2.0×10^4
	7.50^c	6.20	10.5	3.90 (2H), 1.29 (3H)		
6b	7.60^c	6.44	10.8	3.55 (2H), 1.60 (2H), 1.31 (2H), 0.83 (3H)	392	2.2×10^4
	7.50^c	6.20	10.8	3.90 (2H), 1.65 (2H), 1.31 (2H), 0.83 (3H)		
8	8.42	6.08	9.7		466	2.7×10^4

[a] Values for parent molecules **4a**–**4d** are in [$^2H_6$]-DMSO. All other values are in D_2O–[$^2H_6$]-DMSO (80:20, *v*/*v*).
[b] In water–DMSO (80:20, *v*/*v*).
[c] Values for the conformational isomers, see text.



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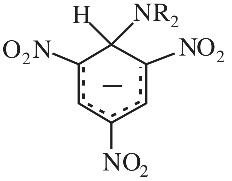

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Here, we are concerned with the reactivities of **1** and its 7-substituted derivatives in σ-adduct formation; in particular, the effect of an amino group or substituted amino group at the 7 position.

One source of interest in 4-nitrobenzofurazans is their potential to act as in vitro inhibitors of nucleic acid and protein biosynthesis in animal cells (12–15). Also, the fluorescence characteristics of 7-amino derivatives have been studied (16–18) and their use as fluorescent probes has been investigated (19).

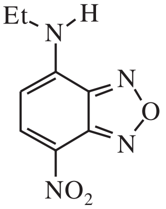
Here, results are reported for the reaction of compounds **4a**–**4d** with sulfite and with hydroxide ions in largely aqueous media. There is evidence for strong conjugation between the groups at the 4 and 7 positions, which stabilizes the parent molecules.

Results and discussion

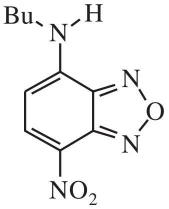
Most measurements relate to a solvent system of water–DMSO (80:20, *v*/*v*). This system was chosen because of the low solubilities ($<5 \times 10^{-5}$ mol dm^{-3}) of **4b**–**4d** in water. The solubility of **4a** in water was higher, therefore, measurements were made both in water–DMSO (80:20) and in water, allowing a comparison of the solvent systems.

Reaction with sulfite

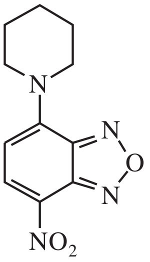
Spectroscopic results for the parent molecules in DMSO and for the products of the reaction with sulfite in water–DMSO (80:20) are in Table 1. The ^{1}H NMR spectra are consistent with sulfite addition at the 5 position to give **5** as shown in Scheme 1. H-5 shows a large shift to lower frequency (ca. δ 5.3) on adduct formation, while H-6 shows a smaller shift.



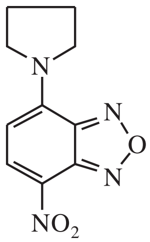
4a



4b

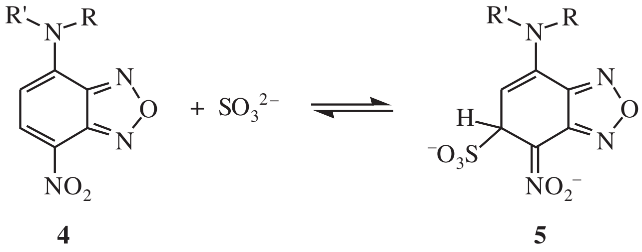


4c



4d

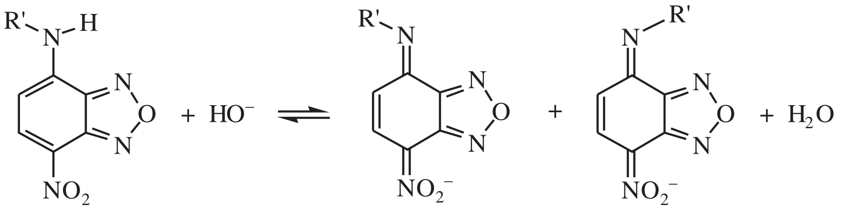
Scheme 1.



The coupling constant J_{56} is reduced from ca. 9 Hz in the parent to ca. 6 Hz, consistent with the change in hybridization at C-5. Since the shifts of H-5 and H-6 are similar, the assignments may be reversed. Due to the low solubility of **4d** and the low equilibrium constant for adduct formation, useful spectra could not be obtained for **5d**.

The spectra of the adducts were unchanged after several days and there was no evidence for sulfite attack at the 7 position. However, after a week, spectra of **4a** showed small bands at δ 8.42 and 6.08, characteristic of the anion of 7-

Scheme 2.



4a, 4b **6a, 6b**

Table 2. Kinetic and equilibrium results for reaction of **4c**^{a} with sulfite in water–DMSO (80:20, *v*/*v*) at 25 °C.

$[SO_3^{2-}]$ (10^{-4} mol dm^{-3})	k_{obs} (s^{-1})	$k_{calcd}{}^b$ (s^{-1})	Abs (510 nm)	$K_5{}^c$ (dm^3 mol^{-1})
0	—	—	1.27	—
8.0	0.24	0.24	0.90	510
12.0	0.28	0.27	0.79	505
16.0	0.31	0.31	0.71	490
20.0	0.33	0.34	0.64	490
40.0	0.50	0.52	0.41	520
60.0	0.71	0.69	0.32	500
100	0.93	1.04	0.21	508
150	1.42	1.48	0.15	500
200	1.98	1.91	0.11	525

Note: Abs = Absorbance.

[a] Concentration (5×10^{-5} mol dm^{-3}).

[b] Calculated from eq. [1] with $k_5 = 87$ dm^3 mol^{-1} s^{-1} and $k_{-5} = 0.17$ s^{-1}.

[c] Calculated as $((1.27 - \text{Abs})/\text{Abs}) \times (1/[SO_3^{2-}])$.

Table 3. Summary of kinetic and equilibrium data for reactions with sulfite ions in water–DMSO (80:20, *v*/*v*) at 25 °C.

Compound	k_5 (dm^3 mol^{-1} s^{-1})	k_{-5} (s^{-1})	K_5 (dm^3 mol^{-1})
4a^a	170	4.5	38
4a	180	1.9	95
4b	154	2.1	73
4c	87	0.17	510
4d	64	19	3.4
1^{a,b}	3.3×10^4	0.020	1.65×10^6
TNB^{a,c}	3.5×10^4	125	290

[a] Measurements in water.

[b] Data from ref. 10.

[c] Data from ref. 20 for the reaction at unsubstituted ring positions in 1,3,5-trinitrobenzene. Data have not been statistically corrected.

hydroxy-4-nitrobenzofurazan (**8**). Presumably in the sulfite solutions, which are weakly alkaline, hydrolysis occurs very slowly. The failure to observe sulfite attack at the 7 position of **4a**–**4d** is presumably steric in origin. It is known that in **1** itself, attack at the 5 position is followed by a slow isomerization to give the adduct at the 7 position.

Rate and equilibrium measurements for the formation of adducts **4a**–**4d** were made spectrophotometrically in solutions where the sulfite concentration was in large excess of the substrate concentration. In these conditions, a single, first-order process was observed, and rate constants were determined by the stopped-flow method.

Plots of k_{obs} vs. sulfite concentration were linear with a positive intercept on the *y* axis, according to eq. [1], allowing the determination of values of k_5 and k_{-5}. Specific results for the reaction of **4c** are in Table 2. Values of the equilibrium constant K_5 calculated as k_5/k_{-5} were in excellent agreement with those determined using equilibrium absorbance values. Results are collected in Table 3. We will delay the detailed discussion, but note that the adducts formed from **4** have stabilities ca. 10^5 times lower than the corresponding adduct from 1.

$$k_{obs} = k_5[SO_3^{2-}] + k_{-5} \quad [1]$$

Reaction with hydroxide

There is no spectroscopic evidence for σ-adduct formation from **4a**–**4d** and hydroxide ions in solutions containing up to 1 mol dm^{-3} hydroxide in water–DMSO (80:20, *v*/*v*). Hence, we may estimate that $K_5 < 0.1$ dm^3 mol^{-1}. This contrasts with the behaviour of **1** where the value (11) of the equilibrium constant for reaction with hydroxide at the 5 position is 2700 dm^3 mol^{-1}. However, this behaviour is not unexpected in light of the results with sulfite, which show that values of K_5 are many orders of magnitude lower for **4** than for **1**.

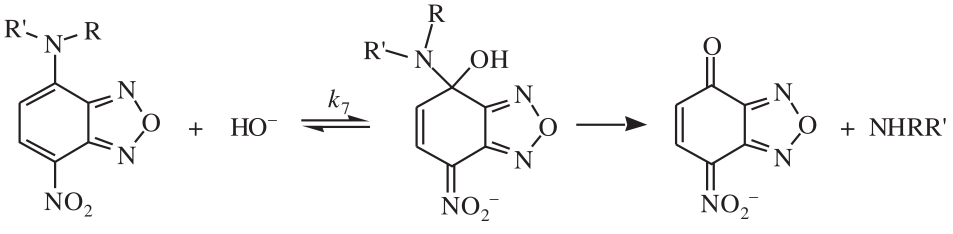
The ^{1}H NMR spectra of **4a** and **4b** in the presence of hydroxide are reported in Table 1 and indicate deprotonation to give the respective conjugate bases **6a** and **6b** as shown in Scheme 2.

Interestingly, the spectra in each case are compatible with the formation of two conformational isomers as indicated in the scheme. For **6a**, bands for H-5 and H-6 are observed at δ 7.62 and 6.42, *J* = 10.5 Hz, for the major isomer, and δ 7.50 and 6.20, *J* = 10.5 Hz, for the minor isomer. For **6a**, the ratio of isomers is 3:1 and for **6b** it is 4:1. Very slow displacement of the 7 substituents is observed so that after 1 week, bands are present due to the anion **8**.

Deprotonation of **4a** and **4b** is accompanied by changes in the UV–vis spectra. In the case of **4b**, λ_{max} is 484 nm in the parent and 392 nm in the anion. These changes were used to measure the pK_a values. An example calculation, in Table 4, yields a pK_a value of 10.15 ± 0.02 for **4b** in water–DMSO (80:20). Values for **4a** were 10.14 ± 0.05 in solvent (80:20) and 10.02 ± 0.02 in water.

In the presence of hydroxide, **4c** and **4d** were irreversibly converted to the anion (**8**) of 7-hydroxy-4-nitrobenzofurazan, which was identified from its ^{1}H NMR and UV–vis spectra (11). Kinetic measurements were made, at λ_{max} for the parent, with hydroxide concentrations in large excess and in the range 0.05–0.20 mol dm^{-3}. First-order kinetics were obtained, and plots of the rate constant vs. hydroxide concentration, which were linear with a zero intercept yielded values of the second-order rate constants. The reaction is likely (3, 4) to proceed by the addition–elimination mecha-

Scheme 3.



4c, 4d **7** **8**

Table 4. Calculation of the pK_a values for **4b**[a] in water–DMSO (80:20, *v*/*v*) at 25 °C.

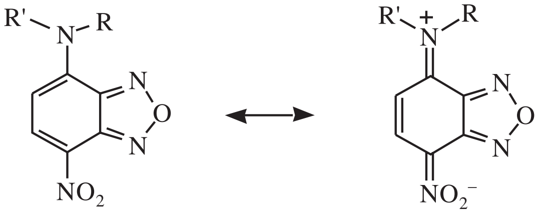
pH[b]	Abs (484 nm)	pK_a[c]
7.0	1.36	—
9.63	1.070	10.14
9.80	0.983	10.16
9.96	0.852	10.17
10.18	0.207	10.13
10.35	0.599	10.14
10.71	0.403	10.17
10.91	0.293	10.11
11.20	0.225	10.15
0.3 NaOH	0.125	—

Note: Abs = Absorbance.
[a] Concentration is 5×10^{-5} mol dm^{-3}.
[b] Borax buffers.
[c] Calculated as pH + log(Abs – 0.125)/(1.36 – Abs).

nism shown in Scheme 3. There was no evidence for the accumulation of the reaction intermediates **7c** and **7d** so that the measured second-order rate constants are likely to represent the values for k_7 for nucleophilic attack at the 7 position. Values obtained were 0.91 ± 0.05 dm^3 mol^{-1} s^{-1} for **4c** and 0.71 ± 0.04 dm^3 mol^{-1} s^{-1} for **4d**. These values may be compared to a value (11) of 0.2 ± 0.1 dm^3 mol^{-1} s^{-1} for hydroxide attack at the 7 position of **1**.

Comparisons

Our results provide evidence for a strong conjugation between the 4-nitro and 7-amino substituents as indicated in **9**. The UV–vis absorbance maxima in **4a**–**4d** are at 482–510 nm, showing a strong bathochromic shift relative to **1** where λ_{max} is 327 nm. A similar, but much weaker, conjugative effect has been noted in 7-methoxy-4-nitrobenzofurazan (10) where λ_{max} is 383 nm. It is interesting that in the ^{1}H NMR spectrum of **4d**, the pyrrolidino derivative, the two pairs of α-CH$_2$ hydrogens show discrete spin-coupled bands at δ 4.19 and 3.69, indicative of the double bond character in the carbon–nitrogen bond.



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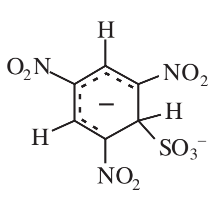
When comparing values of rate and equilibrium constants, it must be noted that here values generally refer to water–DMSO (80:20, *v*/*v*), corresponding to a mol fraction of 0.059 in DMSO. The comparisons with other compounds are generally made with results obtained in water. Nevertheless, the proportion of DMSO is small so that effects are likely to be small. Thus, the results in Table 3 for sulfite addition to **4a** indicate an increase in the value of K_5 by a factor of 2.5 on going from water to the mixed solvent. This is in line with other results showing increases in stability for the σ adducts as the proportion of DMSO in the solvent is increased (3, 4, 10).

One effect of the conjugative stabilization shown in **9** is to dramatically decrease values of equilibrium constants for σ-adduct formation at the 5 position. In the case of sulfite addition, the results in Table 3 show that values of K_5 are reduced by factors of ca. 10^5 relative to the value for the reaction of **1**. Values of k_5 are decreased and values of k_{-5} are increased. The overall effect is notably bigger for the pyrrolidino derivative (**4d**) than for the piperidino analogue (**4c**). Related differences between these amines have been reported previously (21–23) and may be attributed to the particular stability of the resonance form **9** in the pyrrolidino derivative.

It is of interest to contrast the effects of an amino substituted in the 4-nitrobenzofurazans with related effects in 1,3,5-trinitrobenzene derivatives. Thus, the values of the equilibrium constants for the formation of the sulfite adducts **10**, **11**, and **12** are (24) 250, 5.4×10^4, and 5.4×10^4 dm^3 mol^{-1}, respectively. Here, the effect of an *N*-methyl or *N*,*N*-dimethyl substituent is to enhance the stability of the adduct by a factor >100. It is likely that the difference in behaviour in the two systems is largely steric in origin. Hence, in the parent amino-trinitrobenzenes, it is not possible to achieve the degree of planarity required for strong conjugative interaction. The lower aromaticity in the benzofurazans relative to the benzene derivatives (4) may also favour conjugative interaction as shown in **9**.

σ-Adduct formation at the 5 position of **4** results in the loss of conjugation between the 4 and 7 substituents, and



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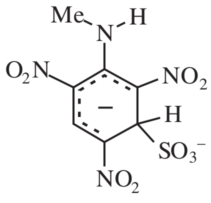

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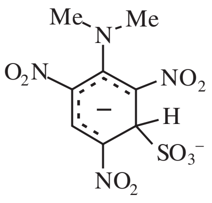

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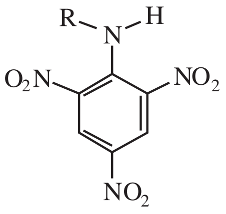
hence, is relatively disfavoured. However, ionization (Scheme 2) is not similarly disadvantaged. Thus, the pK_a values of ca. 10 found for **4a** and **4b** may be compared (3, 4, 25, 26) with corresponding values of ca. 13 for picramide and *N*-alkylpicramides (**13**). In a related fashion, the acidity in water–DMSO (20:80, *v*/*v*) of 7-anilino-4-nitrobenzofurazan (**14**, pK_a 7.68) has been found (27) to be higher than that of 2,4,6-trinitrodiphenylamine (pK_a 8.20).



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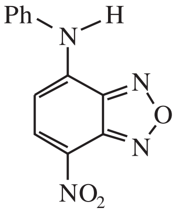

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The high reactivity of **4c** and **4d** towards hydrolysis (Scheme 3) may be attributed to the contribution of the resonance from **9** to the structure. This gives the carbon–nitrogen bond iminium ion character, hence explaining (28) the reactivity towards the attack of hydroxide. The values obtained for k_7 of ca. 1 dm^3 mol^{-1} s^{-1} may be compared (29) with values of 0.0031 and 0.015 dm^3 mol^{-1} s^{-1} for the corresponding attack of hydroxide on 1-piperidino- and 1-pyrrollidino-2,4,6-trinitrobenzene, respectively. It is interesting that in alkaline solutions, **4a** and **4b**, where anion formation predominates, are very slowly hydrolysed. This is likely to involve hydroxide attack on low concentrations of the parent molecules. As in previous work (10), there is no evidence for an attack of sulfite at the 7 position of 4-nitro-7 substituted benzofurazans, presumably owing to unfavourable steric interactions.

Experimental

Compounds **4a**–**4d** were prepared from 7-chloro-4-nitrobenzofurazan by reaction with 4 equiv. of the appropriate amine in DMSO. Mixtures were stirred for 5 h at room temperature and quenched in ice-cold dilute hydrochloric acid. The precipitates were filtered, washed with water and ethanol, and recrystallized from ethanol. ^{1}H NMR spectra are reported in Table 1, and indicated the absence of impurities. **4a**: mp 164 °C. MS (ES$^+$) *m*/*z* 209 corresponds to $C_8H_9N_4O_3$ (M + H$^+$). **4b**: mp 90 °C. MS (ES$^+$) *m*/*z* 237 corresponds to $C_{10}H_{13}N_4O_3$ (M + H$^+$). **4c**: mp 166 °C. MS (ES$^+$) *m*/*z* 249 corresponds to $C_{11}H_{13}N_4O_3$ (M + H$^+$). **4d**: mp 210 °C. MS (ES$^+$) *m*/*z* 235 corresponds to $C_{10}H_{11}N_4O_3$ (M + H$^+$).

Sulfite solutions were prepared from AnalaR sodium sulfite. To check that no depletion of sulfite concentration occurred because of hydrolysis when making kinetic and equilibrium measurements, measurements were also made in solutions buffered at pH 8.3 using mixtures of sodium sulfite and sodium hydrogen sulfite. The values of rate and equilibrium constants obtained were identical, within experimental error, to those obtained in unbuffered solutions with the same sulfite concentration. Solutions of known hydroxide concentration were made by dilution of AnalaR sodium hydroxide solution. The pH values of buffer solutions, borax or phosphate, were measured using a Jenway 3020 pH meter, calibrated using aqueous buffers. All other materials and solvents were the purest available commercial specimens.

^{1}H NMR spectra were measured using Bruker Ultrashield 400 MHz or Varian Inova 500 MHz spectrometers. Parent molecules were dissolved in [$^2H_6$]-DMSO. Measurements in solutions containing sodium sulfite or sodium deuteroxide were made in water–DMSO (80:20, *v*/*v*) using deuteriated solvents. Parent concentrations were in the range 0.005–0.01 mol dm^{-3} with the nucleophile concentration (ca. 0.1 mol dm^{-3}) in large excess. UV–vis spectra and kinetic measurements were made at 25 °C with a PerkinElmer Lambda 2 spectrophotometer, a Shimadzu UV-2101 PC spectrophotometer, or an Applied Photophysics SX-17 MV stopped-flow instrument. Reported rate constants are the mean of several determinations and are precise to ±5%.

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