The super-electrophilic reactivity of 4-nitro-6-trifluoromethanesulfonyl-benzofuroxan in aqueous solution

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Dedicated to Professor Domenico Spinelli on the occasion of his 70th birthday in recognition of his many contributions to heterocyclic chemistry

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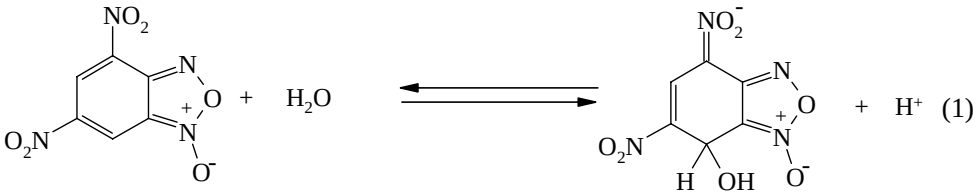
Abstract

A kinetic and thermodynamic study of the covalent hydration of 4-nitro-6-trifluoromethanesulfonylbenzofuroxan, **4**, to give the corresponding hydroxy σ-adduct, **C-4**, in aqueous solution is reported. Analysis of the data obtained in the pH range 0.8–13 has allowed dissection of the observed rates into forward ($k_1^{H_2O}$, $k_2^{OH^-}$) - and reverse ($k_{-1}^{H^+}$, k_{-2}) - rate constants as well as the obtention of pK_a values for water addition to the carbocyclic ring. The results reveal that **C-4** is the most stable hydroxy σ-adduct known to date (pK_a = 2.95) and that its formation arises exclusively from the attack of water molecules between pH 2.5 and 8.5. The related rate constant $k_1^{H_2O}$ is equal to (0.15±0.01) s^{-1}, as compared with $k_1^{H_2O}$ = 0.035 s^{-1} for the hydration of 4,6-dinitrobenzofuroxan (DNBF, pK_a = 3.75). These figures show that substitution of the 6-NO_2 group of this latter compound by an SO_2CF_3 group appreciably increases the electrophilic character of the carbocyclic ring of the benzofuroxan structure. Another manifestation of the activating effect of the SO_2CF_3 group is that the OH group covalently bonded to the 7-carbon of **C-4** undergoes ionization in dilute NaOH solutions (pK_a' = 12.03). Some data pertaining to buffer catalysis and solvent deuterium isotope effects are also reported. From these results, it is concluded that the formation and decomposition of **C-4** proceeds through the same mechanisms as those identified in the hydration of DNBF, in particular with OH^- acting as a general base catalyst and CO_3^{2-} acting as a nucleophilic catalyst.

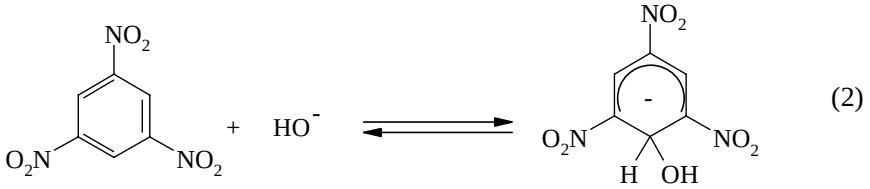
Keywords: Nitrobenzofuroxans, super-electrophiles, covalent hydration, SO_2CF_3 activation, kinetic study

Introduction

The two last decades have witnessed considerable interest in studies of nitrobenzofuroxans, a class of electron-deficient heteroaromatics that exhibit a high susceptibility towards covalent nucleophilic addition or substitution processes.[1–8] The high capability of 4,6-dinitrobenzofuroxan (DNBF, **1**) to form the hydroxy σ-adduct, **C-1**, in aqueous solution is illustrative of this behavior.[1] The pK_a value for formation of **C-1** according to eqn. (1) is equal to 3.75 at 25°C, as compared with a pK_a value of 13.37 for formation of the analogous adduct **C-2** of 1,3,5-trinitrobenzene (TNB, **2**), the conventional reference aromatic electrophile in σ-complex chemistry.[1,9] The use of dilute alkali hydroxide solutions is, in fact, necessary to achieve the formation of **C-2** in aqueous solution (eqn. (2)).[9]



DNBF, **1** **C-1**



2 **C-2**

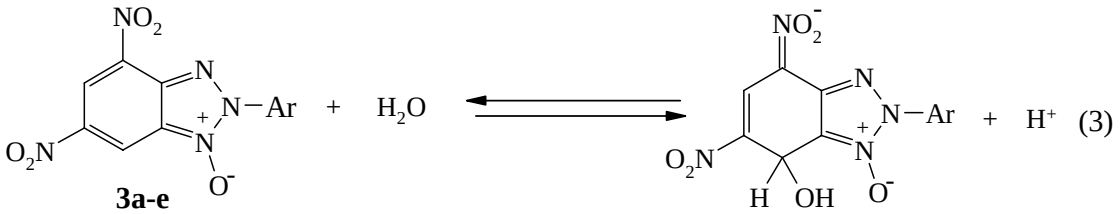
Extensive studies have revealed that DNBF is a stronger electrophile than the positively charged 4-nitrobenzenediazonium cation.[10] This has led to many analytical applications with the use of DNBF as a suitable probe to assess the reactivity of extremely weak carbon nucleophiles such as benzenoid aromatics or π-excessive heteroaromatics with large negative pK_a values, *e.g.*, 1,3-dimethoxybenzene (pK_a = -9) or aniline (pK_a = -6).[4,11] Another important electrophile is 4-chloro-7-nitrobenzofurazan which is largely used for biological processes.[12,13]

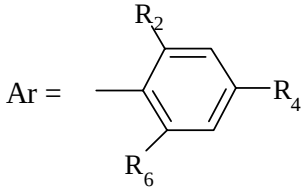
Recently, it has been shown that the high electrophilic character of DNBF is closely related to the low aromaticity of the carbocyclic ring, with the discovery that this compound can be involved in a variety of Diels–Alder processes.[14–16] This new facet of the reactivity of DNBF is very promising for the synthesis of highly functionalized heterocyclic structures.[17]

Obviously, the above results called for the recognition of other heteroaromatic compounds that might behave similarly to, or even surpass, the DNBF structure in terms of electrophilicity and Diels–Alder reactivity. In this regard, two different strategies could be reasonably envisioned where the expected variation in reactivity will arise either from a change in the nature of the annelated five- membered ring or a modification of the electrophilic character of the carbocyclic

ring by the introduction of more powerful electron-withdrawing substituents—including by aza-substitution. Considering the first approach, a recent study has been made[18a] of the series of 2-aryl-4,6-dinitrobenzotriazole 1-oxides, **3a–e** (eqn. (3)), leading to evidence that the electrophilicity of the carbocyclic ring of all compounds of this family ranks somewhat lower than that of DNBF. Concomitantly, the potentiality of this ring to be involved in Diels–Alder processes is reduced and only **3a**, *i.e.*, the most activated benzotriazole in the series, was found to exhibit some dienophilic or heterodienic reactivity.[18b]

Regarding the second strategy, promising results have been recently obtained through aza- and diaza- substitution of the carbocyclic ring,[19,20] but another approach was to look at the effect of the introduction of very strong electron-withdrawing substituents in this ring. In particular, the available literature data indicate that the SO_2CF_3 group is generally more activating than a NO_2 group, especially in σ-complexation- and related S_NAr reactions.[21,22]





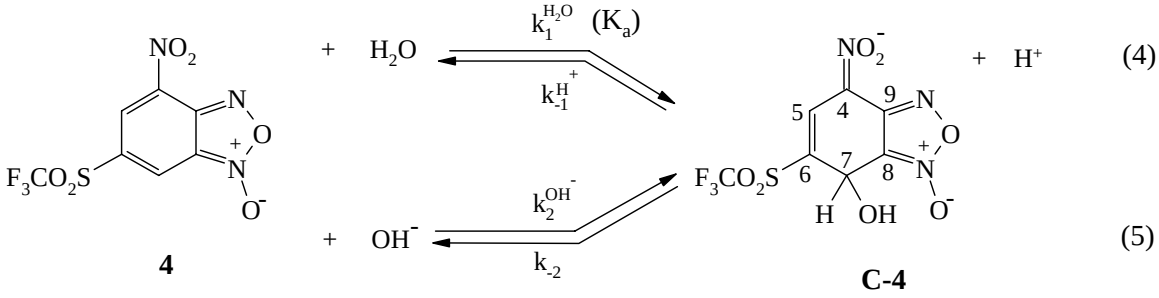
a: $R_2 = R_4 = R_6 = NO_2$
b: $R_2 = R_4 = NO_2$, $R_6 = H$
c: $R_2 = R_6 = H$, $R_4 = NO_2$
d: $R_2 = R_6 = H$, $R_4 = Br$
e: $R_2 = R_4 = R_6 = H$

In this context, we report here the results of a kinetic and thermodynamic study of the covalent hydration of 4-nitro-6-trifluoromethanesulfonylbenzofuroxan, **4**, in aqueous solution, to give the adduct **C-4**, according to Scheme 1. Our results reveal that **4** is the most electrophilic neutral heterocycle known to date. Various features emphasizing this behavior will be discussed. These include a high rate of water attack at the 7-carbon of **4**, as well as the occurrence of nucleophilic catalysis of this process by carbonate ions and the formation of the dianion **D-4** in dilute alkali solution [eqn. (6)].

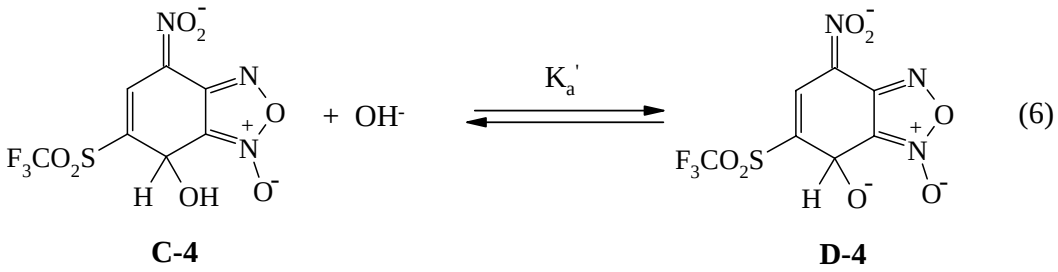
Results

All rate- and equilibrium measurements pertaining to Scheme 1 and eqn. (6) were made at 25°C and constant ionic strength of 0.2 M maintained with KCl. Dilute hydrochloric acid solutions,

various buffer solutions and dilute sodium hydroxide solutions were used to cover a pH range of 0.8–13. All pH values were measured relative to the standard state in pure water. Accordingly, the relation $[H^+] = 10^{-pH}/\gamma_{\pm}$ holds with $\gamma_{\pm}$ being the mean activity coefficient in 0.2 M KCl ($\gamma_{\pm}$ = 0.75 at 25°C).[23]



Scheme 1



Using dilute HCl solutions, as well as formic acid buffers, the pK_a value associated with the σ-complexation of **4** (λ_{max} = 412 nm, ε = 7,670 $M^{-1}cm^{-1}$) according to eqn. (4) was determined from the observed absorbance variations at λ_{max} of the resulting adduct **C-4** (λ_{max} = 395 nm, ε = 31,700 $M^{-1}cm^{-1}$) obtained at equilibrium as a function of pH.[24] These actually describe a clear acid–base type of equilibration, as evidenced by the observation of a good straight line with unit slope, fitting eqn. (7). From this plot (not shown), we readily obtained: pK_a = 2.95±0.05 at I = 0.2 M.

$$\log \frac{[\mathbf{C\text{–}4}]}{[\mathbf{4}]} = pH - pK_a \quad (7)$$

Going to dilute sodium hydroxide solution (pH ≥ 11) resulted in a new set of absorption spectra characterized by the existence of two clear isosbestic points at λ = 360 and 417 nm (Figure 1). As will be considered in the discussion, there is no doubt that these reversible spectral variations are consistent with a fast conversion of the adduct **C-4** into the dianion **D-4** (λ_{max} = 395 nm, ε = 26,000 $M^{-1}cm^{-1}$) according to eqn. (6). From the analysis of the pH dependence of

the absorbance changes at equilibrium, the interconversion of the two species was found to obey eqn. (8), leading to pK_a = 12.03±0.05 at I = 0.2 M.

$$\log \frac{[\mathbf{D}–\mathbf{4}]}{[\mathbf{C}–\mathbf{4}]} = pH – pKa' \quad (8)$$

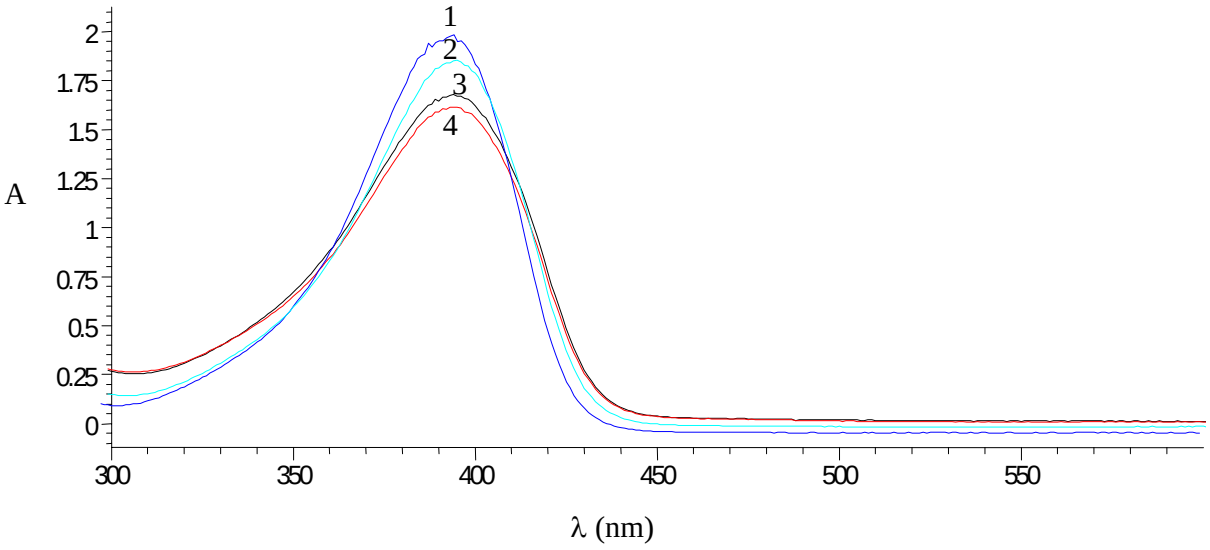


Figure 1. Absorption spectra illustrating the ionization of the hydroxy group of **C-4**, (1) in water ($c = 6.3\times10^{-5}$) and various sodium hydroxide solutions: (2), $[OH^-]$ = 0.01 M; (3), $[OH^-]$ = 0.1 M; (4), $[OH^-]$ = 0.2 M

pH Rate profiles for the complexation of 4

The kinetics of formation and decomposition of the adduct **C-4** according to the two pathways of equations (4) and (5) were studied in the pH range 0.8–13 by stopped-flow spectrophotometry. All rate measurements were carried out under pseudo-first-order conditions with a substrate or adduct concentration of $2–3\times10^{-5}$M. In agreement with the competitive but direct kinetic approaches described by equations (4) and (5), only one relaxation time corresponding to the formation (pH > pK_a) - or decomposition (pH < pK_a) - of the adduct **C-4** was observed. The variations in the first-order rate constant, k_{obsd}, for the combined processes at 25°C are plotted in Figure 2 as a function of pH. In the experiments where buffer catalysis was observed (*vide infra*), the k_{obsd} values used to draw the pH – rate profile were those extrapolated to zero buffer concentration.

As shown previously in related studies of the covalent hydration of DNBF or various heterocyclic cations,[1a,25] the observed rate constants may be expressed at each pH as the sum of the individual first-order rate constants for formation (k_f) and decomposition (k_d) of **C-4** (eqn. (9)). Thus, values of k_f and k_d can be readily derived from k_{obsd} through equations (10) and (11).

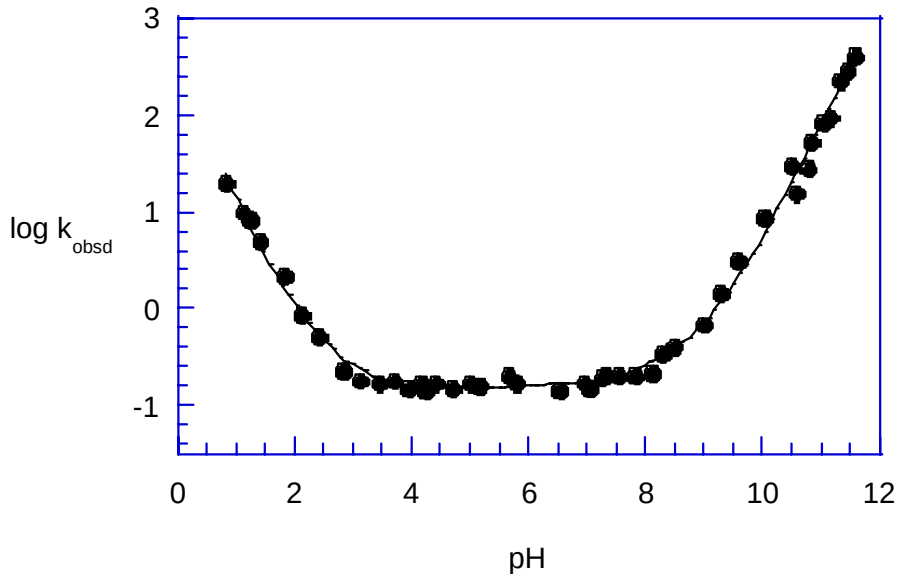


Figure 2. pH dependence of k_{obsd} (s^{-1}) for the formation and decomposition of the adduct **C-4** in aqueous solution (T = 25°C; I = 0.2 M).

The two corresponding pH–rate profiles shown in Figure 3 are nicely consistent with equations (12) and (13), respectively, in which the rate constants $k_1^{H_2O}$, $k_2^{OH^-}$, $k_{-1}^{H^+}$, and k_{-2} refer to the various individual pathways depicted in equations (4) and (5). Least-square fitting of k_f and k_d to equations (12) and (13) gave the parameters which are collected together with those for relevant systems, in Table 1.

$$k_{obsd} = k_f + k_d \quad (9)$$

$$k_f = \frac{k_{obsd}}{1 + \frac{10^{-pH}}{10^{-pK_a}}} \quad (10) \qquad k_d = \frac{k_{obsd}}{1 + \frac{10^{-pK_a}}{10^{-pH}}} \quad (11)$$

$$k_f = k_1^{H_2O} + \frac{k_2^{OH^-} K_w}{10^{-pH}\gamma\pm} \quad (12) \qquad k_d = k_{-2} + \frac{10^{-pH} k_{-1}^{H^+}}{\gamma\pm} \quad (13)$$

Assuming, as proposed above, that the OH group of C-4 behaves as a normal oxygen acid and ionizes instantaneously in the most basic media, the observed rate constant k_{obsd} is then given by eqn. (14) at pH ≥ 11. In view of the measured values of $k_2^{OH^-}$ and k_{-2}, it turns out that the second term of eqn. (14) does not appreciably affect the pH- dependence of k_{obsd} in the pH range 11–13, which is in agreement with the experimental observation.

$$k_{obsd} = \frac{k_2^{OH^-} Kw}{10^{-pH}\gamma\pm} + \frac{k_{-2}}{1 + \frac{Ka'}{10^{-pH}} \frac{\gamma_{C-4}}{\gamma_{D-4}}} \qquad (14)$$

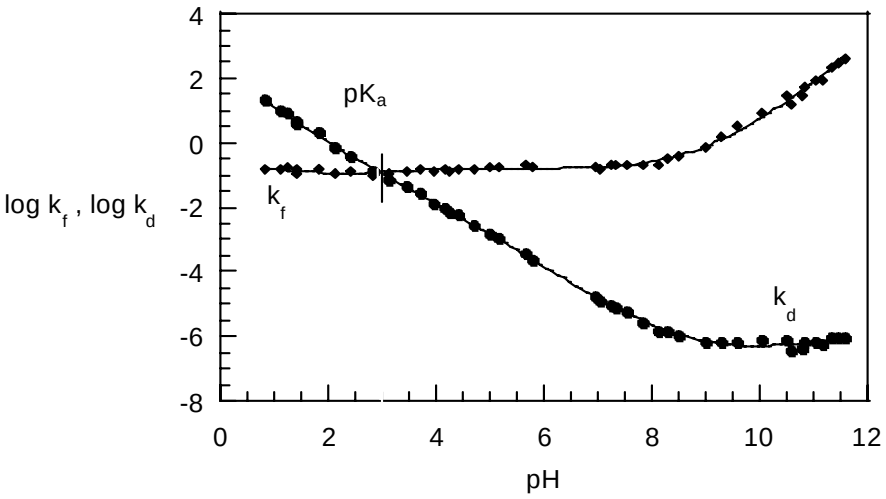


Figure 3. pH-rate profiles of the rate constants k_f (s^{-1}) and k_d (s^{-1}) for the formation and decomposition of the adduct **C-4** in aqueous solution (T = 25°C; I = 0.2 M).

Table 1. Kinetic and thermodynamic parameters for formation and decomposition of hydroxy σ-adducts and relevant pseudobases in aqueous solution[a]

Adduct or Pseudobase	pK_a	pK_a'	$k_1^{H_2O}$, s^{-1}	$k_{-1}^{H^+}$, $M^{-1}s^{-1}$	$k_2^{OH^-}$, $M^{-1}s^{-1}$	k_{-2}, s^{-1}	K_2, M^{-1}
C-1 [b]	3.75	11.80	3.45×10^{-2}	146	3.35×10^{4}	2.50×10^{-6}	1.34×10^{10}
C-2 [c]	13.43	-	-	-	37.5	9.8	3.82
C-3a [c]	6.70	-	1.13×10^{-3}	4215	392	1.96×10^{-5}	2×10^{7}
C-3c [c]	9.00	-	1.80×10^{-5}	1.33×10^{4}	680	3.54×10^{-3}	1.92×10^{5}
C-4 [d]	2.95	12.03	0.15±0.01	100.3	7.20×10^{4}	1.00×10^{-6}	7.20×10^{10}
	(3.65)	-	(0.085)	(241.5)	(7.80×10^{4})	(4.60×10^{-7})	(1.7×10^{11})
C-5 [e]	4.76	-	2.60	1.50×10^{5}	3.10×10^{5}	1.80×10^{-4}	1.72×10^{9}
C-6 [f]	5.11	11.15[g]	1.04	1.30×10^{5}	8.80×10^{6}	0.011	8×10^{8}
C-7 [f]	5.41	11.75[g]	11.00	2.90×10^{6}	3.80×10^{7}	0.097	3.90×10^{8}

(a) T = 25°C, I= 0.20 M unless otherwise stated. (b) ref. 1a. (c) ref. 18a. (d) this work; values in brackets refer to measurements in D_2O. (e) ref. 26; $k_1^{H_2O}$ and $k_2^{OH^-}$ at 23°C; $k_{-1}^{H^+}$ and k_{-2} at 26°C; at I= 0.01 M; (f) ref. 25c at I= 0.10 M. (g) ref. 25d.

Buffer catalysis

Regarding our measurements in buffer solutions, no significant catalysis of the interconversion of **4** and **C-4** has been observed in buffers of $pK_a < 7$, *i.e.*, the formic acid, acetic acid, cacodylic acid, TES and dihydrogenphosphate buffers—at least at the relatively low total buffer concentrations used in our experiments (< 2.10^{-2}M). The situation is exemplified for the acetic acid– acetate buffers in Figure 4.

In contrast, notable base catalysis was observed for formation of the adduct **C-4** in 4-cyanophenoxide (ArO^-), bicarbonate, and carbonate buffers (Table 2). In these three systems, the k_{obsd} data were found to obey eqn. (15) with B = ArO^-, HCO_3^- or CO_3^{2-}, as illustrated in Figure 5 for the ArO^- and HCO_3^- buffers and in Figure 6 for the CO_3^{2-} buffers. The fact that two parallel linear plots were obtained in plotting k_{obsd} vs. [CO_3^{2-}] at pH 9.55 and 10.03 revealed that the catalytic contribution of the dianionic species (CO_3^{2-}) overcomes that of the monoanionic one (HCO_3^-) in the carbonate buffers. From the slopes of the plots of Figures 5 and 6, the following catalytic rate constants were derived: k^{ArO^-} = 22 $M^{-1}s^{-1}$; $k^{HCO^{3-}}$ = 50.2 $M^{-1}s^{-1}$ and $k^{CO_3^{2-}}$ = 8,600 $M^{-1}s^{-1}$. Interestingly, the intercepts of these plots agreed well, within experimental error, with the values of the $k_2^{OH^-}$[OH^-] term, as calculated at each pH using the value of $k_2^{OH^-}$ directly determined in dilute hydroxide solutions.

$$k_{obsd} = k_2^{OH^-}[OH^-] + k^B[B] \qquad (15)$$

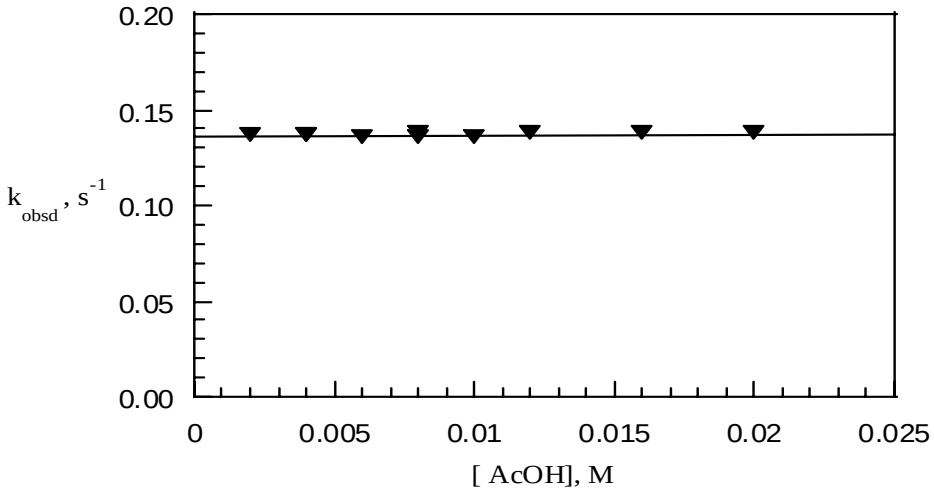


Figure 4. Plot showing the constancy of k_{obsd} in acetate buffers at various pH 4.40 and 4.70 in aqueous solution (T = 25°C; I = 0.2 M).

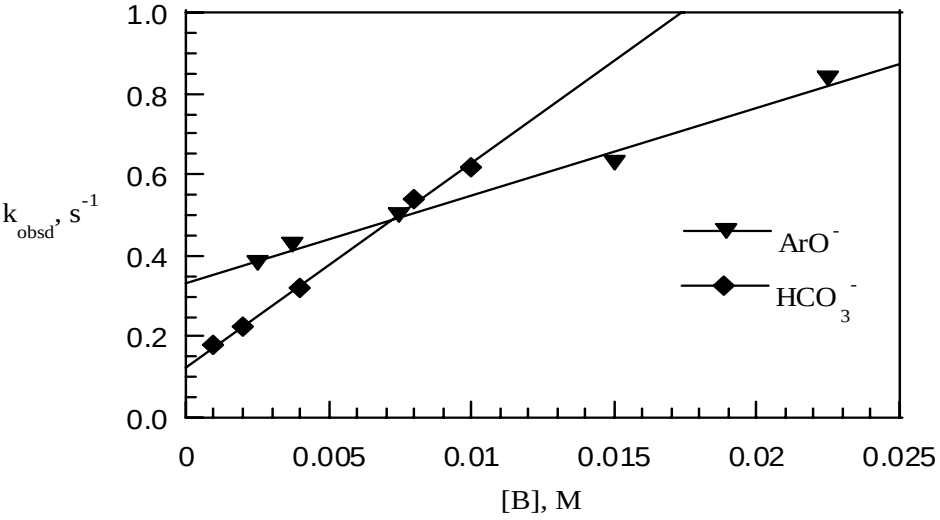


Figure 5. Plots showing the effects of the concentration of 4-cyanophenoxide and bicarbonate buffers on k_{obsd} for formation of the adduct C-4 at pH 8.14 and 6.56 in aqueous solution (T = 25°C; I = 0.2 M).

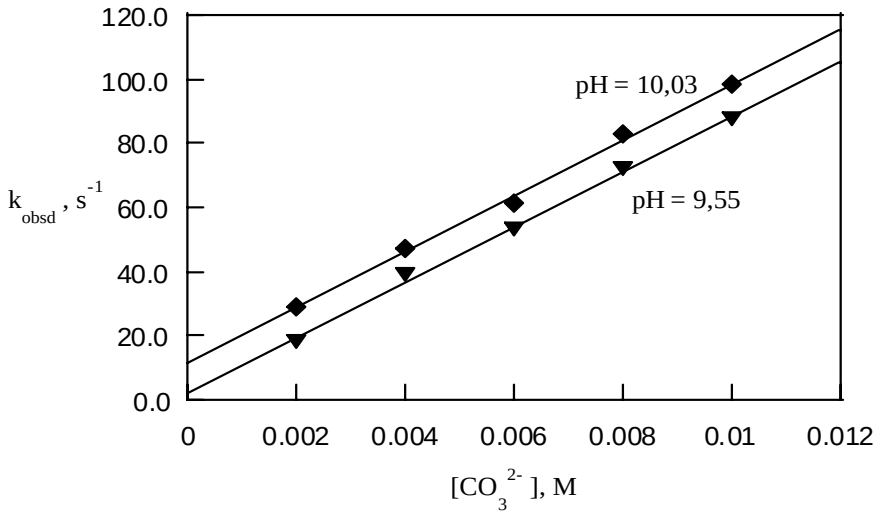


Figure 6. Plots showing the effect of the concentration of carbonate buffers on k_{obsd} for formation of the adduct C-4 at pH 9.55 and 10.03, respectively, in aqueous solution (T = 25°C; I = 0.2 M).

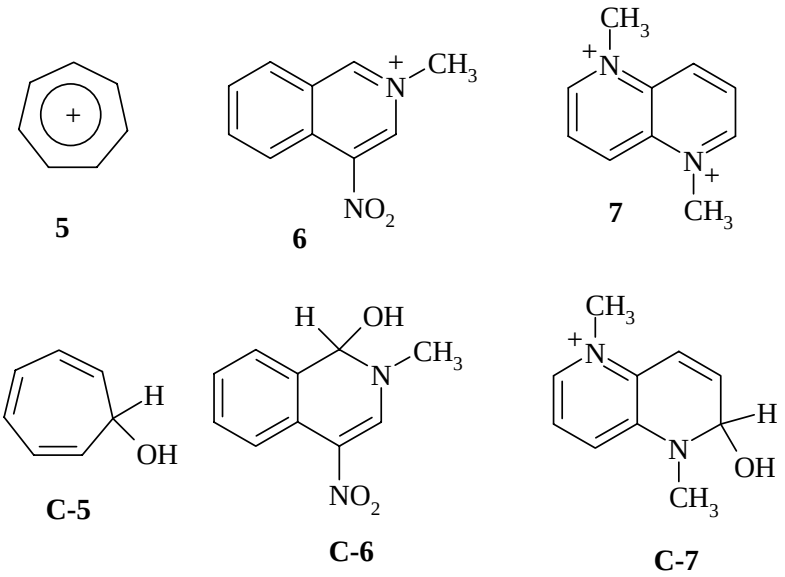
Table 2. Rate constants for base catalysis of adduct formation.

Adduct	k^{ArO-}, $M^{-1}s^{-1}$ (e)	$K_1^{HCO_3^-}$, $M^{-1}s^{-1}$	$k_1^{CO_3^{2-}}$, $M^{-1}s^{-1}$	$k^{OH-} / k_1^{CO_3^{2-}}$
C-1[b]	19.8	58	2370	11.56
C-3a[c]	-	0.78	16	24.5
C-3c[c]	-	-	3.1	220
C-4[d]	22	50.2	8600	8.37

(a) T = 25°C; I= 0.2 M; (b) ref. 1a; (c) ref. 18a; (d) this work; (e) ArO^- = 4-cyanophenoxide ion.

Discussion

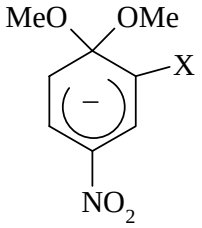
Our study of 4-nitro-6-trifluoromethanesulfonylbenzofuroxan, **4**, has revealed a number of interesting features, especially when compared to the known super-electrophile DNBF and the standard electrophile TNB, as well as positively charged structures such as the tropylium cation **5**[26] or the isoquinolinium- or naphthyridinium- cations **6** and **7**.[25] Salient features can be highlighted under the following headings.



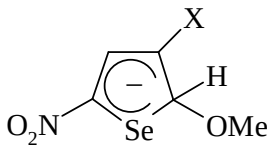
Adduct stability: the role of the SO_2CF_3 group

The high susceptibility of an electron-deficient aromatic or heteroaromatic substrate towards covalent addition through water attack has commonly been the major criterion as to whether it may be accorded super-electrophilic properties. In this regard, Table 1 reveals that the pK_a value for the conversion of **4** into the C-adduct **C-4** is 2.95, as compared with a pK_a of 3.75 for the complexation of DNBF. This makes **4** the most neutral electrophilic heteroaromatic known to date, with a considerable increase in electrophilic character of 10.5 pK units from that of the common reference electrophile (TNB) in σ-complex chemistry. Significantly, the thermodynamic susceptibility of **4** to water addition is greater than that of most positively charged activated structures such as **5** (pK_a = 4.70),[26] **6** (pK_a = 5.11)[25c] or **7** (pK_a = 5.41).[25c]

The fact that substituting the *ortho*-like 6-NO_2 group for a SO_2CF_3 group into the carbocyclic ring of DNBF increases the ease of adduct formation is reminiscent of previous findings in the benzene series.[22,27] For example, the equilibrium constant for formation of the 1,1-dimethoxy complex C-8 from 2-trifluoromethanesulfonyl-4-nitroanisole is 3 times greater than that for the analogous complex, **C-9**, from 2,4-dinitroanisole in MeOH–Me_2SO mixtures having high Me_2SO content.[28] Similar trends have been derived from studies of NO_2/ SO_2CF_3 exchanges in a *para*- position.[27] This analogy between the benzofuroxan and benzene series contrasts, however, with the situation found to prevail in the σ-complexation of five-membered ring heterocycles. For example, the equilibrium constants for formation of the 1-methoxy adducts C-10 and C-11 are equal to $2.1.10^4$ M and $6.4.10^4$ M, respectively, in methanolic solution.[22b]



X = SO_2CF_3, **C-8**
X= NO_2, **C-9**



X = SO_2CF_3, **C-10**
X= NO_2, **C-11**

At present, it is difficult to propose a definitive rationale for such a reversal in the relative activating behavior of NO_2 and SO_2CF_3 groups in σ-complex- formation processes. However, it is noteworthy that a similarly contrasting situation has also been reported in the ionization of carbon acids with, in this instance, a clear demonstration that the electron-withdrawing effects of the NO_2 and SO_2CF_3 substituents are strongly solvent dependent.[29,30] It is therefore possible that the primary role is played by the nature of the solvent, rather than the nature of the aromatic ring, in determining the effects of these two substituents on σ-adduct stability, but this explanation needs further support.

The very high electrophilic character of **4** is further demonstrated by the essentially complete formation of the dianion **D-4** in a 0.1 M NaOH solution. In fact, the pK_a' value for formation of **D-4** from the adduct **C-4** (pK_a' = 12.03) is nearly the same as that for formation of the analogous di-adduct from the DNBF complex **C-1** (pK_a' = 11.80).[1a] This makes the situation for these two anionic σ-complexes reminiscent of that observed for the ionization of the OH group of pseudobases derived from the hydration of heterocyclic cations, *e.g.*, pKa' = 11.15 for C-6.[25] Based on the pK_a value for ionization of water (pK_a = 15.74) the activating inductive –I effect exerted by the negatively charged 4-nitro-6-trifluoromethanesulfonyl- and 4,6-dinitro-benzofuroxan structures of **C-4** and **C-1** amounts to 5.5–6 pK units. This is considerably more than in the benzene series, where a 2,4,6-trinitrocyclohexadienyl moiety like that of the TNB adduct **C-2** is found to exert an activating effect of the order of 1.5–2 pK units on the acidic fragments covalently bonded to the sp^3 carbon.[31,32]

Reactivity of 4

Besides the pK_a value, the rate constant $k_1^{H_2O}$ for attack by water is a parameter which is very revealing of the electrophilicity of an aromatic- or heteroaromatic sp^2- carbon site.[1,18] Thus, no water reaction is operative in the formation of the TNB–hydroxy complex **C-2**.[9] In fact, the evidence is that such a pathway is negligible in the formation of all hydroxy– σ-adducts of $pK_a \geq 9$, a category which includes adducts such as those of 1,3,6,8-tetranitronaphthalene (pK_a = 9.96),[33] 1,2,3,5-tetranitrobenzene (pK_a = 9.62)[34] or the adduct **C-3c** of 2-(4-nitrophenyl)-4,6-dinitrobenzotriazole 1-oxide (pK_a = 9.00).[18a] Also in the benzotriazole 1-oxide family, only the

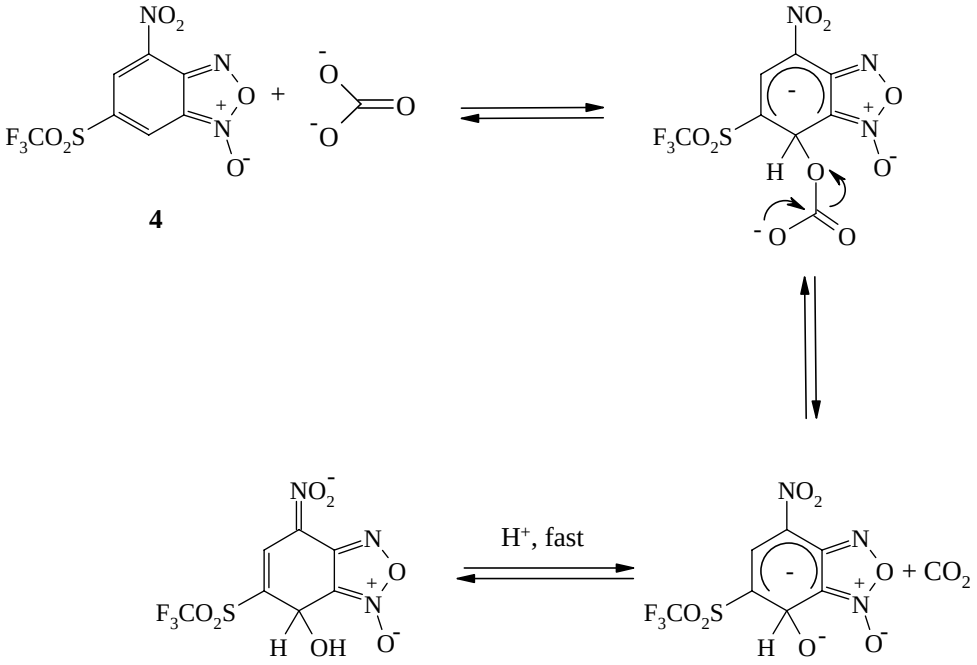
N-picryl adduct **C-3a** is sufficiently stable to form predominantly through attack by water ($k_1^{H_2O}$ = 1.13×10^{-3}s^{-1}) on the parent molecule in a small pH range (pH 7–8).[18a] The only remarkable situation is in the formation of the DNBF adduct **C-1** which arises exclusively from the addition of water between pH = 3 and 7.5 ($k_1^{H_2O}$ = 0.035 s^{-1}).[1a]

In view of the above results, a remarkable result highlighting the exceptional electrophilic character of **4** is the presence of a long plateau of about 6 pH units in the pH–rate profile shown in Figure 2. This long plateau is really illustrative of the great predominance of the pathway involving water in the formation of the adduct **C-4** between pH 3.5 and 8.5. Also, the $k_1^{H_2O}$ rate-constant associated with this reaction is equal to 0.15 s^{-1}, as compared with $k_1^{H_2O}$ = 0.035 s^{-1} for the hydration of DNBF at T= 25°C. It follows that the former value represents the highest rate ever measured for water addition at a sp^2 carbon of a neutral aromatic or heteroaromatic compound. It also follows that **4** ranks among the most powerful electrophiles known to date.

Interestingly, Table 1 shows that the $k_1^{H_2O}$ rate constant for hydration of 4 is somewhat lower than the related rate constants for hydration of the aromatic or heteroaromatic cations **5**, **6**, or **7**.[25,26] In these instances, however, the resulting pseudobases **C-5**, **C-6** or **C-7** are more prone to decomposition through both uncatalyzed and H^+-catalyzed pathways than is the SO_2CF_3 adduct **C-4**, or even the DNBF adduct **C-1**. As a result, these two anionic complexes are thermodynamically more stable than the quoted pseudobases, as discussed above.

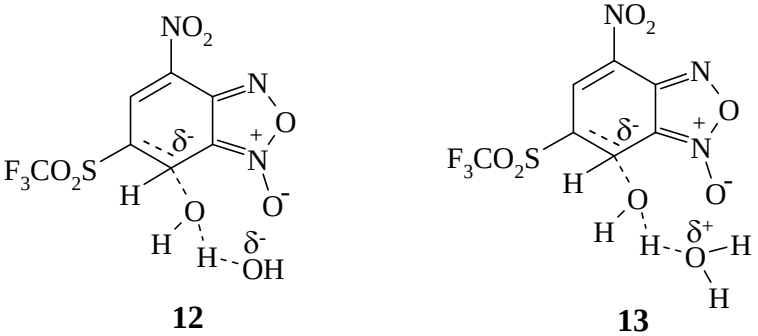
Buffer catalysis and isotope effects

Owing to the exalted contribution of the water pathway ($k_1^{H_2O}$) to the σ-complexation of **4**, the set of base catalysts involved in the formation of **C-4** is restricted to HCO_3^-, 4-cyanophenoxide ion, CO_3^{2-} and OH^- with no possibility of drawing a meaningful Brönsted correlation from the available data (Table 2). A most remarkable feature, however, is the finding that carbonate ions are remarkably efficient catalysts, being only 8 times less reactive than the more basic hydroxide ions. This situation is reminiscent of that observed in the covalent hydration of DNBF. In this instance, an interpretation in terms of nucleophilic catalysis (Scheme 2) was in accord with the fact that the DNBF is known to displace CO_2 from carbonate solutions.[1a]



4

Scheme 2



12 **13**

Regarding the hydroxide reactions, we previously suggested that OH^- behaves as a general base catalyst in the hydration of DNBF. The arguments were the following: (1), the rate constant $k_2^{OH^-}$ fits nicely onto a Brönsted line defined by some other base catalysts; (2), the observed kinetic solvent isotope effect for the reverse direction, *i.e.*, k_{-2}^{H} / k_{-2}^{D}, is equal to 1.69, consistent with a proton transfer being part of a rate-limiting transition state.[1a] In this regard, it is noteworthy that the measured solvent isotope effects on the $k_2^{OH^-}$ and k_{-2} pathways for the formation and decomposition of C-4 according to eqn. (5) are closely similar to those measured in the DNBF system (Table 3). This indicates that we are dealing with the same mechanistic behavior and therefore that OH^- must also act as a general-base catalyst for the reaction of water with **4**. The reaction will thus go through a transition state of type **12**. Interestingly, several authors have discussed the occurrence of such hydroxide- catalyzed water attacks in reactions of

carbonyl compounds,[35–39] and evidence for a similar catalytic behavior of OH^- has been reported in various systems, including S_NAr- and related σ-complexation reactions.[40–44]

Table 3. Deuterium Isotope Effects for Formation and Decomposition of the hydroxy σ-Adducts **C-1**, **C-3a**, **C-3c** and **C-4**[a]

Adduct	$k_1^{H_2O}/k_1^{D_2O}$	$k_{-1}^{H^+}/k_{-1}^{D^+}$	$k_2^{OH^-}/k_2^{OD^-}$	k_{-2}^{H}/k_{-2}^{D}
C-1[b]	1.67	0.380	0.905	1.69
C-3a[c]	1.79	0.386	0.900	1.53
C-3c[c]	-	0.372	0.95	-
C-4[d]	1.76	0.410	0.92	2.17

(a) T = 25°C, I= 0.2 M; (b) ref. 1a; (c) ref. 18a; (d) this work.

Table 3 reveals that the observed solvent isotope effects for water addition to **4** ($k_1^{H_2O}/k_1^{D_2O}$ = 1.76) and DNBF ($k_1^{H_2O}/k_1^{D_2O}$ = 1.67) are also very similar. As elaborated in detail earlier,[1a,18a] such solvent isotope effects are too large to be consistent with a transition state which would not involve a rate-limiting proton transfer. This in turn favors a transition state structure of type **13** with a second water molecule acting as a base catalyst. In agreement with this proposal, the isotope effect $k_{-1}^{H^+}/k_{-1}^{D^+}$ associated with the H^+-catalyzed decomposition of the adduct C-4 is equal to 0.41. This is in the range of values (0.40–0.70) reported for a number of examples of authentic general acid catalysis, *e.g.*, the hydrolysis of orthoesters and some acetals and ketals.[45]

Returning to the catalytic mode of action of CO_3^{2-} in the formation of hydroxy σ-adducts, Table 2 reveals that the ratio $k_1^{OH^-}/k_1^{CO_3^{2-}}$ measuring the relative reactivities of OH^- and CO_3^{2-} suffers a strong increase with decreasing adduct stability. This ratio is of the order of 8–12 for formation of the two most stable complexes **C-4** (pK_a = 2.95) and **C**-1 (pK_a = 3.75), and then it increases to 24.5 for the N-picryl benzotriazole adduct **C-3a** (pK_a = 6.70) and to 220 for the N-(4-nitrophenyl) analogue (pK_a = 9.00). Such a trend seems to be more consistent with a loss in the ability of CO_3^{2-} to act as a nucleophilic catalyst rather than with a systematic change in the transition-state structure associated with the mechanism of nucleophilic catalysis. In other words, the nucleophilic pathway of Scheme 2 will only contribute importantly in the hydration of the strongest electrophiles, while the general-base mechanism is the predominant route in the case of electrophiles having $pK_a \geq 7$.

Experimental Section

Materials

4-Nitro-6-trifluoromethanesulfonylbenzofuroxan, (4). was prepared from 1-chloro-2,6-dinitro-4-trifluoromethanesulfonylbenzene by the procedure of Yagupolskii *et al*., m.p. 180°C (lit. 181°C).[46] The starting chloro derivative was available from a previous study.[47]

The adduct **C-4** was prepared as a sodium salt as follows: 0.9 equivalent of 5M NaOH was added to a stirred solution of 0.313 g (1 mmole) of **4** in 1 ml of Me_2SO at room temperature. After one hour, 10 ml of $CHCl_3$ was added and the solution cooled in an ice bath. When crystals began to deposit, further (5 ml) was added and the mixture stirred for 1h further. Yellow–orange crystals were obtained by filtration, washed ($CHCl_3$), and dried under vacuum to give the sodium salt in essentially quantitative yield.

As with a number of alkali salts of DNBF σ-adducts,[3,5,10,11] the crystals of **C-4, Na^+** decomposed before melting (178°C). Attempts to obtain satisfactory elemental analysis have failed. However, dissolution of the salt in Me_2SO-d_6 gave ^1H- and ^{13}C- NMR spectra identical to those recorded in the *in situ* generation of the adduct in this solvent.

NMR data for **C-4**: ^1H NMR (δ, ppm, Me_2SO-d_6, Me_4Si): 8.16 (s, 1H, H_5), 6.36 (br., 1H, OH), 5.48 (s, 1H, H_7). ^{13}C NMR (δ, ppm, Me_2SO-d_6, Me_4Si): 149.15 (C_9; J_{C9H5} = 6.8 Hz, J_{C9H7} = 3.4 Hz), 140.47 (C_5, J_{C5H5} = 162.2 Hz, J_{C5H7} = 3.38 Hz), 119.88 (CF_3, J_{CF} = 327.5), 113.37 (C_8, J_{C8H7} = 6.8 Hz), 110.77 (C_4, J_{C4H5} = 3.95 Hz), 100.98 (C_6, J_{C6F} = 1.7 Hz), 57.28 (C_7, J_{C7H7} = 156.0 Hz, J_{C7H5} = 6.8 Hz). ^{19}F NMR (δ, ppm, Me_2SO-d, $CFCl_3$): -77.82 (CF_3).

HCl and NaOH solutions were prepared from Titrisol. Buffer solutions were made up from the best available commercial grades of reagents. Buffers used were formate (pH 3–4); acetate (pH 4.2–5.2); succinate (pH 4.8–5.8); cacodylate (pH 5.8–6.8); bicarbonate (pH = 6.56); N-[tris(hydroxymethyl)-methyl]-2-aminoethanesulfonic acid (TES; pH 7–8); 4-cyanophenoxide (pH 7.35–8.35); 1,4-diazabicyclo[2.2.2] octane (DABCO; pH 8.5–9.5); carbonate (pH 9.5–10.5). Solutions were prepared and their pH measured as before.[1a] The pH values are relative to the standard state in pure water. The pD values were obtained by adding 0.40 to the pH meter reading.[48]

Rate and pK_a measurements

Stopped-flow determinations were carried out on an Applied Photophysics Spectrophotometer, with the cell compartment maintained at 25 ± 0.2°C. Other kinetic and pK_a measurements were made using a Varian-Cary Spectrophotometer. All kinetic experiments were performed in triplicate under pseudo- first-order conditions with a substrate concentration of $(2–3)10^{-5}$ M. All rate constants are considered to be accurate to ± 3%.

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