impediment to preparatory applications of the general fluorination procedure. High-boiling residues were not encountered, and the ion chromatograms showed only negligible peaks beyond those of the highest boiling components reported. The percentage yields listed in Table II are therefore based on composition rather than quantity of analysand injected.

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# Reaction of Thiamin Analogues with Sulfite Ion: An Example of Zero-Order Kinetics

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Although the cleavage of thiamin (vitamin $B_1$, 1) and *N*-methyl vitamin $B_1$ (**1a**) with sulfite ion is known to be first order in sulfite ion, two molecules of this nucleophile are involved in the complex process. By contrast, the *N*-methyl analogue **1e** having 3-cyanopyridine as a leaving group does not show any kinetic dependence on the sulfite ion concentration. A proton NMR investigation of the reaction mixture clearly shows the formation of a sulfite adduct, reducing the concentration of the quaternized leaving group dramatically. Coupling constants are observed for the first time in a sulfite adduct of a nitrogen heterocycle. The equilibrium constant was estimated from kinetic data to be $5 \times 10^6$ $M^{-1}$, the highest ever reported. The analogue having nicotinamide as a leaving group has an equilibrium constant of only 62 $M^{-1}$. A model pyrimidine having a cyano group in position 5 and a 4-nitrobenzyl group in position 1 clearly adds sulfite mainly at position 6 to form adduct **4a**, revealing the likely site of attack of this nucleophile during substitution.

Vitamin $B_1$ (thiamin, 1)[1,2] and 1'-methylthiaminium ion[3] **1a** and its pyridinium analogue[4] **1b** are cleaved by sulfite ion in a multistep mechanism[5] to give the sulfonic acids **1c** and **1d**, the free thiazole and pyridine, respectively (Chart I). It is well-established that *two* molecules of sulfite are involved, the first in or before the rate-determining step, the second, that in the final product, reacting after the rate-limiting step.[2,6] A probable position of catalytic attack of the first sulfite ion is C-6 in the pyrimidine part of the vitamin.[2,7] The usual kinetic data show a first-order dependence on both the substrate and sulfite ion concentrations. However, two different approaches employing either very low sulfite concentrations[8] or a common ion effect[9] established the true second-order dependence of sulfite ion.

We now show that under certain conditions the usual first-order kinetic dependence in sulfite ion can change to zero order. Moreover, with a model compound it is possible to make an authentic sulfite ion adduct and thereby provide evidence for the position of addition of sulfite ion to the pyrimidine part of the vitamin.

## Results and Discussion

The rates of cleavage of substituted pyridinium analogues of *N*-methylthiamin (e.g., **1b**, **1f**) with sulfite ion have been measured.[4] Reactivity increases about 700 times when the 3,4-dimethylpyridine ($pK_a$ = 6.5) leaving group is changed to 3-carbamoylpyridine ($pK_a$ = 3.4). A Brønsted plot is linear with slope −0.86.[4] Therefore, it was anticipated that **1e**, with 3-cyanopyridine ($pK_a$ = 1.4) as a leaving group, would be the most reactive pyridine-containing substrate toward sulfite ion studied to date. However, kinetic measurements of the second-order rate constant reveal (Table I) that there is no dependence of the very small pseudo-first-order rate constant on the sulfite concentration. The UV spectrum of **1e** immediately after the addition of sulfite showed a new absorption maximum at 327 nm, which disappeared slowly to give finally the spectra of 3-cyanopyridine and **1d**. An $^1H$ NMR experiment revealed the nature of the retardation: **1e** formed sulfite adduct **2** with the pyridine part of the molecule, changing it to a poor leaving group (Chart I). Chemical shifts are reported in Table II.

**Table I. Observed First-Order Rate Constant ($s^{-1}$) for the Cleavage of 1e with Aqueous Sulfite Ion at 25 °C and Ionic Strength 1.0 (KCl)**

| pH | $10^4[SO_3^{2-}]$,[a] M | $10^4 k_{obs}$, $s^{-1}$ |
|---|---|---|
| 5.98 | 1.96 | 0.910 |
| 6.20 | 7.80 | 0.950 |
| 6.40 | 19.30 | 0.925 |

[a] Free base concentration calculated by using $pK_a$ = 6.59.

The literature shows that there are many sulfite adducts at heterocycles bearing a quaternary center, but these have been characterized usually by UV spectra only.[10-12] Johnson and Woo Smith observed an NMR spectrum of a sulfite adduct of NAD, but they just got very broad signals.[13] Because of the lack of coupling constants, an assignment of their signals is difficult. Better comparison is possible with the data of Damji and Fyfe.[14] They published NMR data of the methoxide adduct **2b** with chemical shifts very similar to those of the sulfite adduct

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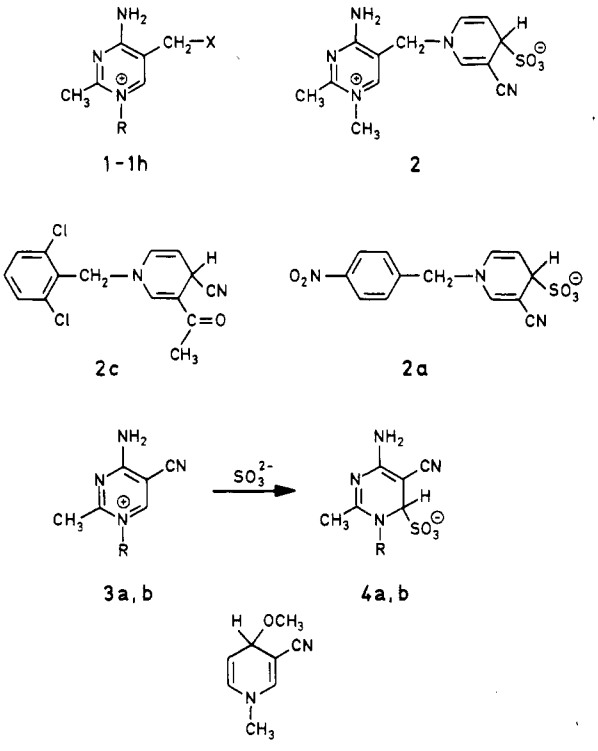
0022-3263/87/1952-0802$01.50/0 

**Table II. $^1$H NMR Spectral Data (ppm) for Some Adducts of Pyridines and Pyrimidines in $D_2O$ (2, 2a, 4a, and 4b at 200 MHz)**

| | position | | | | |
|---|---|---|---|---|---|
| no. | 2 | 4 | 5 | 6 | $CH_2$ |
| **2** | 7.29 (d, 1.4) | 4.40 (d, 5.6) | 5.15 (dd, 8.4/5.6) | 6.38 (dd, 8.4/1.4) | 4.53 |
| **2a** | 7.30 (d, 1.3) | 4.22 (d, 5.7) | 5.19 (dd, 8.4/5.7) | 6.34 (dd, 8.4/1.3) | 4.64 |
| **2b**[14] | 7.53 | 5.50 | 5.10 | 6.30 | |
| **2c**[15] | 7.37 (d, 1.2) | 4.55 (dd, 4.3)[a] | 4.97 (dd, 7.9/4.3) | 6.32 (ddd, 7.9/1.2)[a] | 4.80 |
| **4a**[b] | | | | 5.07 | 5.15 |
| **4b** | | | | ~4.70[c] | 3.75 |

[a] In $CDCl_3$; additional coupling $J_{4,6}$ = 0.9 Hz. [b] At 50 °C and pD 6.5; $CH_3$ 2.20 vs. 2.60 in the aromatic system. [c] Broad, close to HDO.

**Chart I**




| no. | R | X |
|---|---|---|
| **1** | H | 4-methyl-5-(2-hydroxyethyl)thiazolio |
| **1a** | $CH_3$ | 4-methyl-5-(2-hydroxyethyl)thiazolio |
| **1b** | $CH_3$ | 1-pyridinio |
| **1c** | H | $SO_3^-$ |
| **1d** | $CH_3$ | $SO_3^-$ |
| **1e** | $CH_3$ | 3-cyanopyridinio |
| **1f** | $CH_3$ | 3-carbamoylpyridinio |
| **1g** | 4-nitrobenzyl | OH |
| **1h** | $CH_3$ | Br |
| **3a** | 4-nitrobenzyl | |
| **4a** | 4-nitrobenzyl | |
| **3b** | $CH_3$ | |
| **4b** | $CH_3$ | |

**2** (Table II). Chemical shifts and coupling constants in the adduct **2c** formed by the addition of cyanide ion[15] are also very similar to the sulfite adduct of **1e** (Chart I).

There are not many other comparable NMR data for *sulfite* adducts of pyrimidines or pyridines in the literature. Rork and Pitman[16] isolated and characterized a 5-sulfonate of 5,6-dihydrouracil with a chemical shift of 4.05 ppm at H-5. They also characterized the 6-sulfonate in an NMR experiment ($\delta_{H-6}$ 4.64). Perrin and Pitman[7] isolated a sulfite adduct of 1,2-dihydro-2-imino-1-methylpyrimidine, probably the 4-adduct, but they could not get an NMR spectrum. From the comparison of all these data, we believe that the adduct of sulfite ion and **1e** has structure **2**.

To get a more stable sulfite adduct of 3-cyanopyridine, we replaced the *N*-pyrimidinomethyl group in **1e** by the equivalent electron-withdrawing, but unreactive, 4-nitrobenzyl group. After addition of 1 equiv of sulfite ion, we could get **2a** (Chart I), which could be isolated without major decomposition. The NMR spectrum (Table II) of **2a** is very similar to that of **2**.

It was not possible to get an equilibrium constant directly from the UV data of **1e** by adding sulfite ion. Even with concentrations of about $10^{-6}$ M of both sulfite and substrate, the full adduct spectrum was always generated. But an indirect evaluation of $K$ is possible.

Scheme I shows the fast equilibrium ($K$) of **1e** and sulfite with **2** to give then in a slow steady-state reaction ($k_2$) the final products **1d** and free 3-cyanopyridine. The observed rate constant (Table I) in this case is $k_2/K$.

**Scheme I**

$$\mathbf{1e} + SO_3^{2-} \overset{K}{\rightleftharpoons} \mathbf{2}$$

$$\mathbf{1e} + SO_3^{2-} \xrightarrow[k_2]{SO_3^{2-}} \mathbf{1d}$$

From the earlier published kinetic data,[4] we can give a very good estimate for $k_2$ and the equilibrium constant because the increase in the second-order rate constant for different pyridine substrates is calculable with use of a Brønsted plot. One may estimate, by using slope –0.86 and a p$K_a$ for 3-cyanopyridine of 1.4, that the corresponding second-order rate constant will be about 500 $M^{-1}$ $s^{-1}$. Therefore, the equilibrium constant for the sulfite adduct **2** must be about $5 \times 10^6$ $M^{-1}$, the largest value ever observed.[11]

Having found evidence for sulfite addition at the 3-cyanopyridinium derivative **1e** during cleavage with sulfite ion, it is worthwhile to reconsider our published data[5] for the carbamoyl derivative **1f**. This cation is one of the most reactive analogues of thiamin toward sulfite cleavage ($k_2$ = 2.4 $M^{-1}$ $s^{-1}$ at 25 °C and an ionic strength of 1.0). The p$K_a$ value of the leaving group nicotinamide is 3.4 vs. 1.4 for the 3-cyano derivative. The six experimental values we reported earlier can be found in Table III; they are written in order of increasing sulfite concentration. Easily detected now is a small decrease in the second-order rate constant with increasing sulfite concentration. Reexamination of the UV spectra shows a small increase in the absorption at 334 nm immediately after the addition of sulfite ion to a solution of the substrate, which disappeared with a clean isosbestic point at the above-mentioned rate. This new maximum increases with added sulfite ion. On repetition of the measurements using higher sulfite ion concentrations (Table III), the intermediate becomes more important and the calculated second-order rate constant decreases. At very high sulfite ion concentrations, the observed rate constant does not increase further and the

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**Table III. Second-Order Rate Constant for the Sulfite Cleavage of 1f and Change to First Order with Increasing Sulfite Concentration**

| pH | $10^4[SO_3^{2-}]$,[a] M | $10^4k_{obs}$, $s^{-1}$ | $k_2$, $M^{-1}$ $s^{-1}$ |
|---|---|---|---|
| 5.20 | 3.30 | 8.5 | 2.6 |
| 5.21 | 3.60 | 8.6 | 2.4 |
| 5.12 | 14.7 | 34.0 | 2.3 |
| 5.08 | 15.0 | 36.0 | 2.4 |
| 6.32 | 34.9 | 80.0 | 2.3 |
| 6.32 | 34.9 | 73.0 | 2.1 |
| | | avg | 2.35 ± 0.16[c] |
| 6.00 | 6.05 | 17.3 | 2.85 |
| 6.04 | 8.68 | 24.7 | 2.84 |
| 6.12 | 19.8 | 49.6 | 2.50 |
| 6.23 | 35.5 | 78.1 | 2.20 |
| 6.20 | 55.6 | 85.7 | 1.54 |
| 6.64 | 100 | 145.0 | 1.45 |
| 6.45 | 119 | 154.0 | 1.29 |
| 7.60 | 710 | 240.0[b] | 0.338 |
| 6.90 | 1050 | 249.0[b] | 0.237 |
| 7.46 | 1740 | 251.0[b] | 0.144 |

[a] Free base concentration calculated by using $pK_a$ = 6.59. [b] Average 247 $s^{-1}$. [c] Reference 5.

**Table IV. Comparison of the Results of Least-Squares Fit of the Data of Table III Using Equation 2**

| | $k_2$, $M^{-1}$ $s^{-1}$ | $K/k_2$, $s^{-1}$ | $K$, $M^{-1}$ | $r$ |
|---|---|---|---|---|
| points[a] 1–6 | 2.53 | 19.8 | 50.1 | 0.998 |
| all 16 points | 2.62 | 23.6 | 61.8[b] | 0.996 |

[a] Reference 5. [b] $K$ = 120 $M^{-1}$, using 2.6 $M^{-1}$ $s^{-1}$ for $k_2$ and 2.47 × $10^{-2}$ $s^{-1}$, the experimental value of $k_{obs}$ at very high sulfite concentration (Table III).

rates become zero order in sulfite ion concentration. Obviously, there is the same type of inhibition as in **2**, Scheme I, but it is less effective due to a smaller equilibrium constant. When using a known derivation of a second-order consecutive reaction with a fast equilibrium and a slow second step under pseudo-first-order conditions,[17] one derives eq 1 and 2 for Scheme I.

$$\ln A/A_0 = -\frac{k_2}{K + 1/[SO_3^{2-}]}t \quad (1)$$

The complex term must be $k_{obs}$, the observed rate constant. After linearization one gets

$$1/k_{obs} = \frac{K}{k_2} + \frac{1}{k_2[SO_3^{2-}]} \quad (2)$$

Table IV shows the results of a regressional analysis of the data from Table III. Not only do the published data fit very well to eq 2 but all 16 values agree ($r$ = 0.996). Therefore, we believe that the true value for $k_2$ must be 2.6 $M^{-1}$ $s^{-1}$, higher than the value of 2.4 $M^{-1}$ $s^{-1}$ reported.

At very high sulfite concentration, the observed rate constant for **1f** is virtually $k_2/K$, exactly as it is the case at *all* concentrations for **1e**. The calculated equilibrium constant (about 100 $M^{-1}$) is in the expected range, somewhat higher than that for *N*-(2,6-dichlorobenzyl)nicotinium ion (1.3 $M^{-1}$).[11] By contrast, the enormous increase associated with the 3-cyanopyridinium compound is most remarkable.

On the basis of UV spectra, many equilibrium (addition) constants describing sulfite adducts have been published.[10,11,13,14] It is instructive to consider some of these in the light of our own values. When a 2,6-dichlorobenzyl group is bonded to the ring nitrogen of nicotinamide, the sulfite addition equilibrium constant is only about 40 times higher than that of the *N*-methyl compound.[11] But $K$ is about 25 000 times larger for *N*-methyl-3-cyanopyridine (1600 $M^{-1}$) than for *N*-methylnicotinamide (0.063 $M^{-1}$).[11] The influence of the substituent in position 3 is therefore more important than the electronegativity of the substituent at the nitrogen. On the other hand, an ***N*-glycoside**[11] can increase the equilibrium constant by a factor of $10^5$.

Encouraged by these results, we tried to find the same type of sulfite addition to the pyrimidine part of vitamin $B_1$. All kinetic results are consistent with a catalytic addition of sulfite ion at this part of thiamin, facilitating the expulsion of all kinds of leaving groups, including thiophenolate[5] and phenolate[4] ions.

4-Amino-2-methyl-5-(hydroxymethyl)-1-(4-nitrobenzyl)pyrimidinium bromide (**1g**), a substrate with no apparent leaving group and no charged group bonded in position 5, did not give any evidence for adduct formation even at very high sulfite ion concentrations. Compound **3a**, where the hydroxymethyl group in position 5 is replaced by a cyano group, easily added sulfite ion at neutral pH. The $^1H$ NMR spectrum of the adduct at 21 °C showed but a broad unresolved signal at about 5.10 ppm, which became sharp at 50 °C to show two distinct signals, one representing H-6 and the other the 1-$CH_2$ group (Table II). Clearly, addition at C-6 must have occurred and the structure of the adduct must be **4a**. The 1-methyl analogue **3b** also added sulfite ion under the same conditions, but the signals remained broad even at elevated temperature. Both compounds seemed to add hydroxide as a competing reagent at higher pH. The signal for H-6 became very broad and shifted downfield, depending on the pH.

With this study the complex interaction between sulfite ion, thiamin, and its derivatives and analogues becomes markedly enriched, adding zero-order kinetics to the first- and second-order reactions already reported.

## Experimental Section

**4-Amino-5-[(3-cyanopyridinio)methyl]-1,2-dimethylpyrimidinium Dibromide (1e).** A mixture of 0.7 g (2.4 mmol) of 4-amino-5-(bromomethyl)-1,2-dimethylpyrimidinium bromide (**1h**) and 1 g (10 mmol) of 3-cyanopyridine was stirred and heated in 30 mL of ethanol under reflux for 5 h. Recrystallization of the isolated product from ethanol yielded 0.45 g (46%) of colorless pellets: mp 234–236 °C dec; $^1H$ NMR ($D_2O$, 2,2-dimethyl-2-silapentane-5-sulfonate (DSS)) δ 9.43 (2-H), 9.05 (4-H, 6-H), 8.38 (6′-H), 8.30 (5-H), 5.93 ($CH_2$), 3.87 ($NCH_3$), 2.68 ($CH_3$). Anal. Calcd for $C_{13}H_{15}Br_2N_5$ ($M_r$ 401.11): C, 38.93; H, 3.77; N, 17.46. Found: C, 38.34; H, 4.08; N, 16.94.

**4-Amino-5-(hydroxymethyl)-2-methyl-1-(4-nitrobenzyl)-pyrimidinium Bromide (1g).** A mixture of 1 g (7.2 mmol) of 4-amino-5-(hydroxymethyl)-2-methylpyrimidine[18] and 2.16 g (10 mmol) of 4-nitrobenzyl bromide was stirred and heated under reflux for 5 h. The isolated precipitate was treated with three portions of 2 mL of warm (80 °C) water, and the filtrate was reduced to 0.5-mL volume. After cooling, the precipitate was isolated and recrystallized from water, yielding 0.25 g (10%) of slightly yellow crystals: mp 228–230 °C dec; $^1H$ NMR ($D_2O$, DSS) δ 8.25 (CH), 8.18 and 7.46 (aromat), 5.60 ($CH_2$), 4.64 ($CH_2OH$), 2.62 ($CH_3$). Anal. Calcd for $C_{13}H_{15}BrN_4O_3$ ($M_r$ 355.20): C, 43.96; H, 4.26; N, 15.77. Found: C, 43.40; H, 4.08; N, 15.00.

**4-Amino-5-(bromomethyl)-1,2-dimethylpyrimidinium Bromide (1h).** To 3.0 g (14.1 mmol) of 4-amino-1,2-dimethyl-5-(hydroxymethyl)pyrimidinium acetate[19] suspended in 50 mL of glacial acetic acid was added 7–9 g of HBr (100 mmol). The mixture was refluxed for 2 h and then cooled to 5 °C, and the

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precipitate was isolated. It was heated with 150 mL of acetic acid for 1 h and then cooled and isolated. Recrystallization from acetic acid yielded 3.5 g (84%) of colorless needles: mp 250–255 °C dec; $^1$H NMR ($Me_2SO$-$d_6$, $Me_4Si$) δ 9.31 and 8.67 ($NH_2$), 8.78 (6-H), 4.77 ($CH_2$), 3.89 ($NCH_3$), 2.68 ($CH_3$). Anal. Calcd for $C_7H_{11}N_3Br_3$ ($M_r$ 297.00): C, 28.31; H, 3.73; N, 14.15. Found: C, 28.37; H, 3.76; N, 13.82.

**Sodium Salt of 3-Cyano-1-(4-nitrobenzyl)-1,4-dihydropyridine-4-sulfonic Acid (2a).** To 0.4 g (1.45 mmol) of 3-cyano-1-(4-nitrobenzyl)pyridinium chloride[20] dissolved in 2.5 mL of water was added 0.18 g (1.45 mmol) of sodium sulfite. The water was removed on a freeze dryer, and the residue was extracted with three portions of 5 mL of 2-propanol. The solvent was removed, and the yellow residue (4.6 g, 92%) was dried at 100 °C in vacuo: mp 156–159 °C dec; $^1$H NMR ($D_2O$, DSS) δ 8.08 and 7.46 (Ar), 7.30 (2-H, d, $J_{2,6}$ = 1.3 Hz), 6.34 (6-H, dd, $J_{6,2}$ = 1.3 Hz, $J_{6,5}$ = 8.4 Hz), 5.19 (5-H, dd, $J_{5,4}$ = 5.7 Hz, $J_{5,6}$ = 8.4 Hz), 4.64 ($CH_2$), 4.22 (4-H, d, $J_{4,5}$ = 5.7 Hz). Anal. Calcd for $C_{13}H_{10}N_3NaO_5S$ ($M_r$ 343.29): C, 43.22; H, 2.79; N, 11.63. Found: C, 42.50; H, 3.19; N, 10.99.

**4-Amino-5-cyano-2-methyl-1-(4-nitrobenzyl)pyrimidinium Bromide (3a).** A mixture of 1 g (7.5 mmol) of 4-amino-5-cyano-2-methylpyrimidine[21] and 2.16 g (10 mmol) of 4-nitrobenzyl bromide was stirred and heated in 30 mL of 2-propanol for 24 h. After isolation, the precipitate was treated with three portions of 3 mL of water and the combined filtrates were concentrated to a volume of about 1 mL. The yield was 0.4 g (15%), mp 228–230 °C dec. By addition of 0.5 g of sodium iodide, an additional 1.2 g of crude material could be recovered: $^1$H NMR ($D_2O$, DSS) δ 8.83 (CH), 8.32 and 7.46 (Ar), 5.56 ($CH_2$), 2.60 ($CH_3$). Anal. Calcd for $C_{13}H_{12}BrN_5O_2 \cdot H_2O$ ($M_r$ 343.29): C, 42.41; H, 3.83; N, 19.02. Found: C, 42.10; H, 3.87; N, 19.00.

**4-Amino-5-cyano-1,2-dimethylpyrimidinium Iodide (3b).** 4-Amino-5-cyano-2-methylpyrimidine[21] (1 g, 7.5 mmol) and 5 g (35 mmol) of iodomethane were dissolved in 20 mL of dimethylformamide. After 18 h, the precipitate was isolated and washed repeatedly with ether. The yield was 1.8 g (87%) of colorless crystals: mp 185–187 °C dec; $^1$H NMR ($D_2O$, DSS) δ 8.80 (CH), 3.91 ($NCH_3$), 2.72 ($CH_3$). Anal. Calcd for $C_7H_9IN_4 \cdot H_2O$ ($M_r$ 276.07): C, 30.45; H, 3.29; N, 20.29. Found: C, 29.83; H, 3.24; N, 19.94.

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# Effect of Distortion on the Hydrolytic Reactivity of Amides. 2. N-Pyramidalization: Decomposition of *N*-Benzoylaziridines in Aqueous Media

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The decomposition of para-substituted *N*-benzoylaziridines (H, $OCH_3$, $NO_2$, Br) in buffered aqueous media is studied at 25 °C as a function of pH in order to assess the effect of *N*-pyramidalization on the hydrolytic reactivity of the amide bond. Overall, the reaction shows three dominant terms: $OH^-$ and $H_2O$ attack on the neutral form and $H_2O$ attack on the protonated form of the amide. In base, the exclusive reaction is rate-limiting and irreversible attack of $OH^-$ on the C=O unit leading to normal hydrolytic products. This is shown by the first-order dependence on [$OH^-$] from pH 8 to 14 of the hydrolysis rate and by the fact that ~50% $^{18}$O-enriched amide recovered from the hydrolysis medium as a function of time shows no $^{18}$O loss. Relative to *N*,*N*-dimethylbenzamide ($k_{OH^-}^{25°C}$ = 6.0 × $10^{-6}$ $M^{-1}$ $s^{-1}$), *N*-benzoylaziridine is ~200 000-fold more susceptible to $OH^-$ attack ($k_{OH^-}^{25°C}$ = 1.1 $M^{-1}$ $s^{-1}$). The $k_{OH^-}$ terms follow a $\sigma\rho$ relationship with $\rho$ = 1.68. In acid, the products are not the expected hydrolytic ones of benzoic acid and aziridine. Rather, exclusive ring opening occurs to give *p*-X-$C_6H_4C(=O)NHCH_2CH_2OX$. In acetate buffers, product analysis by $^1$H NMR indicates that the ring-opened material consists of alcohol and acetate (X = H and $C(=O)CH_3$).

## I. Introduction

An attractive hypothesis for enzyme-mediated amide hydrolysis suggests that a share of the exothermicity of substrate binding is utilized in a productive way to induce stress or strain in the substrate, enzyme, or enzyme–substrate complex, which is relaxed as the transition state for the acyl transfer reaction is approached.[1] In effect, this notion is equivalent to the widely held view that enzymes bind transition states better than they bind substrates,[1g] the net effect being to lower the activation energy for the catalyzed process. As far as amide hydrolysis is concerned, at some point along the catalyzed hydrolytic pathway, the conjugation between the N: and C=O π-bond in the amide must be significantly reduced in order to allow nucleophilic attack. As part of an on-going program to evaluate the influence of geometric distortion of the amide bond on its hydrolytic reactivity, we recently reported[2a] the syntheses and kinetic studies of the hydrolysis of anilides **1a–d**[2b] and **2**.

Both skeletons render the amide portion extremely reactive toward hydrolysis, the second-order rate constants for $OH^-$ attack on **1a** and **2** at 25 °C being 262 and 60 $M^{-1}$

(1) (a) Haldane, J. B. S. *Enzymes*; Longmans, Green and Co.: London, 1930. (b) Lumry, R. In *The Enzymes*; Boyer, P. D., Ed.; Academic: New York, 1959; Vol. 1, pp 157–258. (c) Jencks, W. P. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1975**, *43*, 219–410. (d) Jencks, W. P. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1980**, *51*, 75–106. (e) Bruice, T. C. In *The Enzymes*; Boyer, P. D., Ed.; Academic: New York, 1970; Vol. 2, pp 217–279. (f) Fersht, A. *Enzymatic Structure and Mechanism*, 2nd ed.; W. H. Freeman and Co.: San Francisco, 1985; pp 311–346. (g) Wolfenden, R. *Acc. Chem. Res.* **1972**, *5*, 10.

(2) (a) Somayaji, V.; Brown, R. S. *J. Org. Chem.* **1986**, *51*, 2676. (b) Compound **1a** had initially been synthesized and its hydrolysis preliminarily studied by Blackburn, G. M.; Skaife, C. J.; Kay, I. T. *J. Chem. Res., Miniprint* **1980**, 3650.

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