UV–vis (hexanes) λ_{max} 266 nm (log ϵ 4.90), 287 (4.42), 301 (4.35), 312 (4.35), 336 (4.05), 3.46 (4.21), 359 (3.54), 410 (3.07), 444 (3.15), 460 (4.20), 486 (3.82), 492 (3.86)] corresponding to that of the product mixture from the reaction of **4** with Cl_2.[24]

1-[(Dimethylamino)methyl]azupyrene. The procedure was adapted from that of Lindsay and Hauser.[25] A 0.5-mL portion (0.5 mmol of reagent) of a clear solution formed by heating (steam bath) 30 mg (1.0 mmol) of paraformaldehyde and 0.15 mL (1.1 mmol) of tetramethyldiaminomethane in 2.0 mL of acetic acid was added to 52.5 mg (0.26 mmol) of **4** suspended in 6.0 mL of acetic acid. As the mixture was warmed to 70–80 °C, **4** dissolved and the solution became green. After 2 h, the mixture was cooled, diluted with 50 mL of H_2O, and extracted with 3 × 20-mL portions of ether. The extracts yielded 10 mg (20%) of unchanged **4**. The cooled (ice bath) aqueous solution was basified (1 N NaOH) and then extracted with ether. Removal of the solvent from the combined, dried (Na_2SO_4) extracts gave 47 mg (70%, 86% net) of 1-[(dimethylamino)methyl]azupyrene as a green solid which decomposed on standing: UV–visible (hexanes) λ_{max} 254 nm (log ϵ 4.40), 267 (4.59), 287 (4.22), 302 (4.00), 312 (3.98), 336 (3.68), 347 (3.74), 359 (3.26), 408 (2.70), 442 (2.85), 452 (2.90), 460 (2.78), 472 (3.15), 484 (3.69); ^1H NMR ($CDCl_3$) δ 2.4 (s, 6, CH_3), 4.3 (s, 2, CH_2), 7.35 (t, 1, H-4, J = 9.5 Hz), 7.40 (t, 1, H-9, J = 9.5 Hz), 8.37 (s, 1, H-2), 8.39 (d, 1, H-6, J = 4.3 Hz), 8.41 (d, 1, H-7, J = 4.3 Hz), 8.64 (d, 1, H-3, J = 9.5 Hz), 8.67 (d, 1, H-5, J = 9.5 Hz), 8.71 (d, 1, H-8, J = 9.5 Hz), 8.86 (d, 1, H-10, J = 9.5 Hz); mass spectrum, m/e (relative intensity) 259 (M^+, 30), 216 (35), 215 (100); exact mass, m/e 259.1378 ($C_{19}H_{17}N$ requires 259.1361).

1-Methylazupyrene (7). A. From 3-Methylcyclopentanone. The procedure indicated for the preparation of **4** was repeated with the substitution of 3-methylcyclopentanone for cyclopentanone. The final product (**7**) was obtained as gold-green leaflets (7% overall), mp 134–135 °C: UV–vis (hexanes) λ_{max} 254 nm (log ϵ 4.30), 267 (4.55), 287 (4.14), 302 (3.90), 312 (3.88), 334 (3.56), 347 (3.68), 359 (3.14), 410 (2.55), 442 (2.71), 452 (2.78), 460 (2.68), 472 (3.01), 484 (3.60); ^1H NMR ($CDCl_3$) δ 3.07 (s, 3, CH_3), 7.34 (t, 1, H-4, J = 9.5 Hz), 7.36 (t, 1, H-9, J = 9.5 Hz), 8.24 (s, 1, H-2), 8.39 (d, 1, H-6, J = 4.5 Hz), 8.42 (d, 1, H-7, J = 4.5 Hz), 8.55 (d, 1, H-10, J = 9.5 Hz), 8.58 (d, 1, H-3, J = 9.5 Hz), 8.65 (d, 1, H-5, J = 9.5 Hz), 8.70 (d, 1, H-8, J = 9.5 Hz); mass spectrum, m/e (relative intensity) 215 (29), 216 (M^+, 50), 217 (9); exact mass, m/e 216.0937 ($C_{17}H_{12}$ requires 216.0939). Anal. Calcd for $C_{17}H_{12}$: C, 94.41; H, 5.59. Found: C, 94.41; H, 5.66.

B. From 1-[(Dimethylamino)methyl]azupyrene. To a solution of 28.5 mg (0.11 mmol) of 1-[(dimethylamino)methyl]-azupyrene in 5 mL of CH_2Cl_2 was added 0.1 mL (1.1 mmol) of CH_3I. The mixture was stirred in the capped flask for 1 h and then placed in a refrigerator overnight. Collection of the green precipitate yielded 38.0 mg (85%) of product presumed to be (1-azupyrenylmethyl)trimethylammonium iodide, mp 222–225 °C dec: UV–vis (EtOH) λ_{max} 252 nm (log ϵ 4.72), 266 (4.90), 287 (4.47), 300 (4.32), 309 (4.26), 336 (4.00), 344 (3.85), 361 (3.64), 440 (3.00), 452 (3.11), 472 (3.45), 484 (4.10); ^1H NMR (Me_2SO-d_6) δ 3.30 (s, 9, CH_3), 5.48 (s, 2, CH_2), 7.51 (t, 1, H-4, J = 9.5 Hz), 7.58 (t, 1, H-9, J = 9.5 Hz), 8.60 (s, 2, H-6,7), 8.82 (s, 1, H-2), 8.89 (d, 1, H-8, J = 9.5 Hz), 8.92 (d, 2, H-3,5, H-3,5, J = 9.5 Hz), 9.13 (d, 1, H-10, J = 9.5 Hz).

A mixture of 29.2 mg (0.0728 mmol) of the above quaternary salt and 4.0 mg (0.106 mmol) of $LiAlH_4$ in 4.0 mL of freshly distilled dioxane was warmed (oil bath) to 50 °C under Ar in a flame-dried flask. After 2 h, the solid had dissolved to form a green solution and TLC (CH_2Cl_2) showed no immobile reagents. The cooled reaction was quenched with a few drops of H_2O and the mixture was added to 10 mL of H_2O. The whole was extracted with ether (3 × 10 mL) and the organic extracts were washed with 20-mL portions of 1 N hydrochloric acid and 10% $NaHCO_3$. The solvent was removed from the dried (Na_2SO_4) organic phase and the residue chromatographed (3 × 0.5 in silica gel column, hexanes) to give 7.5 mg (48%) of **7**, mp 132–133 °C, after sublimation at 150 °C and 0.1 torr, spectrally identical (UV–vis, ^1H NMR, mass spectrum) with the material from A.

Thermal Isomerization of Azupyrene (4).[9] In a 5-mL, thick-walled Vycor tube sealed under dry N_2 at 10^{-4} torr, 5 mg (0.025 mmol) of **4** was heated at 500 °C for 12 h. The cooled solid product was extracted with $HCCl_3$ to give 2 mg (40%) of pyrene (**8**) (no unchanged **4**) identical (mass spectrum, fluorescence spectrum[26]) with an authentic sample.

Repetition of the reaction at 450 °C for 2 h gave 4.5 mg of a mixture of **8** (25.2%) and unchanged **4** (64.8%) as indicated by the ^1H NMR spectrum: ($CDCl_3$) δ 8.00 (t, 2, H-2,7, J = 7.5 Hz), 8.08 (s, 4, H-4,5,9,10), 8.19 (d, 4, H-1,3,6,8, J = 7.5 Hz) for pyrene and 7.37 (t, 2, H-4,9, J = 9.5 Hz), 8.42 (s, 4, H-1,2,6,7), 8.71 (d, 4, H-3,5,8,10, J = 9.5 Hz) for **4**.[3]

Thermal Isomerization of 1-Methylazupyrene (7). In the manner described for the isomerization of **4**, a 3.5 mg (0.016 mmol) sample of sublimed **7** was heated at 500 °C and 0.2 torr to give 2.3 mg of a mixture containing (GC/MS analysis) pyrene (**8**) (67%), methylpyrenes (24%), and **7** (9%). Integration of the intensities of the methyl group singlets in the ^1H NMR spectrum ($CDCl_3$ at δ 2.98, 2.80, and 2.90, respectively,[12] showed a ratio of 23:23:4 for 1- (**9**), 2- (**10**), and 4-methylpyrene (**11**)).

The same reaction with 4.5 mg (2.1 mmol) of **7** at 450–460 °C for 4 h gave 2.1 mg which contained (GC/MS analysis) **8** (39%), methylpyrenes (19%), **4**(39%), and **7**(3%). The ^1H NMR spectrum showed a ratio of 25.5:20.5:4 for **9**, **10**, and **11**.

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Micellar Catalysis of Organic Reactions. 18. Basic Hydrolysis of Diazepam and Some N-Alkyl Derivatives of Nitrazepam

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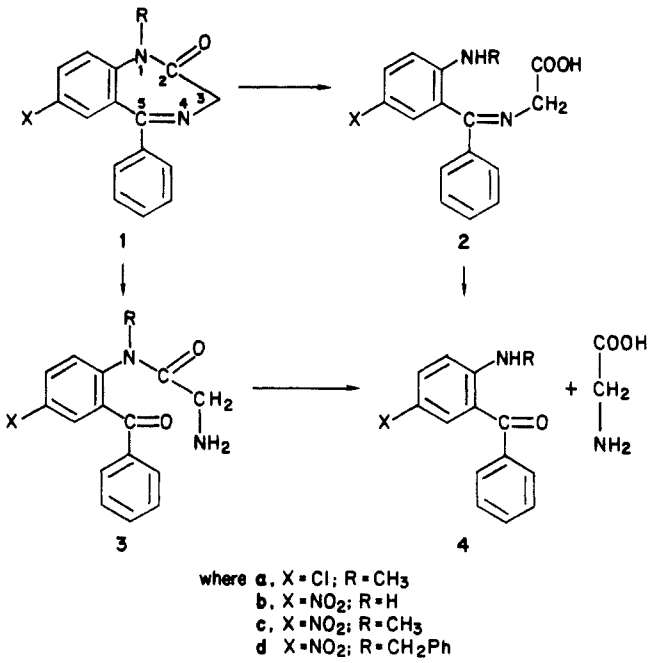
Kinetic and mechanistic studies of the basic hydrolysis of several benzodiazepinone drugs have been carried out in the presence of micelles of cetyltrimethylammonium bromide (CTAB) and in aqueous solution. For diazepam, a change of mechanism from initial azomethine hydrolysis in water to initial amide hydrolysis in the presence of micelles of CTAB is indicated. For nimetazepam and *N*-benzylnitrazepam, initial amide hydrolysis was observed both in the presence of CTAB and in water. For the latter compounds, strong catalysis (50–100) of amide hydrolysis (phase 1) by micelles of CTAB was observed, while azomethine hydrolysis (phase 2) was only very weakly catalyzed (3–4-fold). For diazepam, the catalysis was smaller (9–18-fold), but this was accompanied by a mechanistic change so that here the actual catalysis of amide hydrolysis is masked.

The benzodiazepinones **1** are a class of physiologically active drugs, which include diazepam (**1a**) and nitrazepam (**1b**). These drugs are valuable because of their anxiolytic, anticonvulsant, and muscle relaxant properties.[1]

0022-3263/86/1951-2965$01.50/0

Scheme I



where a, X = Cl; R = CH_3
b, X = NO_2; R = H
c, X = NO_2; R = CH_3
d X = NO_2; R = CH_2Ph

Extensive studies of their stability in aqueous solution have been carried out.[2-5] These studies included a detailed analysis of the mechanism of hydrolysis, both in acidic[2-5] and in basic solution.[2,3] Mechanistically, the hydrolysis of benzodiazepinones is interesting because nucleophilic attack may occur at either C-2, leading to initial amide hydrolysis and production of intermediate **2**, or at C-5, leading to initial azomethine hydrolysis and production of intermediate **3**. Subsequent hydrolysis of both intermediates **2** and **3** leads to the production of the substituted 2-aminobenzophenone **4** and glycine (Scheme I).

In aqueous acidic solution, the hydrolysis of diazepam[2] (**1a**) and nitrazepam[3] (**1b**) was shown to involve initial azomethine hydrolysis and the mechanism **1** → **3** → **4** was proposed. However, the hydrolysis of oxazepam[2] involves initial amide cleavage via the mechanism **1** → **2** → **4**. The hydrolysis of chlordiazepoxide[6] involves preliminary cleavage of a methylamino group leading to demoxepam which then undergoes initial amide cleavage.

Thus, the mechanism of reaction is finely balanced and variation of substituents X and R can result in change of mechanism. Because of our interest in the effects of micelles on the mechanism of reactions and on the hydrolysis of anilides in particular,[7,8] we have studied the effect of micelles of sodium dodecyl sulfate (SDS) on the mechanism of acid-catalyzed hydrolysis of diazepam, nitrazepam, and some N-alkyl derivatives of nitrazepam (**1c,d**).[9,10] It was found that the acid-catalyzed hydrolysis of diazepam was inhibited by micelles of SDS but that the mechanism was unchanged (initial attack of water at C-5 leading to azomethine cleavage).[9] The acid-catalyzed hydrolysis of nitrazepam was not inhibited by micelles of SDS, and the mechanism changed from water attack at C-5, leading to initial azomethine cleavage in the absence of micelles, to initial water attack at C-2, leading to initial amide cleavage in the presence of micelles of SDS. Further work[10] indicated that in nitrazepam derivatives, attack of water at C-2, leading to initial amide cleavage, was favored by high acid concentrations, by micelles of SDS, and by small R groups attached to the amide nitrogen atom. The effect of the size of the R group is exemplified by the study of *N*-benzylnitrazepam (**1d**), for which the change of mechanism from initial azomethine to initial amide hydrolysis is much less than for nitrazepam itself, either in the presence of high acid concentrations (0.47 M HCl) or in the presence of micelles of SDS.

Table I. Observed Pseudo-First-Order Rate Constants for the First Phase of Nimetazepam Hydrolysis at 30.0 °C[a]

[NaOH], mM	at [CTAB], mM	10^4k_1, s^{-1}	
		0	8
1.90		(25.2)	
4.67		2.13 (73.1)	113
9.33		8.24 (137)	211
46.7		55.0	
93.3		123	

[a] Followed production of intermediate **2c** at 400 nm. Values in parentheses obtained at 74.5 °C.

Table II. Observed Pseudo-First-Order Rate Constants for the Second Phase of Nimetazepam Hydrolysis at 74.5 °C

[NaOH], mM	at [CTAB], mM	10^4k_1, s^{-1}	
		0[a]	8[b]
1.90		1.83	5.79
4.75		1.89	7.41
9.5		1.93	7.94

[a] Followed production of product **4c** at 385 nm. [b] Followed loss of intermediate **2c** at 252 nm.

In the present paper, we are concerned with the mechanism of the basic hydrolysis of benzodiazepinones (**1a**, **c** and **d**) and the effects of positively charged micelles of cetyltrimethylammonium bromide (CTAB). Previous work has indicated that the basic hydrolysis of anilides is strongly catalyzed by micelles of CTAB,[7,8] whereas azomethine hydrolysis in basic solution is inhibited.[11] Furthermore, it has been shown that the basic hydrolysis of anilides is dependent on the hydroxide concentration,[7,12] while azomethine hydrolysis is independent of hydroxide concentration.[11]

Results and Discussion

(a) Nimetazepam (1c). Previous studies[3] of the mechanism of basic hydrolysis of nitrazepam (**1b**) at 75 °C showed a monophasic reaction when followed at 370 nm. On this basis, it was proposed that the reaction involved initial azomethine cleavage initiated by water/hydroxide attack at C-5. Since intermediate **3b** would not accumulate at high pH (fast recyclization to reactant), monophasic kinetics are expected for this mechanism.[3] However, it was found that the rate of reaction was dependent on the [hydroxide ion] and this is inconsistent with azomethine hydrolysis.[11]

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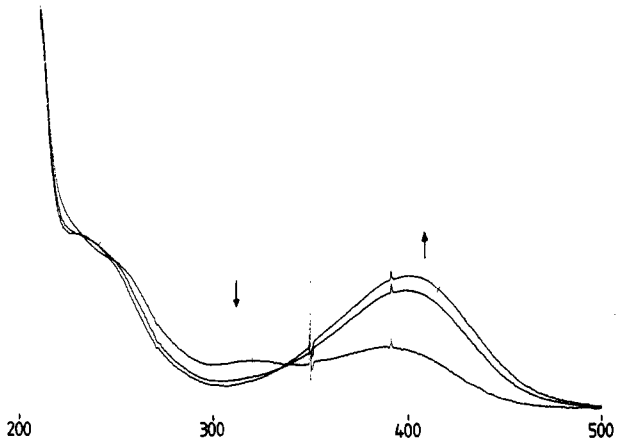

Figure 1. Repetitive scans of the reaction mixture for the first phase (0–6 min) of nimetazepam hydrolysis in 5 mM $NaOH/H_2O$.

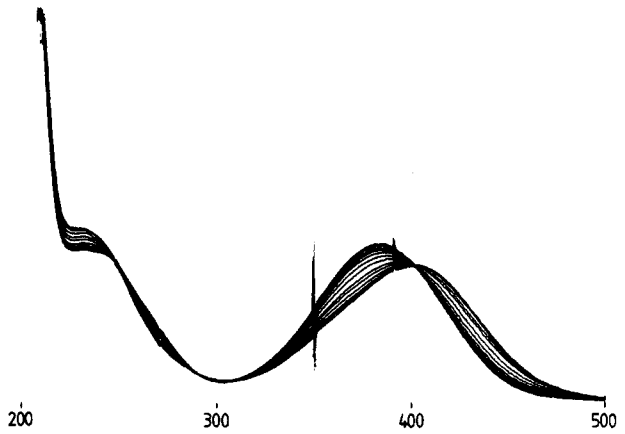

Figure 2. Repetitive scans of the reaction mixture for the second phase (10–205 min) of nimetazepam hydrolysis in 5 mM $NaOH/H_2O$.

Because of complications due to ionization of the N–H group of nitrazepam in basic solution at pH > pK_a (pK_a(nitrazepam) = 10.8), we have studied the basic hydrolysis of the N-methyl derivative, nimetazepam (**1c**), for which no such ionization is possible. Scans of the UV–vis spectrum for the basic hydrolysis of this compound revealed a biphasic reaction. Within each phase, tight isosbestic points were observed. The rapid first phase was characterized by an increase in absorbance (ΔA = 0.6 in 6 min) at 400 nm (isosbestic point 336 nm), while the slower second phase was characterized by an increase in absorbance at (ΔA = 0.2 in 2 h) 385 nm (isosbestic point 402 nm). Repetititive scans for the two phases of reaction are shown in Figures 1 and 2. Rate constants for each phase of reaction are in Tables I and II.

It can be seen that for the rapid first phase of reaction the rate of reaction (at 30 °C) is dependent on the hydroxide concentration and is subject to significant catalysis when the reaction is carried out in the presence of 8 mM CTAB (53-fold catalysis at 4.67 mM NaOH). The spectral changes observed in water and in the presence of micelles of CTAB were very similar for nimetazepam hydrolysis, indicating a similar mechanism of hydrolysis in each case. The dependence on hydroxide concentration and the strong micellar catalysis suggests that the first phase of reaction involves amide cleavage, producing intermediate **2c**.

UV survey spectra of *p*-nitroaniline and *p*-nitro-*N*-methylacetanilide had λ_{max} of 405 and 286 nm, respectively. Thus, the production of a compound having a λ_{max} at 400 nm is indicative of the formation of the *N*-methyl-*p*-nitroaniline chromophore. This is consistent with intermediate **2c** rather than **3c**, indicating initial amide cleavage. From the initial scans of Figures 1 and 3, it can be seen that the intact benzodiazepinone has a negligible absorbance above 350 nm. During the cleavage of the amide bond, the absorbance in the range 350–400 nm increased due to the production of the nitroaniline chromophore. The actual λ_{max} varies slightly within this range, depending on the substituents on the amine nitrogen atom (methyl or benzyl) and on the 2-position of the benzene ring in structures **2** and **4** (Scheme I). The actual λ_{max} also changes slightly on transfer from water to micelles of CTAB.

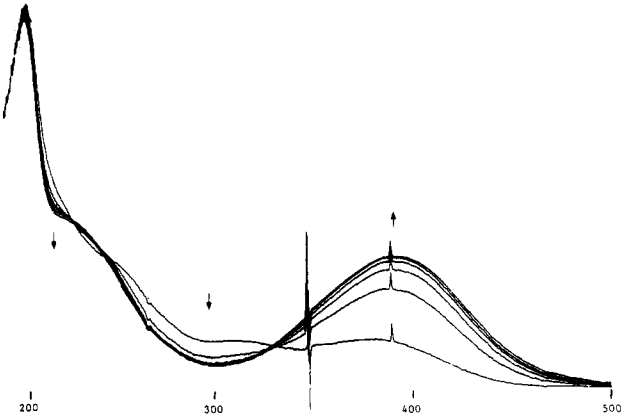

Figure 3. Repetitive scans of the reaction mixture for the first phase (0–15 min) of *N*-benzylnitrazepam hydrolysis in 5 mM $NaOH/H_2O$.

The slower second phase of reaction was followed at 74.5 °C and, in this case, the rate of reaction is independent of hydroxide concentration in water and only very weakly catalyzed by micelles of CTAB. The absorbance change at 385 nm in water for the second stage of nimetazepam hydrolysis (i.e., **2c** → **4c**) was small (ΔA = 0.2) in aqueous solution. Because of slight changes of λ_{max} on transfer to micellar solution, the absorbance change at 385 nm was too small for reliable kinetic measurements. Thus, in micellar solution, the second stage of hydrolysis was followed at 252 nm where a larger absorbance change occurred. This supports the contention that the second phase involves azomethine cleavage in the intermediate (i.e., **2c** → **4c**). Azomethine cleavage has been reported to be inhibited by micelles of CTAB.[11] In our case, the mild catalysis (×3) may arise from electrostatic effects on the attack of a nucleophile on intermediate **2c**. In basic solution, the COOH group of intermediate **2c** would be ionized to COO^- and attack of the electron-rich nucleophile on the azomethine carbon may be hindered electrostatically by the COO^- group. This interaction may be lessened in the presence of micelles of CTAB, either because of the counter effect of the positively charged micellar headgroups or because of the alignment of the intermediate in the micelle.

Thus, for nimetazepam, the kinetic and spectroscopic evidence supports a biphasic reaction with initial amide and subsequent azomethine cleavage (**1c** → **2c** → **4c**). This is in contrast to the conclusions of Han and co-workers in the hydrolysis of nitrazepam. However, we should note that the first phase of hydrolysis for nimetazepam was very rapid, necessitating kinetic studies at 30 °C. Han and co-workers worked at 75 °C and it is possible that they missed the rapid first phase of reaction at that temperature. It is unlikely that they were, in fact, observing the second phase of a biphasic reaction because that would not explain the dependence of the rate on the $[OH^-]$ that they

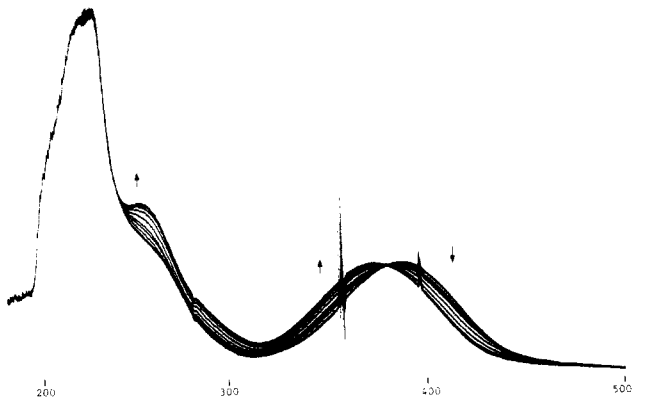

Figure 4. Repetitive scans of the reaction mixture for the second phase (15 min onward) of *N*-benzylnitrazepam hydrolysis in 5 mM borate buffer pH 9.2/8 mM CTAB.

Table III. Observed Pseudo-First-Order Rate Constants for the First Phase of *N*-Benzylnitrazepam Hydrolysis at 30.0 °C

		10^4k_1, s^{-1}	
[NaOH], mM	at [CTAB], mM	0[a,b]	8[c]
4.67		1.09 (43.3)	187
9.33		4.15 (72.3)	362
46.7		36	
94		101	

[a] Results in parentheses at 74.5 °C. [b] Followed production of intermediate **2d** at 395 nm. [c] Followed production of intermediate **2d** at 375 nm.

Table IV. Observed Pseudo-First-Order Rate Constants for the Second Phase of *N*-Benzylnitrazepam Hydrolysis at 74.5 °C

		10^4k_1, s^{-1}	
[NaOH], mM	at [CTAB], mM	0[a]	8
1.9		1.25	
4.67		1.11	
9.33		1.63	

[a] Followed production of product **4d** at 365 nm in the presence of 20% dioxane and potassium chloride to maintain constant ionic strength (0.02 M).

observed. A possible explanation may be that because of extensive ionization of the N–H group of nitrazepam, the first reaction was considerably slower than that for nimetazepam. Consequently, this was the reaction observed by Han at 75 °C ($k = 32 \times 10^{-4}$ s^{-1}). The second reaction was not detected possibly because it is much slower ($k = 1 \times 10^{-4}$ s^{-1} for compound **1c**) than the first phase.

(b) *N*-Benzylnitrazepam (1d). In acidic solution, the presence of a benzyl group on N-1 strongly inhibits amide hydrolysis.[10] It was, thus, of interest to determine the mechanism of basic hydrolysis of compound **1d**, both in H_2O and in micelles of CTAB. As for nimetazepam, scans of the UV–vis spectrum for the hydrolysis of *N*-benzylnitrazepam showed a biphasic reaction. The first phase was characterized by an increase in absorbance ($\Delta A = 0.6$ in 8 min) at 385 nm with an isosbestic point at 336 nm, while the second phase resulted in an increase in absorbance ($\Delta A = 0.1$ in 3 h) at 365 nm with an isosbestic point at 374 nm. Repetitive scans of these reactions are in Figures 3 and 4. Rate constants for the fast and slow phase of *N*-benzylnitrazepam hydrolysis are in Tables III and IV, respectively.

It can be seen that the rate of the first phase at 30 °C was dependent on the [OH^-] and was strongly catalyzed by micelles of CTAB (172-fold catalysis at 4.67 mM NaOH). The spectral changes observed in water and in

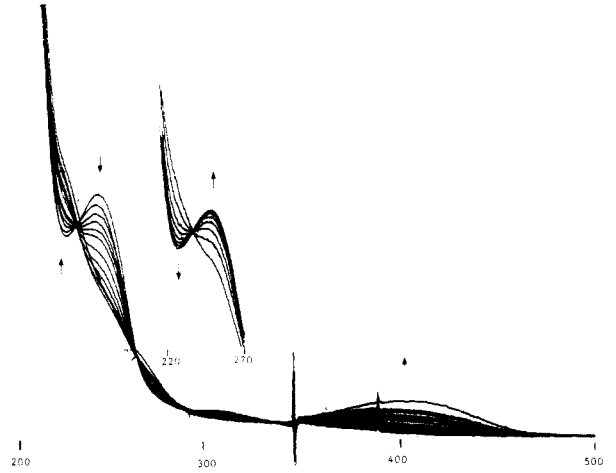

Figure 5. Repetitive scans of the reaction mixture for the hydrolysis of diazepam in 0.11 M NaOH/12 mM CTAB: (inset, first phase 0–10 min) second phase 10 min onward.

Table V. Observed First-Order Rate Constants for the Basic Hydrolysis of Diazepam at 74.5 °C

		10^4k_1, s^{-1}, for			
		phase 1[a]		phase 2[b]	
[NaOH], mM	[CTAB], mM	0	12	0	12
18.5			27.4		3.90
55.4					3.08
73.8		9.20	85.7	0.677	
92.3		8.5		1.04	
111			132		2.60
185		10.4		2.16	
277		15.3	281	2.78	1.99

[a] Followed at 252 nm. In aqueous solution, this corresponds to the production of intermediate **3a**, whereas in the presence of CTAB it is the production of intermediate **2a**. The absorbance change in aqueous solution (i.e., **1a** → **3a**) was significantly greater than that in CTAB (i.e., **1a** → **2a**). [b] Followed decrease of absorbance at 252 nm. In both aqueous solution and in CTAB, this corresponds to production of product **4a**.

the presence of CTAB and the dependence of the rate of each phase on the [OH^-] were similar, indicating that hydrolysis occurs by the same mechanism in water and in CTAB.

The rate of the second phase of reaction was measured at 74.5 °C, and in aqueous solution it was essentially independent of [OH^-]. Because of solubility problems, 20% by volume of dioxane was used. In the presence of CTAB, the spectral changes were smaller and the rate constants so obtained were not reliable.

These results are consistent with hydrolysis by the mechanism **1d** → **2d** → **4d**, both in water and in CTAB. Thus, the basic hydrolysis of the amide bond in compound **1d** is not as succeptible to steric hindrance as is the acidic hydrolysis.

(c) Diazepam (1c). Previous studies[2] of the basic hydrolysis of diazepam at 80 °C showed a monophasic reaction indicative of nucleophilic attack at C-5, leading to initial azomethine cleavage. At pH > pK_a (pK_a(diazepam) = 3.3), the intermediate **3a** would be subject to recyclization leading to monophasic kinetics. However, the reported rate of reaction was dependent on [OH^-] and this is inconsistent with initial azomethine cleavage.[11] Scans of the UV–vis spectrum for the basic hydrolysis of diazepam (Figure 5) showed clear biphasic kinetics. The first phase was characterized by the increase of absorbance ($\Delta A = 0.26$ in 5 min) at 252 nm (isosbestic point 243 nm), while the second phase showed a decrease in absorbance ($\Delta A = -0.40$ in 6 h) at 252 nm with isosbestic points at 237, 268,

and 287. Rate constants for the fast and slow phases of diazepam hydrolysis at 74.5 °C in basic solution are in Table V.

It can be seen that contrary to Han's results, the rate of the first phase was essentially independent of hydroxide concentration, while the second phase was dependent on hydroxide concentration. Reaction in the presence of micelles of CTAB also gave biphasic kinetics, but, in this case, the fast reaction was first order in hydroxide concentration, while the rate of the slow reaction actually decreased slightly as the [OH^-] was increased.

These observations are consistent with a change of mechanism from initial azomethine cleavage in aqueous solution (mechanism **1a** → **3a** → **4a**) to initial amide cleavage in the presence of micelles of CTAB (mechanism **1a** → **2a** → **4a**).

Initial amide cleavage in the presence of micelles of CTAB is indicated by a biphasic reaction in which the rate of the first phase is dependent on [OH^-] (amide cleavage) and the rate of the slower second phase is not increased by increasing [OH^-] (azomethine cleavage in intermediate **2a**).

Initial azomethine cleavage in water is indicated by a biphasic reaction in which the rate of the first phase is essentially independent of [OH^-] (azomethine hydrolysis), while the rate of the slower second phase is dependent on [OH^-] (amide hydrolysis in intermediate **3a**). What remains to be explained is why a reaction involving initial azomethine cleavage at $pH > pK_a$ does not produce monophasic kinetics?

The possibility of recyclization of intermediate **3a** does not necessarily lead to monophasic kinetics if the subsequent breakdown of this intermediate is very slow. We thus achieve a non steady state situation. Intermeidate **3a** accumulates in solution. The first phase is then the establishment of this equilibrium, while the second phase is the slow breakdown of the intermeidate to products.

Since the rate of the second phase of this reaction in water is dependent on the [OH^-], it follows that this is what Han[2] actually observed in his work. The first phase is very fast and could easily have been missed in this original work. If you compare the rate constants obtained by Han at 80 °C in 0.05 M NaOH (4.3×10^{-5} s^{-1}) with our rate constant at 74.5 °C for the second phase of reaction in 0.074 M NaOH (6.8×10^{-5} s^{-1}), this lends support to the above interpretation.

Experimental Section

Materials. Nimetazepam and diazepam were provided by Roche Products Pty. Ltd. *N*-Benzylnitrazepam was available from previous work.[10] Cetyltrimethylammonium bromide (CTAB) (BDH) was purified by the method of Mukerjee and Mysels.[13] Distilled water was further purified by a Millipore system to achieve a resistivity of, at least, 10 MΩ cm^{-1}.

Kinetics. Stock solutions (1×10^{-2} M) of the substrates **1a–d** were prepared in dry dioxane. Stock solutions of NaOH (0.5 M) and CTAB (20 mM) were prepared in purified water. The solutions required for kinetic studies were prepared by mixing appropriate volumes of the stock solutions of NaOH and CTAB and dilution as required. The solutions were placed into cuvettes and allowed 30 min in the constant temperature cell holder of a Varian 634 UV–vis spectrophotometer to reach thermal equilibrium. The temperature within the cuvette was measured with a Jenco thermistor thermometer. Then a sample of the stock solution of the required substrate (12 μL) was added to the cuvette and the contents were mixed thoroughly. The rate of change of absorbance at the desired wavelength was followed by means of a National VP6511A X-T recorder. Repetitive scans of the reaction mixture were obtained with a Hewlett Packard 7041A X–Y recorder.

Reactions were followed to infinity (10 half-lives) where possible or alternatively for very slow reactions or for consecutive reactions an infinity value was calculated by using a computer program designed to give the best straight line fit to data collected over at least 2 half-lives. Good agreement was obtained between rate constants that could be obtained by the two methods. In all cases, the UV–vis spectra of the final products were identical with that of the appropriate substituted 2-aminobenzophenone **4**. Rate constants were all obtained in duplicate and average results are presented in Tables I–V. The reproducibility of the rate constants are all within ±2%.

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Registry No. **1a**, 439-14-5; **1c**, 2011-67-8; **1d**, 102725-58-6; **2a**, 102725-59-7; **2c**, 102725-60-0; **2d**, 102725-61-1; **3a**, 36020-94-7; **4a**, 1022-13-5; **4c**, 4958-56-9; **4d**, 37548-92-8; $NH_2CH_2CO_2H$, 56-40-6; cetyltrimethylammonium bromide, 57-09-0.

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Synthesis of Tetraisopropylethane and Tetracyclopropylethane and Generation of the Pentacyclopropylethyl Carbocation

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The synthesis of tetracyclopropyl- and tetraisopropylethanes has been achieved through the deazatization of the prerequisite azoalkanes. Variations in reactivity among these azoalkanes support the contention that an isopropyl group is sterically more demanding than a cyclopropyl. The synthesis of pentacyclopropylethane and its conversion to the corresponding carbocation are described.

It is clear from comparison of the NMR behavior of tetracyclopropyl- and tetraisopropylethylene that an isopropyl group is considerably more sterically demanding than cyclopropyl. For example, coalescence of the isopropyl groups in **1** occurs at 35 °C[2,3] while no change is noted in **2** at temperatures down to −160 °C.[4] In the synthesis of both tetraisopropyl- and tetracyclopropyl-

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