Reactions of Carbonyl Compounds in Basic Solutions. Part 14.[1] The Alkaline Hydrolysis of Substituted *N*-Methylformanilides, *N*-Methylacetanilides, 1-Phenylazetidin-2-ones, 1-Phenyl-2-pyrrolidones, and 1-Phenyl-2-piperidones

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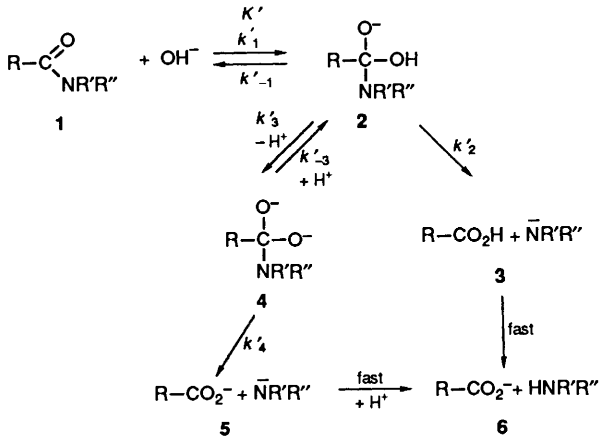
The rate coefficients for the alkaline hydrolysis of a series of substituted 1-phenylazetidin-2-ones, -2-pyrrolidones, and -2-piperidones, and *N*-methylacetanilides and *N*-methylformanilides in aqueous dimethyl sulphoxide and in aqueous dioxane or water have been measured at several temperatures. The reactions were first order in substrate and, for the lactams and acetanilides, first order in base and, for the formanilides, both first and second order in base. Hammett reaction constants and activation parameters have been evaluated for each system. The relative reactivity, salt, solvent and solvent isotope effects have been examined. The following mechanisms for the reactions are suggested. For the β-lactams, the pathway appears to be the rate-determining attack by hydroxide and, for the γ- and δ-lactams and acetanilides, rate-determining fission of the carbon–nitrogen link, which follows equilibrium addition of the base. The formanilides appear to form a tetrahedral intermediate with hydroxide which can collapse to product *via* rate-determining water- or base-catalysis.

The alkaline hydrolysis of amides and lactams has been studied extensively.[2,3] The mechanisms of reaction are similar to those of the alkaline hydrolyses of esters; but the leaving group is often very much poorer in amides and lactams. Tertiary amides and secondary lactams show simpler behaviour than others as concomitant ionisation of the weakly acidic amide or lactam N–H cannot occur. Evidence exists for both first- and second-order reactions in such hydroxide anion reactions.[2] A simplified and generalised mechanistic pathway for the alkaline hydrolysis of tertiary amides and secondary lactams, where ionisation of the substrates is not possible, is shown in Scheme 1.



Scheme 1

The alkaline hydrolysis of a series of substituted *N*-methylformanilides in water and aqueous dimethyl sulphoxide (DMSO) have been investigated by Kavalek *et al.*[4] The dependence of log *k* on σ was found to be non-linear. The reaction was found to be second order in hydroxide for most substrates. However, the *meta*- and *para*-nitro substrates gave more complex kinetics. The mechanism of the alkaline hydrolysis of substituted *N*-methylacetanilides has been studied in aqueous DMSO.[5] The reaction was considered to proceed by a rate-determining water-assisted decomposition of the tetrahedral intermediate for all substituents studied, except the *para*-nitro substrate. The latter apparently reacts with rate-determining formation of the tetrahedral intermediate. Bruylants and coworkers[6] have reviewed their studies on diverse series of amides, including certain *N*-methylformanilides and *N*-methylacetanilides, in which the latter amides conform to the pattern shown in Scheme 1.

An important study of the alkaline hydrolysis of *N*-aryl-β-lactams in water was made by Blackburn and Plackett.[7] The results were contrasted with those for the corresponding γ- and δ-lactams and *N*-methylacetanilides. The Hammett ρ value for substitution in the *N*-aryl-β-lactam clearly indicated rate-determining attack of hydroxide on the β-lactam, followed by rapid ring fission. The other lactams and acetanilides appear to have rate-determining fission of the carbonyl–nitrogen link, following the equilibrium formation of the tetrahedral intermediate. All systems showed first-order dependence on hydroxide.

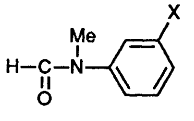
Deslongchamps *et al.*[8,9] have investigated the alkaline hydrolysis and carbonyl-oxygen exchange in both tertiary amides and *N*-aryl-β-lactams. β-Lactams, without severe steric hindrance, showed no carbonyl exchange and facile hydrolysis;[8] while the tertiary amides gave carbonyl-oxygen exchange by invoking a conformational change in the tetrahedral intermediate.[9]

The present study consists of an investigation of the alkaline hydrolysis of directly comparable series of *N*-methylformanilides **7**, *N*-methylacetanilides **8**, *N*-phenyl-β-lactams **9**, *N*-phenyl-γ-lactams **10** and *N*-phenyl-δ-lactams **11**. The substrates studied are those having well-behaved *meta*-substituents and the conditions of the reactions are either identical or very closely comparable. The effects of substitution and the structure of the amides or lactams on the rates of reaction, as well as the kinetics, activation parameters, kinetic solvent isotope and solvent effects, are all considered to enable a complete picture of the reactivity and mechanism of alkaline hydrolysis of this important group of interrelated substrates to be given.

Table 1 Rate coefficients (k_2) for the alkaline hydrolysis of the *N*-(3-substituted phenyl) lactams and *N*-methyl-3-substituted acetanilides in 70% (v/v) aqueous DMSO[a]

Substituent	$k_2/10^{-3}$ dm^3 mol^{-1} s^{-1}				λ/nm
1-Phenylazetidin-2-one	At 30.0 °C	40.0 °C	50.0 °C	60.0 °C	
H	6.63(0.638)[b]	15.7	35.8	71.5	302.5
CH_3	5.25(0.482)[b]	12.1	28.3	57.0	302.5
Cl	35.7(2.52)[b]	—	163	—	302.5
NO_2	145(10.1)[b]	300	632	1170	410
1-Phenyl-2-pyrrolidone	At 30.0 °C	50.0 °C	70.0 °C	90.0 °C	
H	—	—	—	0.267	305
CH_3	—	—	—	0.255	305
Cl	—	—	—	3.67	305
NO_2	1.14	5.7	20.5	67.2	410
1-Phenyl-2-piperidone					
H	—	—	—	0.957	300
CH_3	—	—	—	0.713	300
Cl	—	—	—	10.5_5	300
NO_2	3.38	16.6	54.7	151	410
N-Methylacetanilide					
H	—	—	—	0.710	300
CH_3	—	—	—	0.680	297.5
Cl	—	—	—	11.6	305
NO_2	1.70	9.28	37.0	118	400

[a] The rate coefficients are reproducible to within ±3%. [b] In 70% (v/v) aqueous dioxane at 31.0 °C.



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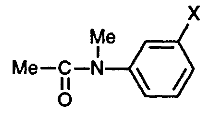

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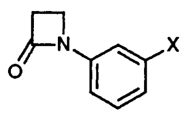

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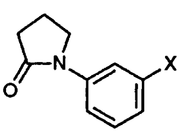

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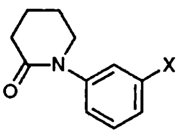

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Results

The alkaline hydrolysis of the substituted *N*-methylacetanilides, 1-phenylazetidin-2-ones, 1-phenyl-2-pyrrolidones and 1-phenyl-2-piperidones are all first order both in substrate and base. The rate coefficients in 70% (v/v) aqueous dimethyl sulphoxide are shown in Table 1. The rate coefficients for the 3-nitro substrates and all the β-lactams have been measured at several temperatures, as shown in Table 1, and the activation parameters are shown in Table 2. The effect of solvent composition, including deuterium oxide, and salt on the rate coefficients for the 3-nitro substrates are shown in Tables 3 and 4. The alkaline hydrolyses of the substituted *N*-methylformanilides are first order in substrate and first and second order in base (see the Experimental). The rate coefficients at constant ionic strength in 70% (v/v) aqueous DMSO for both processes and in water for k_2 are shown in Table 5. The rate coefficients in water for *N*-methyl-3-nitroformanilide for both processes and for *N*-methylformanilide for k_2 have been measured at several temperatures, as shown in Table 5, and the activation parameters are shown in Table 2. The rate coefficients for the latter two substrates in deuterium oxide are also shown in Table 6.

Table 2 Activation parameters for the alkaline hydrolysis of the *N*-(3-substituted phenyl) lactams and *N*-methyl-3-substituted acetanilide in 70% (v/v) aqueous DMSO at 30.0 °C[a]

Substituent	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$ cal mol^{-1} K^{-1}
1-Phenylazetidin-2-one		
H	15.4	−18
CH_3	15.5	−18
Cl	14.3	−18
NO_2	13.5	−18
1-Phenyl-2-pyrrolidone		
NO_2	14.3	−25
1-Phenyl-2-piperidone		
NO_2	13.2	−26
N-Methylacetanilide		
NO_2	14.9	−22
[*N*-Methylformanilide[b]		
H (k_2)	11.4	−36
NO_2 (k_2)	10.9	−36
NO_2 (k_3)[c]	9.6	−39]

[a] Values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are accurate to within ±300 cal mol^{-1} and ±2 cal mol^{-1} K^{-1}, respectively. [b] In water. [c] Values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are accurate to within ±800 cal mol^{-1} and ±3 cal mol^{-1} K^{-1}, respectively.

Discussion

All the alkaline hydrolyses of the lactams, acetanilides, and formanilides studied here undoubtedly proceed to product *via* tetrahedral intermediates.[2,3,8,9] It is the nature of the rate-determining step and the structure of the transition states that are being considered.

Reactivity of Lactams and Anilides.—The relative reactivity of the systems studied here appears to be quite clear and

Table 3 Rate coefficients (k_2) for the alkaline hydrolysis of the *N*-(*m*-nitrophenyl) lactams and *N*-methyl-*m*-nitroacetanilide in various solvent compositions

			$k_2/10^{-3}$ dm^3 mol^{-1} s^{-1}					
System	T/°C		30	50	60	70	80	90% v/v
System		*Solvent*						
Azetidin-2-one	30.0	DMSO	21.0	33.7	53.7	145	350	1280
	70.0	Dioxane	218	222	—	195(283)[b]	165	—
2-Pyrrolidone	70.0	DMSO	0.316	0.687	2.25	10.8	56.5	698
	70.0	Dioxane	—	—	—	0.720(1.14)[b]	—	—
2-Piperidone	70.0	DMSO	2.75	5.07	13.0_5	54.7	228	1660
	70.0	Dioxane	1.20	1.42	—	1.95(3.02)[b]	5.50	—
N-Methylacetanilide	70.0	DMSO	2.05	5.85	10.4_5	37.0	119	478
	70.0	Dioxane	0.747	0.960	—	1.40(2.13)[b]	1.82	—

[a] See Table 1. [b] In 70% v/v dioxane–deuterium oxide.

Table 4 Rate coefficients (k_2) for the alkaline hydrolysis of the *N*-methyl-3-nitroacetanilide and *N*-(3-nitrophenyl) lactams in 70% (v/v) aqueous dioxane containing salts at 70.0 °C[a,b]

System	[Salt]/mol dm^{-3}	$k_2/10^{-3}$ dm^3 mol^{-1} s^{-1}
Azetidin-2-one	—	188
	0.1 (LiCl)	182
	0.2 (LiCl)	134
	0.2 ($PhCH_2NMe_3I$)	194
	0.4 ($PhCH_2NMe_3I$)	201
2-Piperidone	—	1.95
	0.1 (LiCl)	1.92
	0.2 (LiCl)	1.42
	0.2 ($PhCH_2NMe_3I$)	2.15
	0.4 ($PhCH_2NMe_3I$)	2.33
N-Methylacetanilide	—	1.40
	0.1 (LiCl)	1.36
	0.2 (LiCl)	1.05
	0.2 ($PhCH_2NMe_3I$)	1.52
	0.4 ($PhCH_2NMe_3I$)	1.70

[a] See Table 1. [b] Base is NaOH (1.5×10^{-2} mol dm^{-3}).

Table 5 Rate coefficients (k_2 and k_3) for the alkaline hydrolysis of 3-substituted *N*-methylformanilides at constant ionic strength and 30.0 °C[a]

	$k_2/10^{-3}$ dm^3 mol^{-1} s^{-1}		$k_3/10^{-3}$ dm^6 mol^{-2} s^{-1}
Substituent	in water (μ = 1.0 mol dm^{-3})	in 70% (v/v) aqueous DMSO (μ = 0.27 mol dm^{-3})	in 70% (v/v) aqueous DMSO (μ = 0.27 mol dm^{-3})
H	0.402	0.0831	1.29
CH_3	0.347_5	0.0665	0.834
Cl	0.658	0.833	73.4
NO_2	1.33	16.8	2550

[a] See the Experimental section for derivations of k_2 and k_3. k_2 is considered to be ±5% in water and ±10% in 70% (v/v) aqueous DMSO and k_3 to be ±8%.

Table 6 Rate coefficients (k_2 and k_3) for the alkaline hydrolysis of *N*-methyl-3-substituted formanilides at constant ionic strength (μ = 1.0 mol dm^{-3}) in water[a]

	$k_2/10^{-3}$ dm^3 mol^{-1} s^{-1}		$k_3/10^{-3}$ dm^6 mol^{-2} s^{-1}	
T/°C	H	*m*-NO_2	*m*-NO_2	λ/nm
30.0	0.402(0.273)[b]	1.33(1.25)[b]	5.52(5.91)[b]	300
40.0	0.767	2.33	8.95	300
50.0	1.50	4.17	14.5	305
60.0	2.35	7.45	24.1	400

[a] See Table 4. [b] In deuterium oxide.

consistent. From the results in Tables 1 and 4, the order of reactivity in 70% (v/v) aqueous DMSO for k_2 is β-lactam > formanilide ≫ δ-lactam > acetanilide > γ-lactam. This is the same as that found previously, under other conditions, where comparisons are possible.[6,7]

Substituent Effects.—The effect of substitution has been assessed by use of the Hammett eqn. (1), using *meta*-σ values.[10]

$$\log(k/k_o) = \rho\sigma \qquad (1)$$

The reaction constants, ρ, are shown in Table 7. If, for the overall processes, the limiting states are considered, *i.e.* **2**–**5** in Scheme 1, it is possible to estimate the ρ values that can be expected for their formation. For **2**, an estimate for ρ of about 1.7 at 30 °C can be made which is based on the alkaline hydrolysis of phenyl acetates[11] and benzoates.[12] For **3**, the ρ value for the ionisation of anilines in aqueous DMSO[13] at 20 °C can be used as a model and results in an estimate for ρ of about 4.1. An estimate of ρ for the formation of **4** in Scheme 1 would be about twice that for **2**, *i.e. ca.* 3.4. Approximately the same estimate of ρ for **5** in Scheme 1 as that for **3** would apply.

It is clear from both the ρ values found, *i.e. ca.* 1.7 and 1.9 in aqueous dioxane at 31 °C and aqueous DMSO at 30 °C, respectively, and the reactivity of the *N*-phenyl β-lactams, that k_1' in Scheme 1 is the rate-determining step for this system. This can be compared with a ρ value found previously of *ca.* 1.2 in water at 25 °C.[7] The difference in ρ values in different solvents is that expected from studies of the solvent effect on the alkaline hydrolysis of esters.[14] For the *N*-phenyl γ- and δ-lactams and *N*-methylacetanilides, the ρ values found, *i.e. ca.* 3.1 at 90 °C, and the reactivities, indicate the rate-determining step to be k_2' in Scheme 1, which is the formation of the anion of the aniline, following equilibrium formation of the tetrahedral intermediate. Reaction constants can be approximately corrected for temperature using relation (2).[15] Use of eqn. (2) results in a value of ρ

$$\rho_{T2}/\rho_{T1} = T_1/T_2 \qquad (2)$$

equal to *ca.* 3.8 at 20 °C. This result may be used to assign effective charges in a manner similar to that used by Williams.[16] Thus, the ratio of the ρ value above to that for the ionisation of anilines under similar conditions[13] is *ca.* 0.93. This would

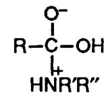
Table 7 The Hammett reaction constants (ρ) for the alkaline hydrolysis of *N*-phenyl lactams, *N*-methylacetanilides and *N*-methylformanilides in 70% (v/v) aqueous DMSO[a]

System	T/°C	ρ	$\log k_o$	r	s	n
2-Azetidinones	30.0	1.87	−2.160	1.000	0.03	4
2-Azetidinones	40.0	1.81	−1.664	0.999	0.05	4
2-Azetidinones	50.0	1.75	−1.365	0.998	0.08	4
(2-Azetidinones	31.0	1.68	−3.203	1.000	0.03	4)[b]
2-Pyrrolidones	90.0	3.17	−3.497	0.995	0.23	4
2-Piperidones	90.0	2.99	−2.999	0.998	0.14	4
N-Methylacetanilides	90.0	2.98	−4.048	0.996	0.18	4
N-Methylformanilides (k_2)	30.0	3.07	−4.057	0.994	0.24	4
N-Methylformanilides (k_3)	30.0	4.54	−2.821	0.999	0.10	4
[*N*-Methylformanilides (k_2)	30.0	0.79_5	−3.457	0.981	0.11	4][c]

[a] s is the standard deviation, r is the correlation coefficient and n is the number of substituents. [b] In 70% (v/v) aqueous dioxane. [c] In water.

indicate an advanced transition state in which the anionic aniline is almost completely formed. For the k_3 process in 70% (v/v) aqueous DMSO for the *N*-methylformanilides, the ρ value found, *i.e. ca.* 4.5 at 30 °C, indicates the rate-determining step as k_4' in Scheme 1. This is the formation of the anion of the aniline, following successive equilibrium formations of the tetrahedral monoanion and dianion.

For the k_2 process for *N*-methylformanilides, the situation appears more complex. In 70% (v/v) aqueous DMSO, the ρ values of *ca.* 3.1 at 30 °C would indicate k_2' in Scheme 1 as the rate-determining step. However, in water, the ρ value of *ca.* 0.8 at 30 °C clearly indicates a different process. This could not be k_1' in Scheme 1 as the first-order reaction in base is accompanied by a higher-order reaction. The latter can only result from catalysis by base of the breakdown of **2** in Scheme 1. Such catalysis by water has been suggested for acetanilides (*cf.* refs. 5 and 17) and the intermediate **12** can be considered as the limiting state. For the formation of **12**, an estimate for ρ of *ca.* −1.1, can be made from the sum of ρ for the equilibrium



$$\mathrm{R{-}\overset{O^-}{\underset{\overset{+}{H}NR'R''}{C}}{-}OH}$$

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protonation of anilines (−2.77)[15] and the formation of **2** (see above). Using the effective charge description,[15] the development of charge would be very small as indicated by the ratio of the observed ρ to that for the ionisation of anilines (see later). Alternatively a water molecule could transfer the proton in **2** in Scheme 1.

Activation Parameters.—The enthalpies and entropies of activation shown in Table 2 for all the β-lactams and for the other *N*-(3-nitrophenyl) lactams and *N*-methyl-3-nitroacetanilide all clearly indicate bimolecular reactions; but do not differ very significantly from one another. However, the activation parameters for the hydrolysis of *N*-methylformanilides differ significantly from the others. For the formanilides in water, the enthalpy of activation for the k_2 process is at least 2.6 kcal mol^{-1} * less than those for comparable substitution in other series. Furthermore, the entropy of activation clearly indicates a termolecular reaction.[18] This clearly implicates a water molecule in the transition state which is intimately and directly involved in that state. Again for comparable substitution, the enthalpy of activation for the k_3 process of the *N*-methylformanilides is significantly lower; while the entropy of activation indicates a termolecular reaction.

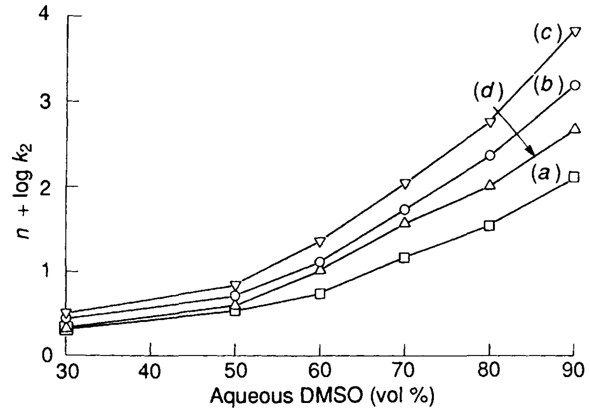

Fig. 1 Relationship between $\log k_2$ for the alkaline hydrolysis of *N*-(*m*-nitrophenyl) lactams and *N*-methyl-*m*-nitroacetanilide and the composition of aqueous DMSO: (*a*) azetidin-2-one at 30.0 °C; (*b*) 2-pyrrolidone; (*c*) 2-piperidone; (*d*) acetanilide at 70.0 °C [*n* equals 2 for (*a*) 3 for (*b*), (*d*) and 4 for (*c*)]

Solvent and Salt Effects.—For the alkaline hydrolysis of esters, the effect of increasing DMSO content in aqueous–DMSO mixtures is dramatically to increase the rate of reaction.[19] This result is paralleled by the behaviour of the alkaline hydrolysis of the lactams and *N*-methylacetanilide studied here, as shown in Fig. 1. Thus, the ratio of the rate coefficients in 70%:30% (v/v) aqueous DMSO is about 7 (β-lactam), 70 (γ-lactam) and 20 (δ-lactam and *N*-methylacetanilide). A previous study[20] has shown the quite different effect of increasing dioxane content on the rates of the alkaline hydrolysis reaction of several different substrates. In this study (as shown in Fig. 2) a small decrease in rate is observed for increasing dioxane content for the β-lactam; whereas, both the δ-lactam and *N*-methylacetanilide show small increases. Thus, those reactions with k_2' in Scheme 1 as the rate-determining step show significantly greater increases in rate as the water content of the medium decreases than those with k_1' in Scheme 1. This results from both the ability of DMSO to solvate charge dispersed structures[19,21] and the greater need for protic solvation of localised charged structures.

The results for the effects of solvent composition on the alkaline hydrolysis of *N*-methylformanilides are shown in Table 5. There is a great contrast between the solvent effects on these two processes. For the k_3 process of the *m*-nitro substrate, the ratio of the rate coefficient in 70% (v/v) aqueous DMSO to that in water is *ca.* 460. This result is greater than that of the

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* 1 cal = 4.184 J.

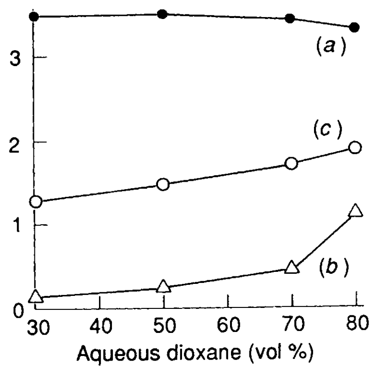


Fig. 2 Relationship between $\log k_2$ for the alkaline hydrolysis of N-(m-nitrophenyl) lactams and N-methyl-m-nitroacetanilide and the composition of aqueous dioxane at 70.0 °C: (*a*) 2-azetidinone; (*b*) 2-piperidone; (*c*) acetanilide [n equals 3 and (*a*) and (*b*), 4.5 for (*c*)]

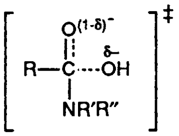
corresponding N-methylacetanilide by a factor of *ca.* 10, which is as expected for the formation of the dianion for the N-methylformanilide and the monoanion for the N-methylacetanilide. For the k_2 process of the N-methylformanilides, the less reactive substrates (*meta*-Me and H) react more slowly in aqueous DMSO than in water; whereas quite modest increases in rate occur for the more reactive substrates (*meta*-Cl and -NO_2). Both the activity coefficient and concentration of water are very much lower in 70% (v/v) aqueous DMSO (about 37 mol% DMSO) than in water itself, *i.e.* f_{H_2O} is equal to *ca.* 0.64 compared with 1.0 in water.[19] This confirms the importance of the role of water in the k_2 process for formanilides.

The salt effects on the rate coefficients for the lactams and N-methylacetanilide in 70% (v/v) aqueous dioxane at 70 °C are shown in Table 4. These results are very similar to those previously observed for ester hydrolysis.[20] The salt effects appear to be a function of the extent of delocalisation of charge in the transition state. The more delocalised structures interact more effectively with large cations and are thus stabilised.

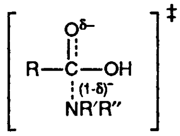
Kinetic Solvent Isotope Effects.—These effects were measured in dioxane–water and –deuterium oxide, as shown in Table 3, because of the isotopic exchange likely in aqueous DMSO. The values of k_{H_2O}/k_{D_2O} at 70 °C for hydrolysis of β-, γ- and δ-lactams and N-methylacetanilide are 0.69, 0.63, 0.65 and 0.66, respectively. The factors determining these effects are the differences between the initial and transition states. The main cause of these effects is the greater nucleophilicity of OD^- in D_2O than OH^- in H_2O.[22] The somewhat lower ratios for the reactions with k_2' in Scheme 1 as the rate-determining step are likely to be characteristic of these reactions. However, the results all exclude any significant water assistance to the leaving group which would involve some measure of primary isotope effect (see below).

The results for the N-methylformanilides in water are shown in Table 6. The value of k_{H_2O}/k_{D_2O} at 30 °C for the k_3 process for the N-methyl-3-nitroformanilide is 0.94. Although this is larger than might have been expected, this value is consistent with $K'k_3'$ in Scheme 1. However, for the k_2 process, k_{H_2O}/k_{D_2O} for the unsubstituted and 3-nitro substrates are 1.47 and 1.07, respectively. If these values are corrected for the formation of the tetrahedral adduct,[22] K', values of k_{H_2O}/k_{D_2O} equal to about 2.1 and 1.6 are given. These small, but definite, primary isotope effects must result from the partial transfer of hydrogen from water in the rate-determining step.[23]

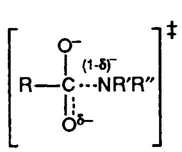
Mechanisms of the Alkaline Hydrolysis Reactions.—The detailed mechanisms of the alkaline hydrolysis of the N-phenyl lactams and anilides have been suggested and are, in general, in agreement with some previous workers.[4,7] The N-phenyl β-lactams react with rate-determining attack of hydroxide on the carbonyl group, followed by rapid ring fission. It could be a concerted process but this appears less likely. The N-phenyl γ-and δ-lactams and acetanilides, as well as the formanilides in aqueous DMSO (k_2 process), all appear to have rate-determining fission of the carbon–nitrogen link, following relatively rapid equilibrium formation of the tetrahedral adduct. The transition states for these two processes are shown as **13** and **14** below. The formanilides (k_3 process) appear to react by successive, relatively rapid formation of the anionic and dianionic tetrahedral adducts, followed by rate-determining fission of the carbon–nitrogen link in the dianion. The transition state is shown as **15** below. The pathway is in contrast with that suggested by Gani and Viout.[5] However, they did consider that a water molecule was involved in the transition state for the hydrolysis of N-methylacetanilides discussed earlier. In water, the formanilides (k_2 process) appear to have a slow rate-determining step involving assistance to the fission step by a water molecule, as shown in the transition state **16** below, *cf.* ref. 17.



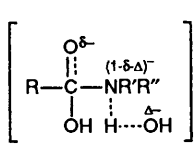
13



14



15



16

The mechanistic switches observed in this study are derived from two main structural factors. Firstly, the initial-state energy of the N-phenyl β-lactams is relatively large due to angular deformation and the concomitant strain effects.[7] Secondly, the favourable polar and steric effects[24] of the hydrogen substituent in formanilides gives rise to a relatively stable tetrahedral intermediate.

Experimental

Materials.—The N-methyl substituted formanilides were prepared from the substituted formanilides by methylation with methyl iodide in a mixture of potassium hydroxide and acetone.[25] The N-methyl substituted acetanilides were prepared by the reaction of the appropriate N-methylaniline with acetic anhydride in the presence of zinc dust.[26] The N-methylanilines have already been synthesised by methylation of the toluene-p-sulphonate derivatives of the substituted anilines by dimethyl sulphate.[26] The N-aryl-3-bromopropionamides were prepared from 3-bromopropionic acid, after treatment with phosphorus trichloride and the appropriate aniline.[27] The latter amides were then cyclised in DMSO containing strong base to give the 1-phenylazetidin-2-ones.[27] The same pathway was repeated using 4-bromobutyric acid and 5-bromovaleric acid to give the 1-aryl-2-pyrrolidones and 1-aryl-2-piperidones.[28]

After repeated recrystallisation or redistillation and drying under reduced pressure (P_2O_5), the compounds had either m.p.s in good agreement with literature values[4,5,7,29] or which are reported in Table 8. Solvents and other materials were purified as described previously.[20,30]

Kinetic Measurements.—Rate coefficients for the alkaline

Table 8 Previously unreported compounds

	M.p./°C	Found (%) C	H	N	Cl	Formula	Required (%) C	H	N	Cl
N-Methyl-3-methylformanilide	132–135/13 mmHg[a]	72.4	7.6	9.5		C_9H_9NO	72.5	7.4	9.4	
1-(3-Chlorophenyl)-azetidin-2-one	55–56	59.3	4.5	7.7	19.4	C_9H_8ClNO	59.5	4.4	7.7	19.5
1-(3-Methylphenyl)-2-pyrrolidone	46–48	75.3	7.3	8.0		$C_{11}H_{13}NO$	75.4	7.4	8.0	
1-(3-Chlorophenyl-2-pyrrolidone	63.5–64.5	61.2	5.1	7.0	18.0	$C_{10}H_{10}ClNO$	61.3	5.1	7.2	18.1
1-(3-Nitrophenyl)-2-pyrrolidone	105–106	58.1	4.8	13.6		$C_{10}H_{10}N_2O_3$	58.3	4.8	13.6	
1-(3-Methylphenyl)-2-piperidone	61–63	75.8	7.8	7.2		$C_{12}H_{15}NO$	76.2	7.9	7.4	
1-(3-Chlorophenyl)-2-piperidone	60–62	62.8	5.7	6.8	16.9	$C_{11}H_{12}ClNO$	63.0	5.7	6.6	16.9
1-(3-Nitrophenyl)-2-piperidone	86–87	60.1	5.1	12.8		$C_{11}H_{12}N_2O_3$	60.0	5.4	12.7	

[a] b.p.

Table 9 Alkaline hydrolysis at constant ionic strength of *N*-methylformanilide in 70% (v/v) aqueous DMSO (μ = 0.27 mol dm^{-3}) and of *N*-methyl-3-nitroformanilide in water (μ = 1.0 mol dm^{-3}) at 30 °C

[OH$^-$]/ mol dm^{-3}	a_{OH^-}/ mol dm^{-3}	Observed $k_1/10^{-6}$ s^{-1}	$k_2a_{OH^-}/10^{-6}$ s^{-1}	$k_3a^2_{OH^-}/10^{-6}$ s^{-1}	Calcd. $k_1/10^{-6}$ s^{-1}
N-Methylformanilide in 70% (v/v) aqueous DMSO[a]					
0.0387	0.0387	5.17	3.25	1.96	5.21
0.0561	0.061	10.2_5	5.08	4.80	9.88
0.0845	0.099	21.0	8.25	12.6	20.8_5
0.124	0.160	48.3	13.3	33.0	46.3
0.182	0.29	$130._5$	24.2	108	132
0.270	0.49	343	40.8	310	351
N-Methyl-3-nitroformanilide in water[b]					
0.10	0.10	0.188	0.133	0.0552	0.188
0.15	0.16	0.368	0.213	0.141	0.354
0.20	0.23	0.610	0.306	0.292	0.598
0.30	0.37	1.29	0.492	0.756	1.25
0.40	0.53	2.43	0.705	1.55	2.26
0.50	0.72	3.85	0.960	2.86	3.82
0.60	0.89	5.82	1.18	4.37	5.55
0.70	1.08	8.30	1.43	6.44	7.87
0.80	1.30	11.1	1.73	9.34	11.1
0.90	1.52	14.7	2.02	12.8	14.8
1.00	1.80	18.3	2.39	17.9	20.3

[a] 10^6k_2 = 83.3 dm^3 mol^{-1} s^{-1} and 10^4k_3 = 12.9 dm^6 mol^{-2} s^{-1}. [b] 10^3k_2 = 1.33 dm^3 mol^{-1} s^{-1} and 10^3k_3 = 5.52 dm^6 mol^{-2} s^{-1}.

hydrolysis of the lactams and amides were determined spectrophotometrically by use of Unicam SP800 and SP8-100 spectrophotometers. The cell temperature was controlled to within ±0.05 °C between 30 and 60 °C and to within ±0.1 °C between 60 and 90.0 °C, by means of a Churchill thermocirculator. The reactions were followed at suitable wavelengths, as shown in Tables 1 and 6, which were normally those having the greatest difference between the substrate and product. The procedure then followed was that described previously[20] using a Beckmann chart recorder. The substrates were dissolved in either dioxane or DMSO and were studied in the range 5 × 10^{-5}–1 × 10^{-4} mol dm^{-3}. The reaction was continuously monitored to infinity reaction after ten half-lives. Kinetic plots gave linear relations to at least 85% reaction. For the lactams and *N*-methylacetanilides, the base, sodium hydroxide, was studied between *ca.* 5 × 10^{-4} and 2 × 10^{-1} mol dm^{-3}, which was at least a tenfold and, normally, a hundredfold excess over substrate to give first-order kinetics. The latter reactions were all found to be first-order in base over this range of base concentrations. For the *N*-methylformanilides, the same procedures were used; but the base dependence was more complex. In water, the base concentrations studied were from 5 × 10^{-4} to 1 mol dm^{-3}. The second-order rate coefficients were obtained by extrapolation of k_1/[OH$^-$] to zero base concentration to give k_2. At low base concentration, the kinetic behaviour approximated to first-order in base. In 70% (v/v) aqueous DMSO, the base concentration studied was 5 × 10^{-4}–0.27 mol dm^{-3}. The same behaviour was found and the same treatment was applied. In both cases the ionic strength was held constant by use of sodium chloride. At higher base concentrations in water ([OH$^-$] > 0.1 mol dm^{-3}) and aqueous DMSO ([OH$^-$] > 0.4 mol dm^{-3}), the activity of hydroxide was no longer equal to the concentration.[31] A kinetic scale of activity of base was constructed using a well-behaved substrate, 1-phenylazetidin-2-one, the rate coefficient of which, k_2, obtained in dilute base was known. At higher base concentrations, the observed values of k_1 were used with the latter value of k_2 to derive values of a_{OH^-}. These activities were then used successfully in the treatment of the rates, as shown in Table 9, to obtain k_3 for all four formanilides in 70% (v/v) aqueous DMSO and the nitro substrate only in water (see Tables 5 and 6). The treatment failed for the three slower-reacting formanilides in water, which all had a higher-order rate process in hydroxide, *cf.* ref. 4. This appears to arise from the change in the activity of water, on which these rates are dependent, in these more concentrated base solutions (see the Discussion). The nitro substrate has a greater difference in k_2 and k_3 and avoids this problem. The advantages of using aqueous DMSO in these studies are the high reactivities of the aqueous base solutions in DMSO and the excellent solvent properties; but also its differentiating power towards kinetic processes.

Product Analysis.—The products of the alkaline hydrolysis of the lactams, acetanilides and formanilides studied here are the anions of *N*-(substituted phenyl)-β-alanines, -γ-aminopropionic and -δ-aminobutyric acids, acetic acid and formic acid with the substituted anilines, respectively (*cf.* refs. 4, 5 and 7). Typical lactams and anilides were subjected to alkaline hydrolysis in aqueous sodium hydroxide (2 mol dm^{-3}). After careful acidification, the products of the reactions were extracted with dichloromethane. The extracts were dried ($MgSO_4$) and evaporated. Examination of these products by TLC and ^1H and ^{13}C NMR spectroscopy indicated their structures to be those expected. Comparison of the UV–VIS spectra of the reaction products after ten half-lives with those of the corresponding *N*-methyl-substituted anilines under the same conditions showed identical or almost identical results.

Acknowledgements

Thanks are due to the SERC for the award of a studentship (to K. Bromley).

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Paper 0/01877E
Received 26*th April* 1990
Accepted 14*th August* 1990