Strain Effects in Acyl Transfer Reactions. Part I. The Kinetics of Hydrolysis of Some *N*-Aryl-lactams

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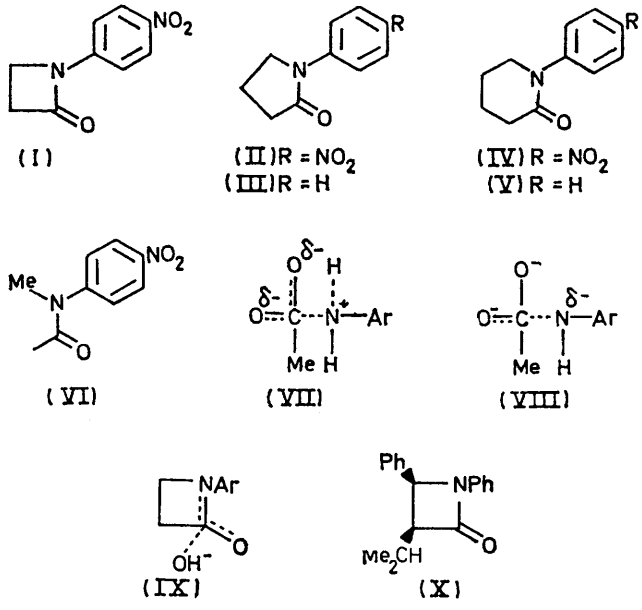
The hydroxide ion-catalysed hydrolysis of nine *N*-aryl-β-lactams have been studied at 298 K with [OH^-] ranging from 10^{-2} to 1M. All show first-order dependence on hydroxide ion at high pH. Their reactivity is markedly increased by electron-withdrawing substituents and correlates well with the Hammett σ^- function to give ρ^- +1·225. The relative rates of hydrolysis of *N*-methyl-*p*-nitroacetanilide and of *N*-*p*-nitrophenyl δ-, γ-, and β-lactams are 1, 1·5, 14, and 110 respectively. It appears from these data that amides are activated in both steps of hydroxide-catalysed hydrolysis, as a result of angular deformation.

THE changes in molecular geometry and electron distribution consequent on the formation of a tetrahedral intermediate during the course of hydrolysis or any other displacement reaction of an amide strongly suggest that both bond-angle strain at the carbonyl group and torsional rotation of the amide linkage [1] in the ground state of the reactant should exert a profound effect on the rate and mechanism of its reactions. Much has been made of the possible role of strain in enzyme-catalysed reactions [2] and the biological activity of benzylpenicillin and the Δ^3-cephalosporins [3,4] has been linked to the conjunction of both types of strain by crystallographic [5] and kinetic studies.[6,7]



The effects of torsional strain can be observed by comparison of the properties of the active Δ^3-cephalosporins and the biologically inactive Δ^2-isomers which have a planar β-lactam ring, and in the enhanced hydrolytic activity of the 1-azabicyclo[2,2,2]octan-2-ones.[1] Although the effects of angle strain on amide reactivity should be evident in the properties of β-lactams, only semiquantitative studies have been reported on their hydrolysis.[7-9] The 1-aryl-2-azetidinones were selected for initial investigation because of their ease of preparation and suitable spectroscopic properties, and because the hydrolysis of anilides is probably the most completely understood reaction of amides.[10,11] Kinetic data on the alkaline hydrolysis of a variety of *N*-aryl-β-lactams and some related amides are reported here. Subsequent papers will describe the aminolysis of β-lactams and kinetic investigations on small-ring lactones.

EXPERIMENTAL

Materials.—*N*-Aryl-3-bromopropionamides were prepared with little modification of the method described by Manhas and Jeng.[12] The two isomeric *N*-nitrophenyl amides were obtained as described by Lee *et al.*[13] with use of dry chloroform as solvent.[14] *N*-Phenyl-3-bromopropionamide had m.p. 392—395 K (lit.,[12] 391—392 K), *N*-*p*-methoxyphenyl-3-bromopropionamide had m.p. 378—380 K (lit.,[12] 384—385 K), *N*-*p*-bromophenyl-3-bromopropionamide had m.p. 407 K (lit.,[12] 407 K), and *N*-*p*-nitrophenyl-3-bromopropionamide had m.p. 458—460 K (lit.,[12] 419 K). Other new *compounds* are described in Table 1.

1-*Aryl*-2-*azetidinones.*—These were obtained by base-catalysed cyclisation of the appropriate *N*-aryl-3-bromopropionamides [12] and purified by chromatography on alumina, with benzene–ethyl acetate as eluant, before repeated crystallisation. 1-Phenylazetidin-2-one had m.p. 350—351 K (lit.,[12] 350—351 K), 1-*p*-methoxyphenylazetidin-2-one had m.p. 371—372 K (lit.,[12] 371—372 K), and 1-*p*-bromophenylazetidin-2-one had m.p. 398—400 K (lit.,[12] 398—399·5 K). Other *compounds* are described in Table 2.

1-*Phenyl*-2-*pyrrolidone.*—This was prepared as described by Meyer and Vaughan,[15] and had m.p. 339—340 K (lit.,[15] 341—342 K).

[1] H. Pracejus, *Chem. Ber.*, 1959, **92**, 988; *Tetrahedron*, 1965, **21**, 2257.
[2] W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, London and New York, 1969, p. 282.
[3] J. L. Strominger, *Antibiotics*, 1967, **1**, 706.
[4] E. P. Abraham, *Topics Pharm. Sci.*, 1968, **1**, 1.
[5] R. M. Sweet and L. F. Dahl, *J. Amer. Chem. Soc.*, 1970, **92**, 5489.
[6] R. W. Holley, *Science*, 1953, **117**, 23.
[7] R. H. Earle, D. T. Hurst, and M. Viney, *J. Chem. Soc.* (*C*), 1969, 2093.
[8] J. C. Sheehan and P. T. Izzo, *J. Amer. Chem. Soc.*, 1948, **70**, 1985; 1949, **71**, 4059.
[9] R. W. Holley, *J. Amer. Chem. Soc.*, 1949, **71**, 2124.
[10] Ref. 2, p. 523 *et seq.*
[11] R. M. Pollock and M. L. Bender, *J. Amer. Chem. Soc.*, 1970, **92**, 7190, and references therein.
[12] M. S. Manhas and S. Jeng, *J. Org. Chem.*, 1967, **32**, 1246.
[13] W. W. Lee, G. L. Tong, A. P. Martinez, B. Weinstein, M. L. Schelstraete, B. R. Baker, and L. Goodman, *J. Medicin. Chem.*, 1963, **6**, 439.
[14] H. W. Johnson and M. Schweitzer, *J. Org. Chem.*, 1961, **26**, 3666.
[15] W. L. Meyer and W. P. Vaughan, *J. Org. Chem.*, 1957, **22**, 1554.

1-*Phenyl-2-piperidone*.—This had m.p. 372—374 K (lit.,[12] 374—375 K).

1-p-*Nitrophenyl-2-pyrrolidone*.—Obtained by the nitration of 1-phenyl-2-pyrrolidone as described by Reppe,[16] this had m.p. 402·5—403 K (lit.,[16] 404 K).

1-p-*Nitrophenyl-2-piperidone*.—This was obtained as the sole *product* from nitration of 1-phenyl-2-piperidone with a mixture of concentrated nitric and sulphuric acids below 280 K, and after repeated crystallisation from methanol had m.p. 369·5—371·5 K (Found: C, 59·7; H, 5·7; N, 12·8. $C_{11}H_{12}N_2O_3$ requires C, 60·0; H, 5·5; N, 12·7%); τ ($CDCl_3$; 60 MHz), 1·54—2·66 (A_2B_2, C_6H_4), 6·06—6·48 (m, CH_2N), 7·16—7·60 (m, CH_2CO), and 7·67—8·20 (m, $CH_2{\cdot}CH_2$).

N-*Methyl*-p-*nitroacetanilide*.—Prepared as described by Morgan and Grist,[17] this had m.p. 423—424 K (lit.,[17] 426 K).

Imidazole was recrystallised from benzene; phosphate and carbonate buffers were prepared from analytical grade reagents; glass-distilled water was used throughout.

Apparatus.—A Radiometer PHM26 was used for measurement of pH with a G2222B glass electrode in a thermostatted vessel flushed with nitrogen. U.v. and visible spectroscopic data were recorded on a Cary 14 or a Gilford 240 spectrophotometer, both having cell temperature controlled by water circulated from a Haake model F thermostat (±0·1 K). N.m.r. spectra were recorded at 60 MHz in $CDCl_3$ solution with tetramethylsilane as internal standard on a Perkin-Elmer R12 machine and mass spectra were measured with an AEI MS12 spectrometer.

TABLE 1

Analytical data for $XC_6H_4NH{\cdot}COCH_2{\cdot}CH_2Br$

		Found (%)					Required (%)			
X	M.p. (K)	C	H	N	Br	Formula	C	H	N	Br
m-Me	348—350	49·5	4·8	5·7	33·1	$C_{10}H_{12}BrNO$	49·6	5·0	5·8	33·1
p-Me	412—413	50·3	5·2	5·8	32·6	$C_{10}H_{12}BrNO$	49·6	5·0	5·8	33·1
m-Br	351—352	35·5	2·7	4·6	54·2	$C_9H_9Br_2NO$	35·2	2·9	4·6	53·9
m-CF_3	334—335	41·4	3·1	4·8	26·8	$C_{10}H_9BrFNO$	40·6	3·0	4·7	27·1
m-NO_2	367—368	39·8	3·6	10·2	29·5	$C_9H_9BrN_2O_3$	39·6	3·3	10·3	29·3

TABLE 2

Analytical data for 1-X-arylazetidinones (as I)

		Found (%)				Required (%)			
X	M.p. (K)	C	H	N	Formula	C	H	N	
m-Me	347—348	74·25	6·7	8·8	$C_{10}H_{11}NO$	74·5	6·9	8·7	
p-Me	370—371	74·2	7·1	8·4	$C_{10}H_{11}NO$	74·5	6·9	8·7	
m-Br	352—354	47·6	3·7	6·0	C_9H_8BrNO	47·9	3·5	6·2 [a]	
m-CF_3	332—333	55·7	3·9	6·8	$C_{10}H_8F_3NO$	55·9	3·7	6·5	
m-NO_2	404—407	56·3	4·3	14·7	$C_9H_8N_2O_3$	56·3	4·2	14·6	
p-NO_2	434—435	56·4	4·4	14·6	$C_9H_8N_2O_3$	56·3	4·2	14·6	

[a] Found: Br, 35·1; required: Br, 35·4%.

TABLE 3

Spectral data for $XC_6H_4NH{\cdot}CO{\cdot}CH_2{\cdot}CH_2Br$

	N.m.r. (τ)					
X	C_6H_4 multiplet	CH_2Br triplet	$COCH_2$ triplet	Me singlet	I.r. $\nu_{C=O}/cm^{-1}$	Mass spectra *P/e*
m-Me	2·10—3·28	6·31 [a]	7·11 [a]	7·70	1660	241, 243
p-Me	2·43—3·28	6·31 [a]	7·12 [a]	7·71	1655	241, 243
m-Br	2·10—2·95	6·31 [b]	7·06 [b]		1665	305, 307, 309
m-CF_3	2·05—2·83	6·28 [a]	7·04 [a]		1705	295, 297
m-NO_2	1·46—2·77	6·26 [b]	6·97 [b]		1700	272, 274
p-NO_2	1·67—2·28	6·28 [b]	6·97 [b]		1710	272, 274

[a] *J* 6·7 Hz. [b] *J* 6·0 Hz.

TABLE 4

Spectral data for 1-X-arylazetidinones (as I)

	N.m.r. (τ)					U.v.		
X	C_6H_4	CH_2N	CH_2CO	Me	I.r. $\nu_{C=O}/cm^{-1}$	$\lambda_{max.}$/nm	$10^{-4}\varepsilon$	Mass spectra *P/e*
m-Me	2·60—3·28	6·39 [a]	6·91 [a]	7·66	1740	251	1·79	161
p-Me	2·60—3·00	6·42 [b]	6·93 [b]	7·70	1740	249	2·07	161
m-Br	2·38—2·90	6·36 [b]	6·87 [b]		1750	253	3·84	225, 227
m-CF_3	2·22—2·90	6·30 [a]	6·84 [a]		1745	251	2·06	215
m-NO_2	1·87—2·80	6·27 [a]	6·80 [a]		1745	248	2·62	192
p-NO_2	1·59—2·60	6·16 [a]	6·80 [a]		1750	226	1·20	192
						321	1·70	

[a] *J* 4·7 Hz. [b] *J* 4·0 Hz.

[16] V. W. Reppe, *et al.*, *Annalen*, 1955, **596**, 158.
[17] G. T. Morgan and W. R. Grist, *J. Chem. Soc.*, 1918, 688.

Kinetic Measurements.—All reactions were run in glass-distilled water at 298 K, except where specified, with ionic strength maintained at 1·0 (KCl), in the presence of 10^{-5}M-EDTA. Reactions were performed in 3 ml aliquot portions of aqueous solution in a thermostatted quartz cuvette and initiated by the addition of the substrate in 10^{-2} ml of pure dioxan to give a final concentration of 3×10^{-5} to 10^{-4}M. The disappearance of reactant was continuously monitored by the change in optical density of the solution at the wavelength of maxima absorption of the lactam near 250 nm (Table 4). For the *p*-nitrophenyl compounds, it was more convenient to observe the formation of product by means of the *p*-nitroaniline absorption near 410 nm. The pH of reaction solutions was determined at the beginning and end of each reaction.

Kinetic data were usually collected for at least 3 half-lives and pseudo-first-order rate constants, k_{obs}, obtained from plots of log $(A_\infty - A_t)$ against t. Very slow reactions were analysed by Guggenheim's method.[18] All reactions displayed good first-order behaviour.

Apparent second-order rate constants, k_1 (Tables 5 and 6), are the mean values calculated from the product $k_{obs}[OH^-]^{-1}$. In the case of compounds (II), (IV), and (V), and the *p*-tolyl-β-lactam data at the highest hydroxide concentration were omitted from this calculation because of marked upward deviations.

Product Analysis.—The products of alkaline hydrolysis of 1-phenyl- and 1-*p*-bromophenylazetidin-2-one have been characterised as *N*-phenyl- and *N*-*p*-bromophenyl-β-alanine respectively.[8] Samples of 1-*p*-nitrophenyl-azetidinone, -pyrrolidone, and -piperidone were completely hydrolysed in 2M-potassium hydroxide solution. The products were extracted from the acidified reaction solutions with dichloromethane and examined by t.l.c. and n.m.r. spectroxcopy. Thus the product from the β-lactam was proved to be *N*-*p*-nitrophenyl-β-alanine by comparison with an authentic sample and the properties of the products from the γ- and δ-lactams were consistent with their identities as *N*-*p*-nitrophenyl-γ-aminopropionic and -δ-aminobutyric acids respectively. In other reactions of lactams, the absorption of the reaction solution after ten half-lives was characteristic of the appropriate substituted aniline.

RESULTS

The nine aryl-β-lactams were hydrolysed at 298 K in potassium hydroxide solutions between 0·015 and 1·0M at unit ionic strength. The pseudo-first-order rate constants proved to be directly dependent on $[OH^-]$ except for the least reactive β-lactams at lowest hydroxide concentration, where the rates appear to decline below that predicted from equation (1)

$$\text{Rate} = k_1[OH^-]\ s^{-1} \qquad (1)$$

Second-order rate constants were obtained from the apparent first-order rate constants and the hydroxide ion concentration at several pH's. The average value was computed (Table 5) and used to provide the theoretical slopes in Figure 1. In addition, the hydrolysis of *N*-*p*-nitrophenyl-β-lactam (I) was followed at pH values down to 10 by the use of auxiliary phosphate and butylamine buffers, with significant correction for buffer reaction in the latter case.

[18] E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.
[19] J. E. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions,' Wiley, New York, 1963, p. 211.

Alkaline hydrolysis of *N*-*p*-nitrophenyl-γ- and δ-lactams (II) and (IV), *N*-phenyl-γ-lactam (V), and *N*-methyl-*p*-nitroacetanilide (VI) were carried out in the same way and provide the second-order rate constants given (Table 6).

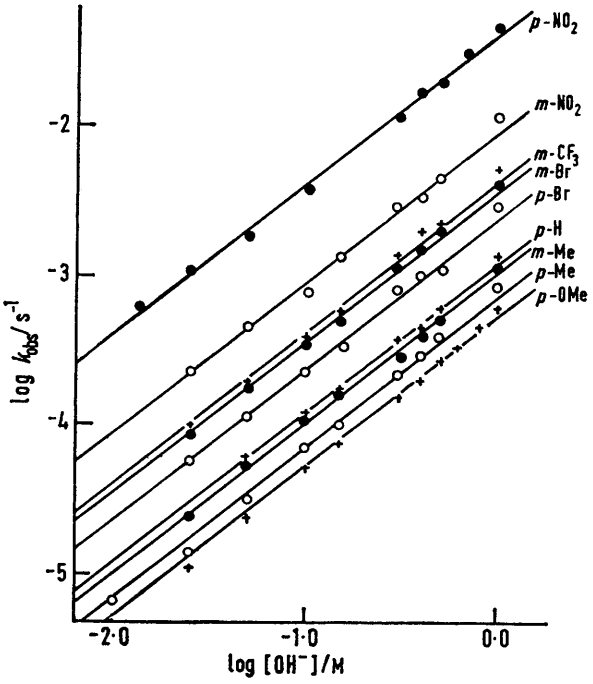


FIGURE 1 Plots of log k_{obs} against log $[OH^-]$ for the alkaline hydrolysis of *N*-aryl-β-lactams (aryl substituent shown). Curves calculated from equation (1) by use of values of k_1 from Table 5

TABLE 5

Data for the reaction of 1-arylazetidin-2-ones with potassium hydroxide (298 K, unit ionic strength)

Substituent	$[OH^-]$/M	No. of runs	10^3k_1 / l mol^{-1} s^{-1}	σ^- [19]
p-MeO	0·025—1·0	10	0·55 ± 0·04	−0·268
p-Me	0·01—1·0	9	0·76 ± 0·09	−0·17
m-Me	0·025—1·0	8	1·07 ± 0·05	−0·069
H	0·05—1·0	7	1·27 ± 0·07	0·0
p-Br	0·025—1·0	8	2·46 ± 0·38	+0·232
m-Br	0·025—1·0	8	3·80 ± 0·3	+0·391
m-CF_3	0·025—1·0	8	4·57 ± 0·5	+0·430
m-NO_2	0·025—1·0	8	9·55 ± 1·0	+0·710
p-NO_2	0·01—1·0	9	44·2 ± 2·0	+1·27
	$1·5 \times 10^{-2}$	4 [a]	41	
	$1·5 \times 10^{-3}$	4 [a]	44	
	$1·6 \times 10^{-4}$	4 [b]	46	
	0·05—1·0	5 [c]		
	0·05—1·0	5 [d]	44·2 ± 2·0	
	0·05—1·0	5 [e]		

[a] Phosphate buffer 10^{-3}—0·2M at constant pH extrapolated to zero [buffer]. [b] n-Butylamine buffer 10^{-3}—0·2M at constant pH extrapolated to zero [buffer]. [c] 303·2 K. [d] 308 K. [e] 313 K.

As before, plots of log k_{obs} against log $[OH^-]$ are linear with unit slope (Figure 2) though the fit for (IV) suggests the incursion of a term second-order in hydroxide either at high or low pH.

No change could be detected in the spectrum of *N*-phenyl-γ-lactam after 10^5 s in 1M-potassium hydroxide. Thus the second-order rate constant for the hydrolysis of (III) must be less than 10^{-6} l mol^{-1} s^{-1}

Rate data were collected at temperatures between 298 and 313 K for compounds (II) and (VI) and the activation parameters for hydrolysis computed by linear regression analysis

TABLE 6

Data for the alkaline hydrolysis of cyclic and acyclic anilides

Compound	$[OH^-]$/M	No. of runs	k_1/l mol^{-1} s^{-1}
1-*p*-Nitrophenyl-2-pyrrolidone (II)	0·025—1·0	8	5·60 ± 0·5 × 10^{-3}
1-*p*-Nitrophenyl-2-piperidone (IV)	0·025—1·0	8	6·0 ± 1·0 × 10^{-4}
1-Phenyl-2-piperidone (V)	0·05—1·0	7	2·00 ± 0·15 × 10^{-5}
N-Methyl-*p*-nitroacetanilide (VI)	0·02—1·0	7	3·83 ± 0·23 × 10^{-4}
	0·05—1·0	4 [a]	
	0·05—1·0	4 [b]	
	0·05—1·0	4 [c]	

[a] 303 K; [b] 308 K; [c] 313 K.

TABLE 7

Activation parameters for the hydrolysis of anilides

	$\Delta G^{\ddagger}$(298 K) / kJ mol^{-1}	$\Delta H^{\ddagger}$ / kJ mol^{-1}	$\Delta S^{\ddagger}$ / J mol^{-1} K^{-1}
N-Methyl-*p*-nitroacetanilide (VI)	92·2 ± 0·8	66·0 ± 6·1	−88·1 ± 5·8
1-*p*-Nitrophenylazetidin-2-one (I)	80·5 ± 0·5	56·6 ± 5·0	−80·2 ± 5·9

of a plot of log k_1 against $1/T$ (Table 7). The same analysis provided the second-order rate constants adopted for these compounds (Table 5 and 6).

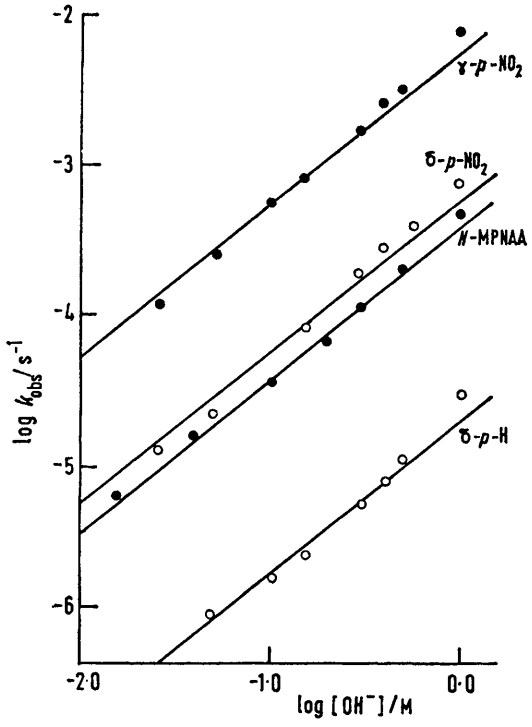


FIGURE 2 Plots of log k_{obs} against log $[OH^-]$ for alkaline hydrolysis of *N*-aryl-γ- and -δ-lactams (II), (IV), and (V) and of *N*-methyl-*p*-nitroacetanilide (*N*-MPNAA). Curves calculation from equation (1) by use of values of k_2 from Table 6

A plot of log k_1 for the nine β-lactams against the Hammett substituent constant σ^-, adopted in reactions involving increased delocalisation between the reaction centre and the aromatic ring,[19] provides an excellent correlation (Figure 3) with a slope, $\rho^- = +1{\cdot}225 \pm 0{\cdot}013$, computed by weighted linear regression analysis. Figure 3 also contains points for the γ-lactams (IV) and (V) and for (II) and (VI).

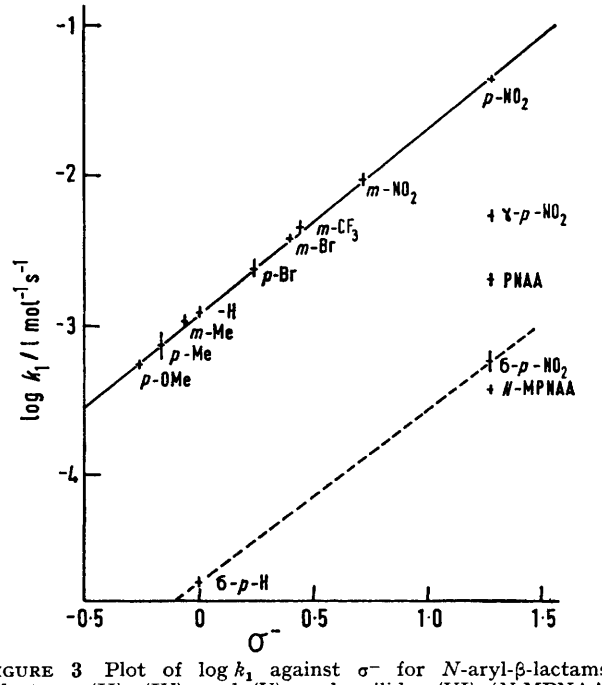


FIGURE 3 Plot of log k_1 against σ^- for *N*-aryl-β-lactams, lactams (II), (IV), and (V), and anilides (VI) (*N*-MPNAA) and *p*-nitroacetanilide [21] (PNAA)

Attempts to observe general catalysis of the hydrolysis of compound (I) and the *p*-methoxyphenyl-β-lactam were unsuccessful. Imidazole, phosphate, and carbonate buffers showed no significant catalysis in the range $7 < pH < 12$ and over 100-fold change in catalyst concentration. Significant acceleration of the disappearance of (I) was observed in n-butylamine buffers but this was entirely accounted for by aminolysis,[20] and extrapolation to zero buffer concentration gave hydrolysis rates in excellent agreement with those predicted from the rate constant determined at high pH (Table 5).

TABLE 8

Relative rate constants for hydrolysis at 298 K

Compound	*N*-Phenyl	*N*-*p*-Nitrophenyl
β-Lactam	60	2200
γ-Lactam	0·1	280
δ-Lactam	1·0	30
N-Methylacetanilide		20
Acetanilide	2 [a]	110 [b]

[a] Ref. 21; [b] Ref. 11.

DISCUSSION

N-aryl-β-lactams hydrolyse in alkaline solution to give the corresponding *N*-aryl-β-alanines. The rate of this reaction exhibits simple first-order dependence on hydroxide-ion concentration over most of the range studied and gives little evidence for the higher-order dependence on hydroxide seen in the hydrolyses of some

[20] G. M. Blackburn and J. D. Plackett, unpublished results.

acyclic acetanilides [21] (Figure 1). The ring-opening of the most reactive amide investigated, 1-*p*-nitrophenylazetidin-2-one (I), continues to show first-order response to hydroxide concentration at least to pH 10. The other β-lactams were studied only in the pH range 12—14 and the least reactive, the *p*-tolyl and *p*-methoxyphenyl compounds, gave slight evidence of a decline in the apparent second-order rate constant at pH 12.

The hydrolyses of the γ- and δ-lactams (II)—(IV) also showed no change in kinetic behaviour between pH 14 and 12 and the same linear dependence on hydroxide concentration characterised the hydrolysis of the acyclic secondary anilide (VI) not only at 298 K but also at higher temperatures. This simple behaviour contrasts markedly with the more complex pattern observed for *p*-nitroacetanilide [11] and for 2,2,2-trifluoroacetanilide [22] which are both subject to a change in mechanism in this pH range.

Because the same rate law [equation (1)] describes the kinetic behaviour of all the compounds investigated, a direct comparison of the second-order rate constants is valid and shows (Table 8) a steady increase in reactivity with ring-constraint for the *p*-nitroanilides (I), (II), (IV), and (VI). Within the group of β-lactams (Figure 1) there is a clear dependence of reactivity on substitution and an excellent linear correlation between log k_1 and the Hammett substituent constant [23] σ with a slope $\rho = 1{\cdot}225 \pm 0{\cdot}013$. The rate constant for the *p*-nitro-compound (I) lies well off this line ($\sigma = 0{\cdot}78$) but is brought into coincidence by the use of the modified substituent constant [19] $\sigma^- = 1{\cdot}27$ (Figure 3).

In order to interpret the significance of the ring-size effect on hydrolysis rates it is necessary to identify the nature of the transition state for the reaction. Although studies on other anilides have revealed that either hydroxide addition to or amine expulsion from the amide can be rate-determining,[10,11,21,22] three facts support the former assignment for β-lactams, though an unambiguous assignment can only be made by the use of oxygen-18 isotope exchange, as was effectively applied to the hydrolysis of acyclic anilides.[21]

First-order kinetic dependence on hydroxide-ion concentration is usually associated with rate-determining addition of hydroxide to the amine. In the few cases where it is a manifestation of rate-determining expulsion of the aniline, it is observed with, and, at high pH, dominated by second-order dependence on hydroxide.[10] Thus the kinetic behaviour of all the compounds investigated in this work is consistent with rate-determining attack of hydroxide. Additionally, breakdown of the tetrahedral intermediate anion is usually subject not only to specific base catalysis but also to general base catalysis [22] which is not detectable for either (I) or the *p*-methoxyphenyl-β-lactam, although these were selected to give the maximum advantage to general base and general acid catalysis respectively. Finally, a characteristic dependence on substituent effects has been established for rate-limiting expulsion of the aniline from the tetrahedral intermediate. In those cases where breakdown does involve a monoanionic transition state, Bender and Thomas [21] observed an overall cancellation of substituent effects ($\rho = +0{\cdot}1$) which both they and Jencks *et al.*[24] have interpreted to describe a transition state (VII) in which the nitrogen is more positively charged than in the aniline product. On the other hand, for *p*-nitro- and *p*-formyl-acetanilide, where rate-determining breakdown proceeds from the dianionic intermediate, Pollock and Bender [11] have suggested a very high dependence on substituent effects ($\rho = +11$) corresponding to the expulsion of the anilide anion (VIII). The susceptibility of hydroxide addition to substituent effects in anilides has been determined indirectly from the rates of oxygen-18 exchange [21] ($\rho = +1{\cdot}0$) and agrees well with that now determined for β-lactam hydrolysis ($\rho = +1{\cdot}225$).

In conjunction, these three comparisons support the identification of the transition state for β-lactam hydrolysis as rate-determining hydroxide attack (IX). Although detailed substituent correlations are not available for the γ- and δ-lactams, it seems reasonable to assign the same transition state to the other *p*-nitroanilides investigated.

Crystallographic [25] and spectroscopic [26] evidence shows that the *N*-aryl-β-lactams are effectively planar. Thus the 100-fold acceleration in attack of hydroxide on (I) over (VI) must arise from the acute modification of bond angles in the cyclic transition state. This conclusion is reinforced by consideration of the activation parameters (Table 7) which show that the enhanced reactivity is associated with a decrease in the enthalpy of activation for compound (I). Several factors may provide some part of the acceleration of hydrolysis of the β- over the δ-lactam and acyclic amide: angle deformation, bond-opposition, bond stress, and conformational effects will be considered in turn.

In three- and four-membered rings, bond-angle strain is large and usually considered to have a predominant effect on change in reactivity.[27] The deformation of the C–C–N bond angle [25] in (X) from the normal amide angle [28] (116 ⟶ 93°) is greater than the corresponding deformation for a tetrahedral carbon atom (109·5 ⟶ 93°). Because the strong dependence of hydrolysis on the aromatic substituent effect shows that the transition state (IX) has geometry close to the tetrahedral, most of the strain relieved by the $sp^2 \longrightarrow sp^3$ change at C(2) of the azetidin-2-one will assist the hydrolysis. This

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view is supported by the similarity between the relative rates of hydrolysis of compounds (I), (II), and (VI) to the relative rates of borohydride reduction of cyclobutanone, cyclopentanone, and acyclic ketones.[29]

This comparison fails for six-membered rings. The accelerated reduction of cyclohexanone over acyclic ketones has been attributed to the relief of bond opposition present in the cyclic ketone.[29] Since no such acceleration is seen in the reaction of (IV) relative to (VI), it appears that bond-opposition effects are unimportant in lactam hydrolyses and thus make a negligible contribution to the acceleration in hydrolysis of (I).

The amide bond in (X) is somewhat stretched over that for a normal amide (0·004 nm) [24,27] but even the relaxation of all this strain in the transition state (IX) could only provide a threefold rate acceleration, so bond-stressing appears to contribute but little to the reactivity of (I). Finally, lactams necessarily hold the amide in the *cis*- against the normal *trans*-conformation. While Huisgen and Ott have suggested [30] that this conformational change might be an accelerating factor in the hydrolysis of small-ring lactones, its operation for amides ought to provide similar acceleration for δ-, γ-, and β-lactams, a prediction in contrast to observation.

It therefore appears reasonable to conclude that bond-angle strain provides the major part of the rate-enhancement seen in the hydrolysis of β-lactams.

The fact that the same transition state controls the hydrolysis of (I) down to pH 10 while *p*-nitroacetanilide is subject to rate-determining *breakdown* below pH 13 shows that ring-strain in (I) accelerates nitrogen expulsion from the tetrahedral intermediate by a factor in excess of 10^4, a factor which is small in comparison with the standard enthalpy for angle strain in cyclobutane [31] of 110 kJ mol^{-1}. The reaction of anilines with 2,4-dinitrophenylacetate proceeds with a Brønsted coefficient of $\beta = 0{\cdot}9$, showing that the C–N bond is largely formed in the transition state.[24,32] It follows that in the reverse process, the C–N bond is little stretched in the transition state for aniline expulsion so that only a part of the strain energy in the four-membered ring can be applied to accelerate ring-cleavage, in accord with observation.

The effect of angle strain on acyl-group reactivity can be investigated in monocyclic small-ring compounds only in a discontinuous fashion. Consideration of bond angles for normal trigonal and tetrahedral hybridisation at carbon suggests that in five-membered rings there is little and in four-membered rings more than the optimum angle strain to facilitate ligand addition to a carbonyl group. Unfortunately, resource to more complex molecules for the provision of intermediate values of angular deformation is likely to create problems, especially from steric hindrance and solvation effects, which would impede simple comparative interpretation of kinetic data.

Nonetheless, the present study clearly demonstrates that amides are activated in *both* steps of hydroxide-catalysed hydrolysis as a result of angular deformation. That this acceleration is likely to be even greater for weaker nucleophiles is supported by observations on the aminolysis of compounds (I), (II), and (IV).[20] Since the nucleophilic groups employed by enzymes are ' soft ' [33] in character, this investigation supports the contention [2] that the employment by an enzyme of some part of the substrate binding energy to distort the enzyme–substrate complex in the direction of reaction may well be one of the significant aspects of peptide hydrolysis by enzymes.

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