Hydroxy-group Participation in the Hydrolysis of Amides and its Effective Concentration in the Absence of Strain Effects

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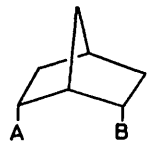
Rate constants are reported for the alkaline- and acid-catalysed hydrolysis of *endo*-6-hydroxybicyclo[2.2.1]-heptane-*endo*-2-carboxamides in aqueous solution. The product of the acid-catalysed reaction is *endo*-6-hydroxybicyclo[2.2.1]heptane-*endo*-2-carboxylic acid lactone and this lactone is also formed as an intermediate in alkaline solution before giving the hydroxy-acid anion as the product. The effective concentration of the intramolecular alkoxide ion group is *ca.* 10^8M. This is in good agreement with the maximum entropic advantage predicted for intramolecular reactions as the system is thought to be free of major strain energy and solvation effects. Variation of substituents in the amine leaving group gives a β_{lg} value of +0.30 for the hydroxide-ion-catalysed lactonisation reaction. This is interpreted in terms of rate-limiting breakdown of the tetrahedral intermediate in which there is considerable positive charge on the amine nitrogen. Mechanisms consistent with this involve either proton transfer from water to the amine nitrogen occurring synchronously with carbon–nitrogen bond fission or a stepwise process in which the nitrogen of the tetrahedral intermediate is fully protonated and the rate-limiting step is either diffusion apart of this intermediate and hydroxide ion or collapse of this intermediate with hydroxide ion acting as a ' spectator.' The β_{lg} value for the acid-catalysed lactonisation reaction is 0.0.

It has been suggested that the magnitude of the rate enhancement observed in most intramolecular reactions may be rationalised by considering the differences in entropy changes and the variation in potential energy effects in the systems being compared.[1-3] According to ' molecular mechanics ' calculations [4] the ring closure of 2,6-*endo,endo*-disubstituted norbornanes (I) to give the tricyclic derivative (II) involves little change in the strain-energy of the system [2,3,5] and hence such ring closures should give an indication of the advantage of



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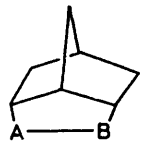


(II)

intra- compared with inter-molecular reactions in the absence of strain energy effects.

There has been much interest in hydroxy-group participation in the hydrolysis of amides.[6] This reaction is of relevance to the mechanism of action of the serine proteinases which catalyse the hydrolysis of amides. This class of enzymes acts through the formation of an acyl–enzyme intermediate by the transfer of the acyl group from the substrate to a serine hydroxy-group in the enzyme.[7]

Herein is reported an investigation of the hydrolysis of *N*-substituted *endo*-6-hydroxybicyclo[2.2.1]heptane-*endo*-2-carboxamide (I; A = OH, B = CONHR) and a determination of the effective concentration of the hydroxy-group. Also described, in this and the following paper,[8] is a detailed mechanism of the reaction.

EXPERIMENTAL

Materials.— *endo*-6-Hydroxybicyclo[2.2.1]heptane-*endo*-2-carboxylic acid lactone (III) was prepared from the acid-catalysed isomerisation of bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxylic acid [9] followed by sublimation at 100 °C and 1 mmHg, m.p. 157—158 °C (lit.,[9] 158 °C) (Found: C, 69.6; H, 7.15. Calc. for $C_8H_{10}O_2$: C, 69.6; H, 7.25%), $\nu_{max.}$ ($CHCl_3$) 1 770 cm^{-1}.

endo-6-*Hydroxybicyclo*[2.2.1]*heptane*-endo-2-*carboxamides*. For the more basic amines the hydroxy-amides could be prepared in low yield (*ca.* 25%) by refluxing the lactone (III) in excess of amine. Hydroxy-amides of the less basic amines were prepared by a modification of the Boudroux reaction.[10] Examples of each of these methods will be briefly described.

endo-6-*Hydroxybicyclo*[2.2.1]*heptane*-endo-2-N-*propylcarboxamide*. The lactone (III) (0.5 g) was refluxed with redistilled n-propylamine (35 cm^3) for 24 h. The amine was removed under nitrogen and the residue chromatographed on silica gel with ether to give the product (0.15 g, 16%), R_F 0.2.

endo-6-*Hydroxybicyclo*[2.2.1]*heptane*-endo-2-N-*benzylcarboxamide*. To a stirred solution of freshly prepared methylmagnesium iodide (0.06 mol) in dry ether was added dropwise redistilled benzylamine (0.06 mol) in dry benzene (10 cm^3). After the addition was complete the mixture was stirred and refluxed for 1 h. The lactone (III) (0.01 mol) in dry benzene (10 cm^3) was then added over 5 min and the mixture stirred and refluxed for 8 h. The resulting complex was decomposed with 25% ammonium chloride solution (980 cm^3) with vigorous stirring. The product (14%) was extracted with ether and, after removal of ether, chromatographed on silica gel with ether.

Physical data. N-*Propylamide* (Found: C, 66.7; H, 6.85; N, 9.5. $C_{11}H_{17}NO_2$ requires C, 67.0; H, 7.1; N, 9.65%), $\nu_{max.}$ (film) 3 480, 3 300, 3 120, 1 635, and 1 550 cm^{-1}, δ ($CDCl_3$) 6.97 (OH), 5.38 (NH), 4.18 (m, *exo*-6-H), 3.24 (2 H, q, *J* 7.0 Hz), 2.84 (m, *exo*-2-H), and 0.94 (3 H, t, *J* 7.0 Hz); N-2-*aminoethylamide*, m.p. 105—106 °C (Found: C, 60.4; H, 9.05; N, 14.1. $C_{10}H_{16}N_2O_2$ requires C, 60.6; H, 9.1; N, 14.15%), $\nu_{max.}$ (Nujol) 3 410, 3 290, 3 150, 3 050, and 1 640 cm^{-1}, δ (CD_3OD) 4.22 (m, *exo*-2-H), 3.30 (m, CH_2 and *exo*-6-H), and 2.73 (m, *exo*-2-H and CH_2); N-*prop*-2-*enylamide* (Found: C, 66.9; H, 8.1; N, 9.4. $C_{11}H_{15}NO_2$ requires C, 67.0; H, 7.1; N, 9.65%), $\nu_{max.}$ (film) 3 240, 3 150, 1 635, and 1 530 cm^{-1}, δ ($CDCl_3$) 6.53 (OH), 6.36—5.07 (m, vinyl H), 4.28 (m, *exo*-6-H and NH), 3.94 (t, *J* 6 Hz, CH_2), and 2.90 (m, *exo*-2-H); N-2-*methoxyethylamide* (Found: C, 61.4; H, 8.45; N, 6.35. $C_{11}H_{17}NO_3$ requires

C, 61.95; H, 8.9; N, 6.55%), $\nu_{max.}$ (film) 3 240, 3 150, 1 637, and 1 530 cm^{-1}, δ ($CDCl_3$) 6.68 (OH), 4.23 (m, *exo*-6-H), 3.80 (NH), 3.42 (s, OMe), and 3.50 (t, CH_2); N-*benzylamide*, m.p. 99—100° (Found: C, 73.5; H, 7.85; N, 5.8. $C_{15}H_{17}NO_2$ requires C, 73.45; H, 8.15; N, 6.0%), $\nu_{max.}$ (Nujol) 3 400, 3 270, 1 635, 1 550, and 710 cm^{-1}, δ ($CDCl_3$) 7.28 (s, C_6H_5), 6.96 (OH), 4.58 (NH), 4.41 (d, *J* 6 Hz, CH_2), 4.11 (m, *exo*-6-H), and 2.79 (m, *exo*-2-H); N-2,2,2-*trifluoroethylamide*, m.p. 104—105° (Found: C, 52.4; H, 6.15; N, 5.75; F, 23.05. $C_{10}H_{12}F_3NO_2$ requires C, 52.6; H, 6.35; N, 5.6; F, 22.7%), $\nu_{max.}$ ($CHCl_3$) 3 400, 3 250, 3 050, 1 665, 1 520, and 1 168 cm^{-1}, δ ($CHCl_3$) 7.50 (OH), 4.46 (NH), 3.89 (m, CH_2 and *exo*-6-H), 2.90 (m, *exo*-2-H); N-o-*chlorobenzylamide*, m.p. 136—137° (Found: C, 63.25; H, 6.4; N, 5.0; Cl, 12.2. $C_{15}H_{16}ClNO_2$ requires C, 64.4, H, 6.45; N, 5.0; Cl, 12.7%), $\nu_{max.}$ (Nujol) 3 380, 3 270, 1 640, 1 540, and 745 cm^{-1}; δ ($CDCl_3$) 7.17 (m, C_6H_4), 4.47 (d, CH_2), 4.10 (m, *exo*-6-H), and 2.81 (m, *exo*-2-H).

Bicyclo[2.2.1]*heptane*-endo-2-N-*propylcarboxamide*. Bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxylic acid [9] (10 g) was hydrogenated at 1 atm and at 25° in glacial acetic acid (80 cm^3) with Pt. Recrystallisation from ethanol yielded bicyclo[2.2.1]heptane-*endo*-2-carboxylic acid (9 g), m.p. 63° (lit., 64%), which was converted into the acid chloride with thionyl chloride. The acid chloride in benzene was treated with propylamine to give the amide which was purified by sublimation (100° and 0.5 mmHg), m.p. 58—59° (Found: C, 73.1; H, 10.55; N, 7.4. $C_{11}H_{17}NO$ requires C, 73.3; H, 10.55; N, 7.2%), $\nu_{max.}$ (Nujol) 3 300, 1 640, and 1 542 cm^{-1}, δ ($CDCl_3$) 6.10 (NH), 3.25 (dd, CH_2), 2.73 (m, *exo*-2-H), and 0.91 (t, *J* 7.0 Hz, CH_3).

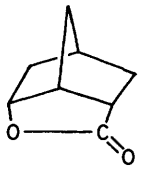
Product Isolation.—Product isolation was carried out on the hydrolysis of all hydroxy-amides. For example, the *N*-propylamide (50 mg) in 0.1M-sodium hydroxide (250 cm^3) was left at 30 °C for 5 min (10 $t_{\frac{1}{2}}$), the solution cooled in ice, acidified to pH 1. The aqueous solution was extracted with ether to give a product (30 mg) identical with the lactone (III) by m.p., i.r., n.m.r., and t.l.c.

Other materials used for kinetics were of AnalaR grade. Freshly boiled deionised water was used throughout and the ionic strength maintained at 0.20M with potassium chloride unless otherwise stated.

Kinetics.—The reactions were initiated by the addition of 5—25 μl of the amide in methanol (0.5M) to 2.5 cm^3 of the aqueous solution, preincubated at 30.0 ± 0.05°, with thorough mixing to give an initial concentration of 1—5 × 10^{-3}M. The disappearance of the amide was followed spectrophotometrically on a Gilford 240 spectrophotometer at 220—235 nm. The output from the spectrophotometer was fed into a Solartron data logger equipped with a Facit tape punch thus enabling voltages proportional to the absorbance to be punched at constant time intervals. Rate constants were calculated on an IBM 1130 or ICL 2960 computer using a generalised least-squares method which, for first-order reactions, treated the absorbances at time zero and infinity and the first-order rate constant as disposable parameters.[11] For consecutive first-order reactions, the two first-order rate constants and the ratio of the extinction coefficients were treated as disposable parameters. For the pH–rate profile of an ionisable substrate the rate constants for the two forms of the substrate and the dissociation constant were treated as disposable parameters. The slopes and intercepts of linear relationships were determined using a linear least squares method. The pH of the solutions was checked before and after each kinetic experiment and if it had changed by more than 0.03 the experiment was rejected.

RESULTS

The product (>90%) of hydrolysis of the *N*-substituted amides (IV) in acidic solution is the lactone (III). In



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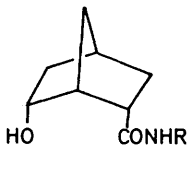

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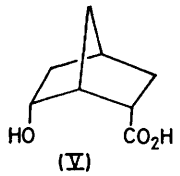


(V)

alkaline solution the product of hydrolysis is the bicyclic carboxylate ion of acid (V). This was shown by acidification of the reaction mixture, after completion of the alkaline hydrolysis, to pH 3 and from which the lactone (III) (>90%) could be isolated. The lactone (III) does not result from the acid-catalysed hydrolysis of the hydroxy-amide because the reaction was complete before acidification and, in any case, at pH 3 the rate of lactonisation of acid (V) is *ca.* 1000-fold faster than the rate of acid-catalysed lactonisation of the hydroxy-amide (IV). Together with the enormous rate enhancement provided by the neighbouring hydroxy-group this is taken to indicate that in alkaline solution the hydroxy-amide (IV) is initially converted into the lactone (III) followed by hydrolysis to the anion of the corresponding hydroxy-acid (V).

The second-order rate constant for the hydroxide-ion-catalysed hydrolysis of the lactone (III) to the hydroxy-carboxylate ion (V) at 30° and ionic strength 0.2M is 1.00 l mol^{-1} s^{-1}, in good agreement with a previously determined value.[12] In alkaline solution the rate constants for the hydrolysis of the hydroxy-amides (IV) were obtained spectrophotometrically as pseudo-first-order rate constants at a wavelength where the extinction coefficients of the lactone (III) and the hydroxy-carboxylate ion of acid (V) were the same or very similar. The rate constant for the conversion of the hydroxy-amide into the lactone was also obtained by treating the change in absorbance as the result of two consecutive first-order reactions,[13] as the rate of conversion of the hydroxy-amide (IV) into the lactone (III) was sometimes not much slower (a factor of *ca.* 2—5) than the rate of hydrolysis of the lactone (III) to the hydroxy-carboxylate ion of acid (V). The calculated pseudo-first-order rate constant for the conversion of the hydroxy-amide (IV) into the lactone (III) agreed well (±10%) with those determined as previously described.

The conversion of the amides (IV) into the lactone (III) at 30° in aqueous solutions of sodium hydroxide and hydrochloric acid follows the rate law (1) where k_{obs} is the observed pseudo-first-order rate constant. The experimental conditions for the rate measurements and the observed rate

$$\text{Rate}/[(\text{IV})] = k_{obs} = k_{OH}[OH^-] + k_H[H^+] \quad (1)$$

Summary of the rate constants for the hydroxide-ion and the acid-catalysed lactonisation of *N*-substituted *endo*-6-hydroxybicyclo[2.2.1]heptane-*endo*-2-carboxamides in water at 30.0 °C and ionic strength 0.2M (KCl)

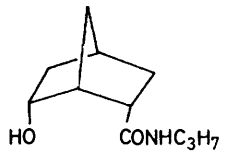
Amide substituent	pK_a of amine leaving group	k_{OH}/ l mol^{-1} s^{-1}	$10^2 k_H$/ l mol^{-1} s^{-1}
1 Propyl	10.89	0.483 ± 0.035	2.70 ± 0.15
2 2-Aminoethyl	10.20	0.301 ± 0.05	
3 Prop-2-enyl	10.08	0.560 ± 0.02	2.85 ± 0.03
4 2-Methoxyethyl	9.72	0.402 ± 0.019	1.76 ± 0.09
5 Benzyl [a]	9.32	0.211 ± 0.03	1.91 ± 0.24
6 2-Chlorobenzyl [b]	8.44	0.0409 ± 0.0049	2.08 ± 0.06
7 2-Aminoethyl cation	7.55		1.15 ± 0.04
8 2,2,2-Trifluoroethyl	5.81	2.90 ± 0.20 × 10^{-2}	2.61 ± 0.40

[a] Determined in 10% (v/v) methanol–water. [b] Determined in 40% (v/v) methanol–water.

constants are given in Supplementary Publication No. SUP 22712 (4 pp.) * and the derived rate constants are summarised in the Table; k_{OH} and k_H are, respectively, the second-order rate constants for the hydroxide-ion- and the hydrogen-ion-catalysed conversion of the hydroxy-amide (IV) into the lactone (III).

DISCUSSION

(i) *Hydroxide-ion Catalysis.*—(a) *Intramolecular nucleophilic catalysis.* The rate of the hydroxide-ion-catalysed hydrolysis of the *N*-propylamide (VI) is *ca.* 2 × 10^6-fold faster than that of the analogous *N*-propylamide (VII) lacking the neighbouring hydroxy-group. This rate enhancement needs to be qualified because the hydrolysis of (VII) was carried out at 50 and 60° and, because of solubility problems, in 50% v/v methanol–water. The estimated second-order rate constant in this solvent mixture for the hydroxide-ion-catalysed hydrolysis of (VII) at 30° is 2 × 10^{-7} l mol s^{-1}. This may be compared with the rate constant k_{OH} for the hydrolysis of *N*-propylacetamide in water at 30° of 3.6 × 10^{-6} l mol^{-1} s^{-1}.[14] Changing the solvent from 50% alcohol–water to water generally increases the rate constants for the alkaline hydrolysis of amides and esters by a factor of <5.[15] With reasonable confidence, therefore, it can be stated that under the same conditions the rate of alkaline hydrolysis of (VI) proceeds at least 5 × 10^5-fold faster than (VII).



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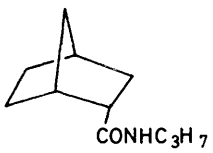
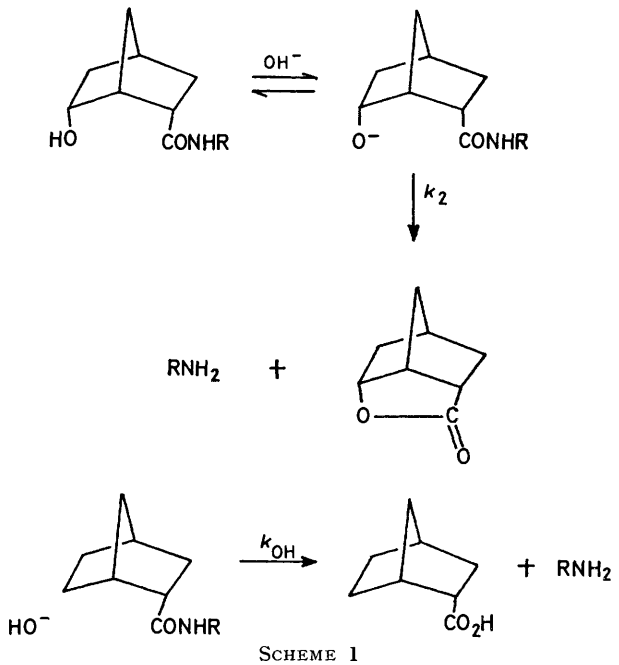


(VII)

This enormous rate enhancement is attributed to neighbouring group participation [16] by the hydroxy-group in (IV). The simplest reaction scheme consistent with this involves formation of the lactone (III) as an intermediate which at alkaline pH is known to be further hydrolysed to the corresponding hydroxycarboxylate ion (V).[12] Hydroxy-group participation in the hydrolysis of amides has been previously suggested.[6,17] This system is of particular interest as the rate enhancement results almost entirely from the entropy effect. The reaction mechanism for the hydroxide-ion-catalysed hydrolysis of the hydroxy-amides (IV) involves ionisation of the hydroxy-group followed by intramolecular nucleophilic attack of the alkoxide-ion on the amide, k_2 (Scheme 1). The ' effective concentration ' [2] of the



SCHEME 1

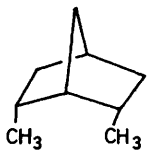
hydroxy-group may be estimated from a comparison of the intramolecular first-order rate constant k_2 with the intermolecular second-order rate constant for the hydroxide-ion-catalysed hydrolysis of the amide (VII) (Scheme 1). Assuming a pK_a of 16 for the hydroxy-group in (IV) [18] the ' effective concentration ' is 5 × 10^{7}M. This is the hypothetical concentration of hydroxide ion required to make the intermolecular reaction proceed at the same rate as the intramolecular reaction (Scheme 1). The ' effective concentration ' compares attack on the amide by intramolecular alkoxide ion with that by intermolecular hydroxide ion. The rate of the methoxide-ion-catalysed methanolysis of *N*-methyltrifluoroacetanilide is 20-fold less than the rate of the hydroxide-ion-catalysed hydrolysis of the same substrate.[19] But changing the solvent for the hydrolysis of esters and amides from alcohol to water generally increases the rate of reaction.[15] It seems probable, therefore, that the rate of intermolecular alkoxide ion attack on the unsubstituted amide (VII) in water will not be very different from the rate of hydroxide ion attack. The true ' effective concentration ' of the intramolecular alkoxide ion in (IV) is therefore *ca.* 10^{8}M.

Until recently,[1] there has been much discussion in the literature regarding the maximum rate enhancement that

* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1979, Index issue.

could be obtained in an intramolecular reaction in the absence of strain and solvation effects.[2,3,20] It has been suggested that the ' effective concentration ' may be as high as 10^8M simply as a result of the large loss of translational and rotational entropy that occurs in a bimolecular but not in a unimolecular reaction.[1] We believe that our observed ' effective concentration ' is the result of this entropy effect and that strain and solvation effects are minimal in the ring closure of the hydroxy-amide (IV). Our observed ' effective concentration ' is therefore in good agreement with that predicted.[1,2]

Changes in strain energy accompanying the ring closure of the hydroxy-amide (IV) to the lactone (III) are thought to make a negligible contribution to the rate enhancement. As a model for the changes that occur when a molecule undergoes cyclisation one may examine the analogous hydrocarbon system.[2,3] It has been shown that there is a good correlation between the relative rates or equilibrium constants for a series of intramolecular reactions and the changes in strain energy, calculated from a ' molecular mechanics ' procedure,[21] that accompany ' ring-closure ' of analogous hydrocarbons.[3] The strain energies, calculated by the ' molecular mechanics ' method,[22] of 2,6-*endo*-dimethylbicyclo[2.2.1]-heptane (VIII) and tricyclo[4.2.1.$0^{3,7}$]nonane (IX) are 98.7 and 94.6 kJ mol^{-1}, respectively. It seems probable, therefore, that there is little change in the strain energy accompanying the ring closure of the hydroxy-amide (IV) to the lactone (III). It has been suggested that, compared with the *trans*-conformation, the constraint of the ester function to a *cis*-conformation in a lactone



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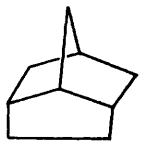

(IX)

leads to an increase in energy of 10—16 kJ mol^{-1}.[23] However, the problems associated with distinguishing the conformational effect from general strain-energy effects in explaining relative rate of reactions have been emphasised.[24] It appears that the balance of possible unfavourable and favourable strain-energy effects does not make a significant (by a factor of <10-fold) contribution to the rate enhancement of the hydroxy-amide (VI) compared with (VII).

It has been suggested that the desolvation of anionic nucleophiles may be very different in intra- and intermolecular reactions and that this may account for the large ' effective concentrations ' sometimes observed in neighbouring group participation reactions.[25] It is claimed that this accounts for the small ' effective concentrations ' observed with intramolecular neutral nucleophiles.[26] However, there are many examples where neutral nucleophiles, *e.g.* amino-groups, show large rate enhancements.[2,16,27] The effective concentration of an intramolecular carboxylate anion is very similar in water and 1M-water–dimethyl sulphoxide[28] but, of course, anions may still be well solvated in such solvent mixtures.[29] In the present case there is no evidence to suggest that solvation is severely hindred in the *endo*-cavity of the norbornyl skeleton. The pK_a of *endo*-2-dimethylaminobicyclo[2.2.1]heptane is 10.11 compared with 10.36 for the corresponding *exo*-isomer.[30] The pK_a of bicyclo[2.2.1]heptane-*endo*-2-carboxylic acid is 5.30 in 10% (v/v) ethanol–water compared with 4.82 for butyric acid under the same conditions.[12] It seems reasonable, therefore, to propose that solvation of the alkoxide ion derived from (IV) will not be severely impaired (even if it occurred it is likely that the lower concentration of the alkoxide ion, due to an increased pK, would cancel the effect of increased reactivity) and that solvation effects do not contribute significantly to the observed ' effective concentration '.

We conclude that the observed ' effective concentration ' of *ca.* 10^8M is mainly the result of a more favourable entropy change in the intramolecular compared with the intermolecular reaction.

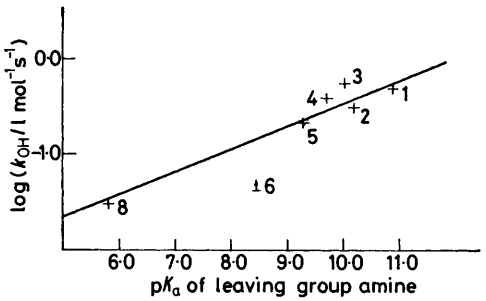
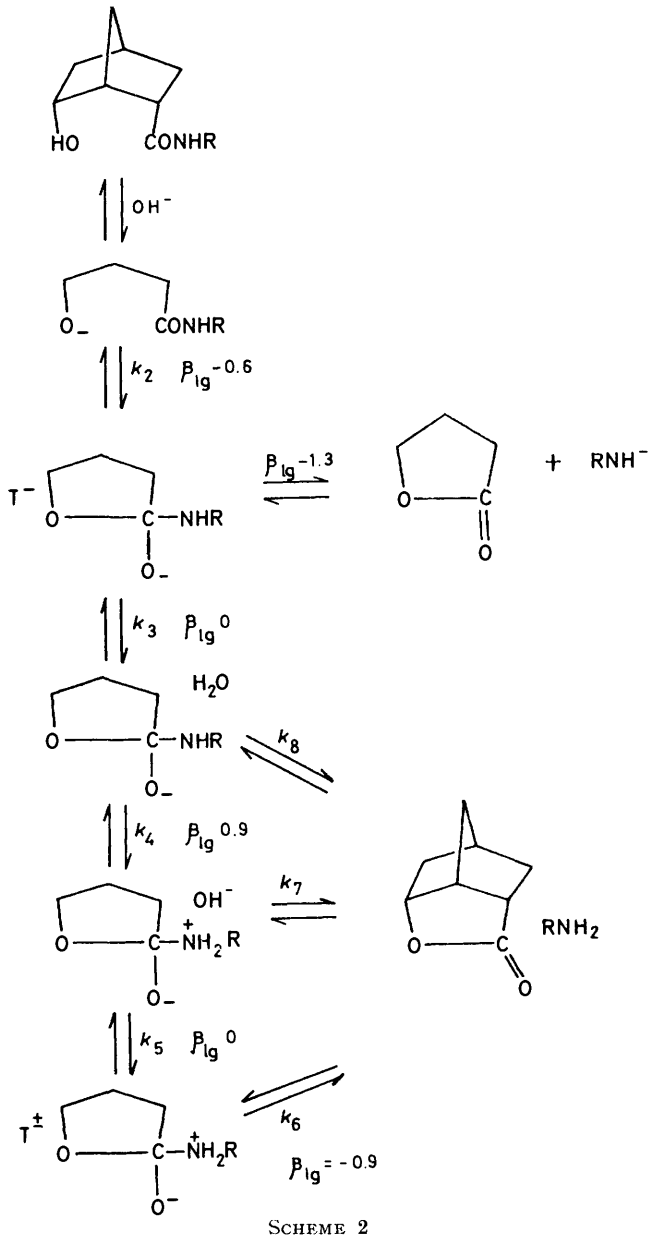


FIGURE 1 Plot of the logarithm of the second-order rate constants, k_{OH}, for the hydroxide-ion-catalysed lactonisation of *N*-substituted *endo*-6-hydroxybicyclo[2.2.1]heptane-*endo*-2-carboxamides in water at 30° and *I* 0.2M (KCl), as a function of the pK of the leaving amine group. The numbers refer to the hydroxy-amides listed in the Table. The arrow represents a lower limit for the rate constant in water which was determined in 40% v/v MeOH–H_2O

(b) *Mechanism.* The dependence of the rate constants for the hydroxide-ion-catalysed lactonisation of the hydroxy-amides (IV) upon the basicity of the leaving amine group is shown in Figure 1. The slope of this line, the Brønsted β_{lg} value, is $+0.30 \pm 0.06$; the rate constants *increase* with increasing basicity of the leaving amine. The mechanism of this reaction is discussed in more detail in the following paper [18] but it will be shown here that the observed β_{lg} value is consistent with rate-limiting breakdown of a tetrahedral intermediate.

The lactonisation of (IV) is an acyl transfer reaction involving the alcoholysis of an amide which is the reverse of the aminolysis of esters. The latter reactions have been well studied and shown to proceed through the formation of tetrahedral intermediates.[31] Due mainly to the work of Jencks and co-workers the Brønsted β values for the formation of possible intermediates in this class of reactions are known and can thus be used to elucidate the nature of the rate-limiting step in the lactonisation of the hydroxy-amide (IV) (Scheme 2).

The proposed mechanism involves ionisation of the hydroxy-group followed by alkoxide-ion attack on the carbonyl group to form the tetrahedral intermediate, T^- (Scheme 2). The formation of T^- will be facilitated by



SCHEME 2

electron-withdrawing groups in the amine and β_{lg} for the equilibrium formation of this intermediate is -0.6.[31,32] Formation of T^- cannot, therefore, be the rate-limiting step of the reaction. The intermediate T^- could collapse directly to the lactone (III) but this would involve expulsion of the amine anion, a very unlikely process.[25] Amine expulsion will be facilitated by protonation of the nitrogen and, as the pathway is hydroxide-ion catalysed, this must be by proton donation from water (general acid catalysis is observed in the presence of buffer species [8]). Proton transfer to nitrogen may either be concerted with or occur in a separate step from carbon–nitrogen bond fission.[33] For the stepwise mechanism, proton transfer will initially require either little change in solvent organisation or, if T^- is not at equilibrium with respect to solvation, solvent reorientation (k_3, Scheme 2). As proton transfer from water to the amine nitrogen is thermodynamically unfavourable in the cases studied neither k_3 or k_4 can be rate limiting.[34] The β value for the k_3 step will be 0 and this, therefore, is also incompatible with k_3 being rate limiting. Proton transfer itself, k_4, between electronegative atoms is never rate limiting when there is a significant difference in the pK_a of the proton donor and acceptor.[34] The formation of $T^\pm$ (pK_a 5—10) by proton transfer from water (pK_a 15.7) to T^- cannot therefore be rate limiting. The β value for formation of $T^\pm$ from T^- (Scheme 2) is *ca.* 0.9.[35] In the stepwise mechanism the rate-limiting step for proton transfer would be diffusion apart of hydroxide-ion and $T^\pm$ [34] (k_5) and, if this is the rate-limiting step for the overall reaction, the observed β_{lg} value should be *ca.* $+0.3$ (-0.6 $+0.9$) in good agreement with the observed value. The expulsion of the amine from $T^\pm$ (k_6, Scheme 2) to form the products cannot be rate limiting as this does not correspond to hydroxide-ion catalysis of the reaction. If the life-time of $T^\pm$ is short then it may expel amine at a rate which is faster than hydroxide ion can diffuse away, and the base will therefore be present as a 'spectator' or, in the reverse pathway, act by a pre-association mechanism [33,36] (k_7, Scheme 2). The equilibrium β_{lg} value for this step, k_7, will be *ca.* -0.9 [35] and the overall β_{lg}-value would change from $+0.3$ to -0.6 (-0.6 $+0.9$ -0.9) which is compatible with our observed value if the transition state for breakdown of $T^\pm$ is very 'early', *i.e.* little or no carbon–nitrogen bond fission. If the life-time of $T^\pm$ is very short then proton transfer from water to the amine nitrogen may be concerted with carbon–nitrogen bond fission (k_8, Scheme 2). The observed β_{lg} value would then be between $+0.3$ and -0.6 depending on the relative amount of proton transfer and carbon–nitrogen bond fission.

In summary, the observed β_{lg} value of $+0.3$ is indicative of a rate-limiting step which involves diffusion apart of $T^\pm$ and hydroxide ion (k_5), or expulsion of amine from $T^\pm$ in the presence of hydroxide ion with little carbon–nitrogen bond fission (k_7), or a fully concerted breakdown of T^- (k_8). These alternatives are discussed in further detail in the following paper.[8]

The deuterium solvent isotope effect $k_{OH}^{H_2O}/k_{OD}^{D_2O}$ for the hydroxide-ion-catalysed lactonisation of (VI) was found to be 1.58, which is compatible with the above postulated mechanisms.

(ii) *Acid Catalysis.*—The rate of the acid-catalysed lactonisation of the hydroxy-amide (VI) is *ca.* 10^4-fold faster than that of the acid-catalysed hydrolysis of the unsubstituted amide (VII). Reservations about the exact rate enhancement are similar to those made for hydroxide-ion catalysis [section (i) (a)]. The rate enhancement is also attributed to neighbouring group participation by the hydroxy-group to form the lactone

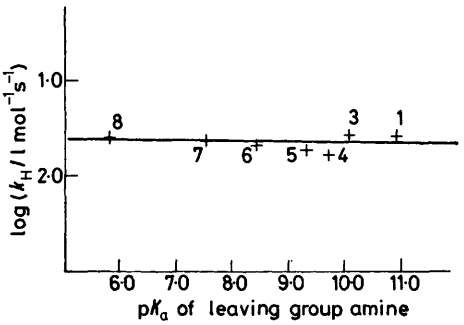
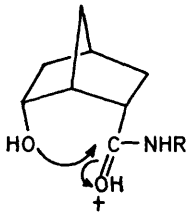


FIGURE 2 Plot of the logarithm of the second-order rate constants, k_H, for the acid-catalysed lactonisation of *N*-substituted *endo*-6-hydroxybicyclo[2.2.1]heptane-*endo*-2-carboxamides in water at 30° and *I* 0.20M (KCl), as a function of the p*K* of the leaving group amine. The numbers refer to the hydroxy-amides listed in the Table

(III) as the product. The ' effective concentration ' is *ca.* 10^6M which compares the efficiency of intramolecular hydroxy-attack on the protonated amide in water with intermolecular attack by water on the protonated amide in 50% v/v methanol–water.

The dependence of the rate constants for the hydrogen-ion-catalysed lactonisation of the hydroxy-amide (IV) upon the basicity of the leaving amine group is shown in Figure 2. The slope of this line gives a Brønsted β_{lg}



(X)

value of 0.0. This is consistent with rate-limiting attack of the hydroxy-group upon the *O*-protonated amide (X).[37]

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