Kinetics and Equilibria of Ring Closure through an Amide Linkage. Part 2.[1] 1-Aryl-2-pyrrolidones

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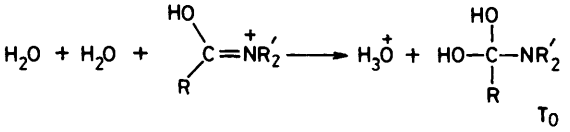
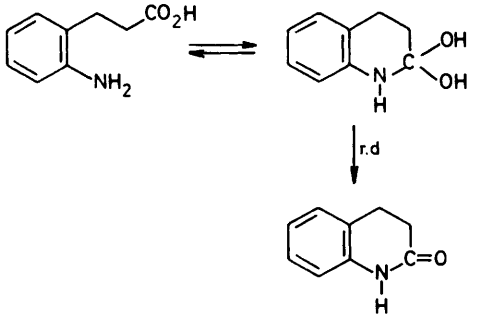
Equilibrium constants, and rate constants for forward and reverse reactions, for ring closure of several 4-(arylamino)butanoic acids to 1-aryl-2-pyrrolidones in aqueous acid, together with ionisation constants of the former group of compounds, are reported. The equilibrium constants K at 50 °C between neutral protonic forms of open-chain and ring compounds are related to the ionisation constants of the nitrogen-protonated 4-(arylamino)butanoic acids, K_1, by the equation: $\log K = 0.70\ (pK_1) + 1.53$. The value of K for pyrrolidone itself was measured for comparison. Studies of ^{18}O exchange reveal that (except in the case of the substrate which bears the most electron-withdrawing substituents in the aryl ring, namely 2,4-dinitro) the rate-determining step lies between the tetrahedral intermediate and the ring compound. Substituent effects and solvent deuterium isotope effects on the hydronium-ion catalysed reaction are consistent with a transition state close to the neutral tetrahedral intermediate. The effects of methyl substituents in the heterocyclic ring on rate and equilibrium constants have also been studied. The variation of K with temperature, and derived thermodynamic parameters, are reported in two cases.

This study was undertaken in order to clarify certain aspects of the mechanism of amide hydrolysis (the reverse of the title reaction) and to provide information about the stability of five-membered rings.

Amide Hydrolysis in Aqueous Acids.—Evidence concerning mechanism has been summarised.[2] It has been shown [3] that reaction through the nitrogen-protonated form (having regard to its estimated concentration, and using an acyltrialkylammonium ion as a model for its reactivity) would be too slow to account for the observed rate of acid-catalysed hydrolysis, and reaction through the oxygen-protonated form is thus implicated. The extent of carbonyl oxygen exchange of amides during the course of their acidic hydrolysis is very small,[4] which indicates that the step in which water attacks the oxygen-protonated amide is rate determining. The tetrahedral intermediate so formed may be of oxonium type [5] but studies of many other reactions in which water attacks electrophilic centres [6] make it more likely that the intermediate product of attack of water on the oxygen-protonated amide is the neutral tetrahedral intermediate, T_0, as in Scheme 1.



Scheme 1.



Scheme 2.

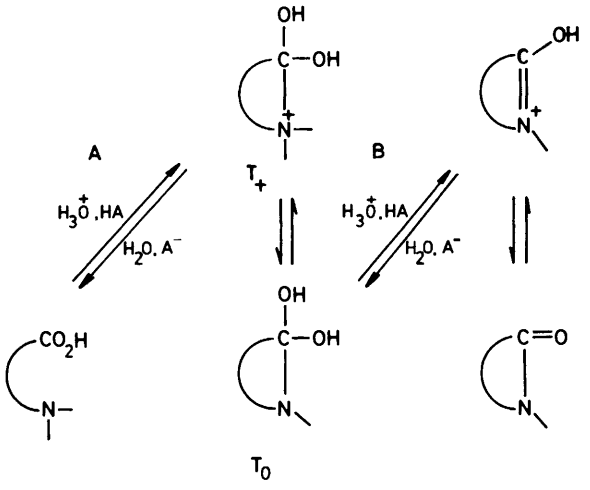
Cyclic Amide Formation and Hydrolysis in Aqueous Acids.—The kinetics of hydrolysis of lactams of ring size 5—7 in aqueous sulphuric acid solutions have been shown to be essentially similar to these of their open-chain analogues and to proceed to completion.[7] There have also been several investigations of cyclic amide *formation* in acid solution. The cyclisation of 3-(2-aminoaryl)propanoic acids proceeds to completion in aqueous acid, and evidence has been presented [8] for rate-determining general acid-catalysed breakdown of a neutral tetrahedral intermediate (Scheme 2). If the second and rate-determining step is one which produces initially the oxygen-protonated amide, it may be recognised as the reverse of Scheme 1, and is thus in accord with the supposed mechanism of amide hydrolysis.

Hydantoins are known [9] to be formed from hydantoic acids in acid solution (Scheme 3). Limits to the equilibrium constant of the reaction in Scheme 3 (R = Me) of 10^3—10^6 have been established.[1] The mechanism differs in one important respect from that of the reaction in Scheme 2; oxygen-exchange studies have shown that tetrahedral intermediate formation, rather than breakdown, is rate determining. The reaction is susceptible to general acid catalysis.

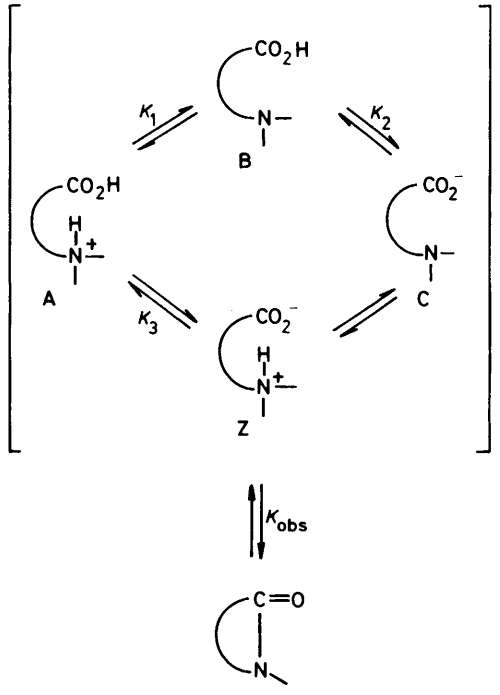
Scheme 3.

From this and other evidence, a minimum scheme for the description of cyclic amide formation and hydrolysis in acid is considered to be Scheme 4. If the transition states for steps A and B resemble T_+ and T_0 respectively, then the greater positive charge on nitrogen in step A accounts for this step being rate determining when the terminal nitrogen is of very low basicity as with hydantoic acids, whilst step B is rate determining otherwise.

The basicity of the terminal nitrogen will also be a major factor in determining the value, in dilute aqueous acid, of the overall equilibrium ratio, $K_{obs.}$, of the concentration of the cyclic amide to that of the open-chain compound in its various protonic forms (Scheme 5).



Scheme 4.

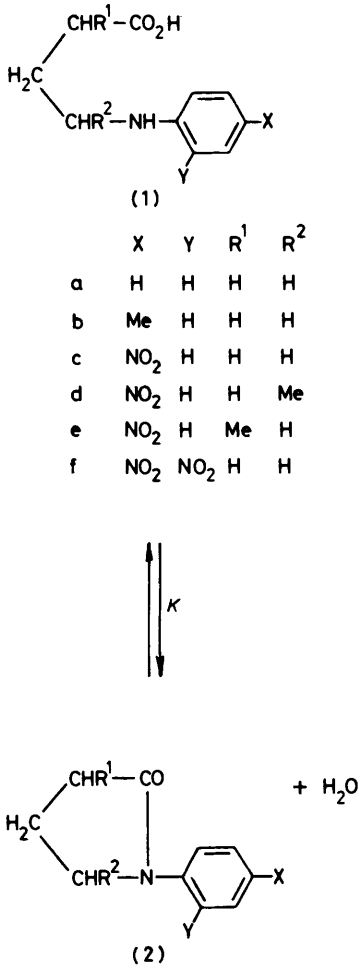


Scheme 5.

In this study the aims were firstly to seek a system in which it would be possible for the first time to measure the equilibrium constant for formation of five-membered cyclic amides in aqueous acids, and secondly to seek further evidence regarding the change in rate-determining step from A to B (Scheme 4). The compounds studied are in Scheme 6.

Results

Protonation Equilibria.—In order to compare equilibrium contants K (Scheme 6) between the neutral open-chain species and the cyclic amide, it was necessary separately to study the protonation equilibria of Scheme 5. The constants K' and K'' of equation (i) were determined for (1a and b) by pH measurements in the usual way.[10] These are related to K_1—K_3 of Scheme 5 by equations (ii) and (iii). Values of K_1 and K_3 were



Scheme 6.

Table 1. Acidity constants [a]

Compd.	T/°C	pK_1	pK_2	pK_3
(1a)	25	4.32	*b*	3.98
	50	4.24	*b*	4.00
(1b)	25	4.86	*b*	3.99
	50	4.78	*b*	4.03
(1c)	25	0.49 [c,d]	4.74 [d]	
	38	0.31 [c,d]		
	50	0.15 [c]	4.61 [d]	
(1d)	25	0.47 [c,d]	4.64 [d]	
	50	0.16 [c]	4.61 [d]	
(1e)	38	0.30 [c,d]		
	50	0.14 [c]	4.64 [d]	

[a] As in Scheme 5. Ionic strength adjusted to 1.0M with KCl. K_1, K_2, and K_3 are defined as in equation (iv) or analogously, unless otherwise stated. Errors in pK estimated as ±0.03 unless otherwise stated. [b] Assumed the same as for (1c). [c] Concentration constants, defined as in (iv) but with $[H^+]$ in place of a_{H^+}. [d] Error estimated to be ±0.02.

$$A \underset{}{\overset{K'}{\rightleftharpoons}} (B + Z) \overset{K''}{\rightleftharpoons} C \qquad \text{(i)}$$

$$K' = K_1 + K_3 \qquad \text{(ii)}$$

$$K'K'' = K_1K_2 \qquad \text{(iii)}$$

obtained by assuming K_2 to be the same for (1a—c), an assumption which seems justified by the long distance between

Table 2. Equilibrium constants and thermodynamic parameters for ring closure [a]

Equilibrium	T/°C	$K_{obs.}$	f	$\log_{10}K$	$\Delta H^{\ominus}$ [b] / kJ mol^{-1}	$\Delta S^{\ominus}$ [b] / J mol^{-1} K^{-1}
(2a)–(1a)	50	1.64	7.3×10^{-5} [c]	4.35 (±0.04)		
	65	1.46				
	80	1.34				
(2b)–(1b)	50	1.36	2.1×10^{-5} [c]	4.81 (±0.04)		
	65	1.16				
	80	1.08				
(2c)–(1c)	25	25.8	0.24	2.02 (±0.02)		
	38	22.0	0.32	1.84 (±0.02)	−23 (±2)	−39 (±6)
	50	21.2	0.41	1.71 (±0.02)		
(2d)–(1d)	25	60.9	0.25	2.38 (±0.02)		
	38	39.6	0.32	2.10 (±0.02)	−30 (±2)	−57 (±6)
	50	38.4	0.41	1.97 (±0.02)		
(2e)–(1e)	25	70	0.25	2.4 (±0.1)		
(2f)–(1f)	80	0.05	1	−1.3 (±0.2)		

[a] $K_{obs.}$ and f are for 1M-HCl. These and K are defined in the text. [b] For the reaction of Scheme 6 between neutral species. Standard state is 1M-HCl. [c] In the calculation of this quantity, the activity of H^+ in 1M-HCl was taken to be numerically equal to the activity coefficient of HCl.

the aryl substituent and the carboxy-group. Values are so-called [10] ' mixed ' constants defined as in equation (iv) or analogously. The values of K_2 for (1c—e) were measured straightforwardly from pH measurements because for these,

$$K_1 = [B]a_{H^+}/[A] \quad \text{(iv)}$$

K_1 and K_2 do not overlap. Values of K_1 for (1c—e) were determined spectrophotometrically, or from kinetic studies as described below. Hydrogen ion concentrations rather than activities were known in the determinations of K_1 for (1c—e); reported values are therefore concentration constants, not mixed constants as in the other cases. B Was the predominant species of (1f) in 1M-HCl; protonation equilibria for this compound were not investigated.

The Equilibrium Constant K (*Scheme* 6).—It was found that the same equilibrium mixture of (1) and (2) was obtained starting with either (1) or with (2), and the observed first-order rate constant for approach to equilibrium, $k_{obs.}$, was also independent of the starting material. These observations show the reactions of Schemes 5 and 6 to be clean equilibria with no side reactions [instability of the equilibrium mixture was observed only in the (2f)—(1f) system, reducing in this case the accuracy of the determined constants]. Comparison of initial and final spectra of (1a—e) and (2a—e) in 1M-HCl led to the equilibrium constant $K_{obs.}$ of equation (v) and Scheme 5; $[(1)]_t$ represents the total concentration of all protonic forms, A, B, Z, and C, of (1). The data on protonation equilibria permitted calculation of the fraction, $f = [B]/[(1)]_t$, of open-chain compound present in the neutral form. Equation (vi) was then used to calculate the equilibrium constant K of Scheme 6. (The water molecule of Scheme 6 is not included in the defined, dimensionless K.) Values are in Table 2.

$$K_{obs.} = [(2)]/[(1)]_t \quad \text{(v)}$$

$$K = K_{obs.}/f \quad \text{(vi)}$$

For the equilibria (2c)–(1c) and (2d)–(1d), least-squares regression of $\ln K$ upon $(1/T)$ led to values of $\Delta H^{\ominus}$ and $\Delta S^{\ominus}$, as reported in Table 2. In other cases errors were judged to be too large to justify such calculations. Error assessments throughout were made using standard formulae for error propagation.[11]

The Kinetics of Ring Closure and Opening.—The observed first-order rate constant, $k_{obs.}$, for approach to the equilibrium mixture, starting with either $(1)_t$ or (2), is the sum of the first-order rate constants for reaction in forward and back reactions, k_f and k_b. The equilibrium of Scheme 6 is general acid-catalysed; catalysis by species other than H^+ will be discussed

$$k_{obs.} = k_f + k_b \quad \text{(vii)}$$

$$K_{obs.} = k_f/k_b \quad \text{(viii)}$$

in a later publication. Specific second-order rate constants for H^+-catalysed forward and back reactions of the neutral species, k_{close} and k_{open}, respectively, can be obtained using equations (ix) and (x). Values are in Table 3. k_{close} and k_{open}

$$k_{close} = k_f/f[H^+] \quad \text{(ix)}$$

$$k_{open} = k_b/[H^+] \quad \text{(x)}$$

are found to be independent of pH, showing that there is no significant contribution from an uncatalysed reaction under the conditions of these experiments.

Approach to equilibria of (1c—e) at 50 °C was too fast for separate investigation of protonation equilibria, so k_{close} and K_1 were derived simultaneously as follows. Equations (vi)—(ix) can be combined with equation (xi) (which is satisfactory for the calculation of f because ionisation of the carboxy-group is negligible) to give equation (xii). From data at other

$$f = K_1/(K_1 + [H^+]) \quad \text{(xi)}$$

$$\frac{(1 + f/K)}{k_{obs.}} = \frac{1}{k_{close}[H^+]} + \frac{1}{K_1 k_{close}} \quad \text{(xii)}$$

temperatures it was clear that $K > 50$. It follows that $1 < (1 + f/K) < 1.02$. It was therefore satisfactory to use approxi-

Talbe 3. Kinetics of approach to equilibrium in aqueous HCl [a]

Reaction [b]	T/°C	[H$^+$]/M	$10^6k_{obs.}$ [c]/s^{-1}	k_{close}/l mol^{-1} s^{-1}	k_{open}/l mol^{-1} s^{-1}
(2a)–(1a)	50	0.60	8.6	0.10	4.8×10^{-6}
	50	0.80	9.1	0.10	4.2×10^{-6}
	50	1.00	12	0.13	4.6×10^{-6}
	65	1.00	47	0.43	1.9×10^{-5}
	80	1.00	130	1.08	5.7×10^{-5}
(2b)–(1b)	50	1.00	6.5	0.23	2.8×10^{-6}
	65	1.00	24	0.71	1.1×10^{-5}
	80	1.00	90	2.32	4.3×10^{-5}
	80	0.10	47	2.21	3.6×10^{-5}
(2c)–(1c)	25	1.00	94 (99)	4.0×10^{-4}	4.0×10^{-6}
	38	0.25	100	6.2×10^{-4}	9.0×10^{-6}
	38	0.50	150	6.0×10^{-4}	9.0×10^{-6}
	38	0.75	170	5.9×10^{-4}	8.0×10^{-6}
	38	1.00	220 (210)	6.4×10^{-4}	9.0×10^{-6}
	50	0.01	21.4, 22.2	2.2×10^{-3}	—
	50	0.01 [d]	25.6, 25.4	2.6×10^{-3}	—
	50	0.07	150	2.3×10^{-3}	4.4×10^{-5}
	50	0.07	150	2.3×10^{-3}	4.4×10^{-5}
	50	0.10	200	2.2×10^{-3}	4.3×10^{-5}
	50	0.15	290	2.3×10^{-3}	4.5×10^{-5}
	50	0.30	500	2.3×10^{-3}	4.5×10^{-5}
	50	0.50	680	2.3×10^{-3}	4.4×10^{-5}
	50	1.00	1 000 (1 010)	2.3×10^{-3}	4.5×10^{-5}
(2d)–(1d)	25	1.00	(95)	3.8×10^{-4}	2×10^{-6}
	38	1.00	350	1.1×10^{-3}	9×10^{-6}
	50	0.20	360	2.5×10^{-3}	2.4×10^{-5}
	50	0.30	420	2.0×10^{-3}	2.1×10^{-5}
	50	0.40	600	2.3×10^{-3}	2.5×10^{-5}
	50	0.50	660	2.2×10^{-3}	2.4×10^{-5}
	50	0.60	750	2.3×10^{-3}	2.4×10^{-5}
	50	0.80	870 (880)	2.3×10^{-3}	2.4×10^{-5}
	50	1.00	900 (890)	2.1×10^{-3}	2.3×10^{-5}
(2e)–(1e)	25	1.00	510	2.0×10^{-3}	7.2×10^{-6}
(2f)–(1f)	80	1.00	7.8	3.6×10^{-7}	7.4×10^{-6}

[a] Ionic strength adjusted to 1.0M with KCl. [b] See Scheme 6. [c] Figures in parentheses refer to reactions in which (2) was the starting material. Otherwise (1) was the starting material. [d] DCl in D_2O.

mate values of K_1 and K to calculate $(1 + f/K)$. Plots of $(1 + f/K)/k_{obs.}$ against $1/[H^+]$ were linear (Figure) and led using equation (xii) to values of k_{close} and K_1. Values of $(1 + f/K)$ were then modified and the process repeated; one iteration was sufficient. The use of this technique with the data for 38 °C for (1c) led to a value of K_1 in good agreement with that determined independently by the spectroscopic method.

Kinetics of ^{18}O Exchange.—First-order rate constants, $k_{exch.}$, for exchange of ^{18}O by (2b, c, and f) in $H_2{}^{18}O$-enriched 1M-HCl were determined by g.c.–m.s. investigation of quenched samples. Rate constants are in Table 4, where they are compared with first-order rate constants for ring opening, k_b, under the same conditions.

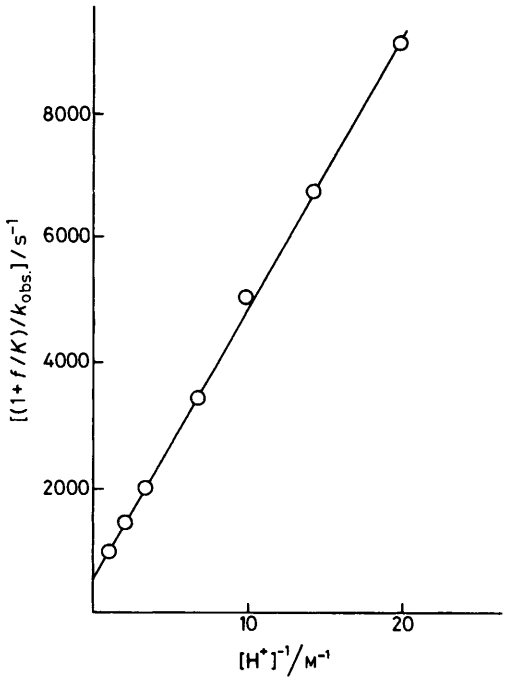
Kinetic Hydrogen Isotope Effect.—The rate constants (Table 3) for ring closure of (1c) in 0.01M-HCl in H_2O and 0.01M-DCl in D_2O [media in which ring closure goes almost to completion and in which protonation of (1c) is insignificant] lead directly to the ratio $k^H{}_{close}/k^D{}_{close} = 0.85$ (mean value).

Table 4. Kinetics of ^{18}O exchange of 1-aryl-2-pyrrolidones

Compd.	T/°C	[HCl]/M	$K_{obs.}$	10^6k_b/s^{-1}	$10^6k_{exch.}$/s^{-1}
(2b)	80	0.1	12	4.3	4.8 (± 0.7)
(2c)	50	1.0	21	44	19 (± 3)
(2f)	80	1.0	0.047	7.4	4.6 (± 0.7)

Discussion

The Rate-determining Step.—Information comes from the kinetics of ^{18}O exchange (Table 4). The interpretation of the results is different for each of the three compounds. Compounds (2b and c) are preferred over their open-chain forms



Plot of $(1 + f/K)/k_{obs.}$ against $1/[H^+]$ for cyclisation of (1c) in aqueous HCl (50 °C)

($K_{obs.} \gg 1$) under the conditions of study. The ratio $k_{exch.}/k_b$ would then be expected to be much greater than unity if step A (Scheme 4) were rate determining. This is not the case. If step B were rate determining, the ratio should take the value 1 for (2b) and between 0.5 and 1 for (2c). [The difference arises because the oxygen exchange of the open-chain carboxylic acid (other than by ring closure and opening) would be expected, using ethanoic acid [11b] as a model, to be much faster than ring closure in the case of (1b), and comparable in rate to ring closure in the case of (1c) in each case under the conditions described in Table 4.] Within experimental error, these expectations are realised; the results are therefore consistent with step B being rate determining for (2b and c).

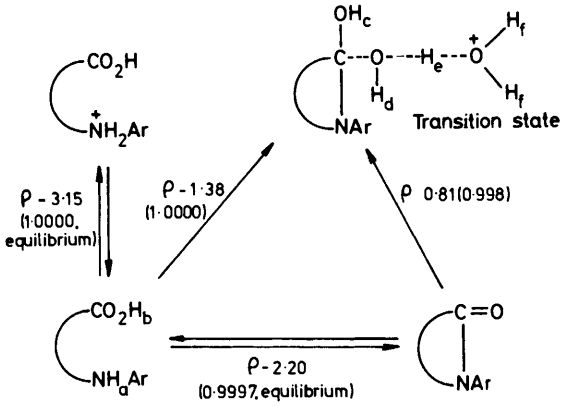
Compound (2f) undergoes almost complete hydrolysis ($K_{obs.} \ll 1$) under the conditions of study (Table 4). The observation of substantial ^{18}O exchange during the course of acid hydrolysis is unusual [4] and indicates that exit from the tetrahedral intermediates by steps A and B (Scheme 4) occurs in this case with approximately equal facility. This strengthens the conclusion (see Introduction) that decrease in the basicity of the terminal nitrogen can cause a change in rate-determining step from B to A. The remainder of the discussion will be confined to (1a—e) and their cyclisations, which are believed on the basis of the above evidence to be rate limited by step B of Scheme 4. (We note here that our results give no information as to whether step A remains the preferred route between open-chain compound and tetrahedral intermediate for these cases.)

Equilibrium Constants K (*Scheme* 6).—There is a linear relation between log K and pK_1 for (1a—c), as in equation (xiii). [The value of K_1 for (1c) was multiplied by the activity

$$\log K = 0.70\ (pK_1) + 1.53 \qquad \text{(xiii)}$$

coefficient of 1M-HCl to convert it to a ' mixed ' constant, and thus render it directly comparable with the values for (1a and b). Data for 50 °C were used. The correlation coefficient was 0.9994.] Effects of substituents on cyclisation are seen to be comparable with their effects upon protonation, and support the view [11c] that in (2) the nitrogen atom bears a considerable positive charge (Scheme 7).

Scheme 7.



Scheme 8.

We investigated whether equation (xiii) were useful for approximate predictions relating to 2-pyrrolidones bearing nitrogen substituents other than aryl. We studied 2-pyrrolidone itself, for which literature data [12] leads to the estimate $pK_1 = 9.9$ (50 °C). From equation (xiii) the value of K is then expected to be 2.9×10^8. Taking into account the fraction of the open-chain compound present in the neutral form, this leads to the expectation $K_{obs.} = 0.18$ (0.2M-HCl, 50 °C). The reaction is too slow under these conditions for convenient study, but our analysis of the mixture in 0.2M-HCl equilibrated at 100 °C gave $K_{obs.}$ 3.5×10^{-3} and thus K 5.6×10^6 (details are in the Experimental section). Equation (xiii) is seen to give only a very approximate guide to values of K for other 2-pyrrolidones.

Comparison of values of K for (1c—e) (Table 2) shows that 3- and 5-methyl substituents enhance ring stability as expected.[13] The effect of the 5-methyl substituent is closely similar to its effect on the equilibrium constant for formation of the corresponding lactones.[14]

The thermodynamic parameters relating to the equilibrium of Scheme 6 for (2c)–(1c) and (2d)–(1d) (Table 2) show that ring closure is exothermic, that the 3-methyl substituent enhances this exothermicity, and that ring closure leads to considerable loss of entropy despite the freeing of a molecule of water.

The Kinetics of Ring Closure and Opening.—The second-order rate constants for hydronium-ion-catalysed ring opening and closing of neutral species, k_{open} and k_{close}, respectively, show opposite trends with aryl ring substituents. Comparison of these trends can be made using Hammett ρ values. These are compared with ρ values for protonation and ring-closure equilibria in Scheme 8. As expected, correlation with σ^- values was better than with σ values, except for ring opening. For consistency, σ^- values are used throughout. Correlation coefficients are given in parentheses. (It is emphasised that these values are derived from studies of only three substituents, *p*-Me, H, and *p*-NO_2).

Table 5. Analyses and m.p.s for the compounds in Scheme 6

Compd.	Analyses found (%) C	H	N	Calculated (%) C	H	N	Solvent [a]	M.p. (lit. value) (°C)
(1a)	66.55	7.35	7.6	67.0	7.25	7.8	Petroleum (40—60 °C)	56.8 (55 [18])
(1b)	68.4	7.65	7.05	68.4	7.75	7.25	Petroleum (60—80 °C)	104—105
(1c)	53.35	5.4	12.45	53.55	5.35	12.5	MeOH	184—186 (186 [18])
(1d)	55.55	5.85	11.7	55.45	5.9	11.75	MeOH	126—127
(1e)	55.5	5.85	11.75	55.45	5.9	11.75	MeOH	119—120
(1f)	44.6	4.1	15.6	44.25	3.95	15.25	MeOH	140—142 (142 [18])
(2a)	74.4	7.0	8.75	74.55	6.85	8.7	Petroleum (60—80 °C)	66—67 (68—69 [17])
(2b)	75.45	7.65	8.0	75.45	7.45	8.0	Petroleum (60—80 °C)	87—88 (88 [19])
(2c)	58.1	4.85	13.6	58.25	4.85	13.6	MeOH	130—131 (131 [18])
(2d)	59.7	5.55	13.1	60.0	5.45	12.75	EtOH	124—126 (105—110 [20])
(2e)	59.7	5.4	12.6	60.0	5.45	12.75	EtOH	174—176
(2f)	47.8	3.6	16.75	47.6	3.3	16.5	MeOH–H_2O	117—119 (86 [18])

[a] For recrystallisation.

The ρ value for acid-catalysed ring-opening of neutral pyrrolidones at 50 °C is 0.81 (comparable to but somewhat larger than that which may be deduced for acid-catalysed hydrolysis of neutral acetanilides [15] at 100 °C, namely 0.47) and demonstrates that there is a decrease in positive charge on nitrogen going from the neutral ring compound to the transition state for acid-catalysed hydrolysis. This is consistent with a transition state which resembles the neutral tetrahedral intermediate.

The observed kinetic hydrogen isotope effect on ring closure is also consistent with the transition state in Scheme 8, though providing little positive evidence for it. Allotting suggested [16] fractionation factors, φ_a 0.92, φ_b 1.0, φ_c 1.2, φ_d 1.0, φ_e 0.4, φ_f 0.83, and for each proton of the hydronium ion, φ 0.69, leads to an estimated isotope effect, k^H_{close}/k^D_{close} 0.91, which is satisfactorily close to the observed value (data are in Table 3), k^H_{close}/k^D_{close} 0.85.

The effects of 3- and 5-methyl substituents in the five-membered ring on the kinetics are quite different, even though their effects on the equilibrium constant are similar. The 5-methyl substituent [(1d) and (2d)] has little effect on ring closure, and slows down ring opening. The 3-methyl substituent on the other hand accelerates both processes (Table 3). More data on comparable systems is needed before these observations can be interpreted.

Experimental

Compounds are numbered as in Scheme 6.

Materials.—Compounds (2a), (2b), (2; X = Y = R^2 = H, R^1 = Me), and (2; X = Y = R^1 = H, R^2 = Me) were prepared from the corresponding lactones and arylamines by a standard method.[17] The 4-nitro-derivatives (2c—e) were prepared by nitration of the appropriate 1-phenyl-2-pyrrolidone in mixed acid. In each case only the 4-nitro-isomer was detected. Compound (2f) was prepared by nitration of (2c) in a similar manner. Compounds (1a—e) were prepared by alkaline hydrolysis of the corresponding 2-pyrrolidone. The latter (2 g) was added to aqueous NaOH (50 cm^3, 2M) and either allowed to stand at room temperature for 30 min [(1f)] or heated [50 °C until all solid had dissolved in cases (1c—e), 100 °C for 6 h in cases (1a and b)]. The reaction mixture was cooled and aqueous HCl (50 cm^3, 2M) added. The product was filtered off [(1c—f)] or extracted with dichloromethane [(1a and b)]. Analyses, *etc.*, are in Table 5.

2-Pyrrolidone and 4-aminobutanoic acid were purified by distillation and recrystallisation (1 : 1 MeOH–H_2O) respectively, and purities were checked by n.m.r. and g.c.

Protonation Equilibria.—Values of K_1 for (1c—e) were determined spectrophotometrically; absorbances at 410—440 nm were measured with an SP 1800 spectrophotometer. Solutions were in aqueous HCl (0.01—1.0M). The ionic strength was adjusted to 1.0M with KCl.

Values of K_2 for (1c—e) and of K' and K'' for (1a and b), were determined by potentiometric titration; calculations were as described.[10]

Kinetics.—A spectrophotometric method was used to study the kinetics of formation of the equilibrium mixture of (1) and (2). Wavelengths used depended on the starting material as follows: (1a and b), 240—245 nm; (1c—e), 320—324 nm; (2c—e), 410—414 nm; (2f), 320 nm. Reactions were followed for at least four half-lives; absorbance–time data were stored, and rate constants calculated, by computer. Sealed tubes were used for all runs at temperatures >50 °C.

The kinetics of ^{18}O exchange of (2b, c, and f) were studied as follows; a solution of HCl in $H_2{}^{18}O$ (20 atom % enriched and normalised, from Prochem Ltd.) was prepared by weight. The substrate was added and portions were sealed in tubes and left for various times at the appropriate temperature. The samples were cooled, and extracted with dichloromethane (2 × 8 cm^3). The combined extracts were dried and reduced in volume by evaporation to *ca.* 1 cm^3. They were then analysed by g.c.–m.s., and the ratio of the M^+ to the $(M + 2)^+$ peaks determined. (The mean of 4—6 determinations was taken in each case.) In the case of (2f), the M^+ peak was very small, so the ratio of the $(M - 30)^+$ to the $(M - 28)^+$ peak was determined.

Ring Closure Equilibria.—Absorbances of $(1)_t$, (2), and the equilibrium mixture were measured at appropriate wavelengths. Errors in $K_{obs.}$ are minimised when $K_{obs.}$ is close to unity, in other words when the spectrum of the equilibrium mixture is nearly midway between those of $(1)_t$ and (2). This was the case for the equilibria involving (1a and b) in 1M-HCl, but for (1c—e) could not be attained without further increase in acidity and consequent departure from the adopted standard conditions of 1M ionic strength. (The alternative use of more basic solutions, where $K_{obs.}$ can be expected again to fall, is precluded by the extreme slowness with which equili-

brium is attained.) Values of $K_{obs.}$ for (1c—e) were therefore measured for 1M-HCl, minimising errors by use of wavelengths at which the minor component (1) absorbs strongly, and the major component (2), and the equilibrium mixture, absorb weakly. Absorbances of the latter two were measured at concentrations as high as possible (limited either by solubility, or by the need to keep absorbances <1 for accurate measurement) to maximise the difference between them. The absorbance of (1) was measured at a lower concentration.

Equilibrium between 4-Aminobutanoic Acid and 2-Pyrrolidone.—Sealed tubes each containing 10 cm^3 of an aqueous solution of HCl (0.2M) and 4-aminobutanoic acid (0.2M) were kept at 100 °C for 17—42 h, then cooled and opened. *p*-Nitroanisole (reference standard) was added and the solution was neutralised with aqueous NaOH and extracted with dichloromethane (10×2.5 cm^3). The combined extracts were reduced to 2 cm^3 by distillation of solvent, and analysed by g.c. [3% OV225 on Chromasorb W.H.P.; 115 °C; retention time of 2-pyrrolidone (reference standard); 160 s (470 s)]. Area ratios were compared with those from mixtures of known concentration which had been extracted and analysed in the same way. Concentrations of 2-pyrrolidone at equilibrium were in the range 7.0 ($\pm$ 1.0) $\times$ 10^{-4}M.

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