Intramolecular Nucleophilic Attack by Urea Nitrogen. Reactivity–Selectivity Relationships for the General Acid–Base Catalysed Cyclisations of Ureido Acids and Esters

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The cyclisation of *N*-substituted hydantoic acids involves general acid–base catalysed attack of urea nitrogen on the CO_2H group. The variation of the Brønsted exponents for the reactions of the *N*-methyl and *N*-phenyl derivatives (**2**) and (**3**) allows a choice between kinetically equivalent mechanisms. Stereoelectronic effects on the nucleophilic reactions of urea NH are considered, and a mechanism involving an initial rotation about the terminal C–N bond of the ureido group is suggested.

The nucleophilic reactivity of ureas towards the CO_2H and CO_2^- groups is of interest in the context of model studies of biotin action. The intramolecular reaction is involved in the ring-closure of hydantoic acids[1,2] and different patterns of substitution allow us to study different aspects of the chemistry involved. The introduction of methyl groups in positions 2 and 3 results in accelerations of up to 10^5 in the rate of cyclisation,[1,2] as increased ground-state strain is relieved on ring formation. Thus we have been able to study the remarkable ring-closure reaction of the anion of (**1**), which involves general acid-catalysed nucleophilic attack by ureido anion nitrogen on the carboxylate anion.[1]

The cyclisation of (**1**) is too fast to be measured conveniently at pH < 7,[1] but modifying the pattern of substitution enabled us to follow the cyclisation of the *N*-phenylhydantoic acid (**2**) over the complete pH range.[2] The general base-catalysed cyclisation of the anion was identified as before, but the mechanism of the general acid-catalysed reaction of the neutral acid (SH) could not be unambiguously assigned.

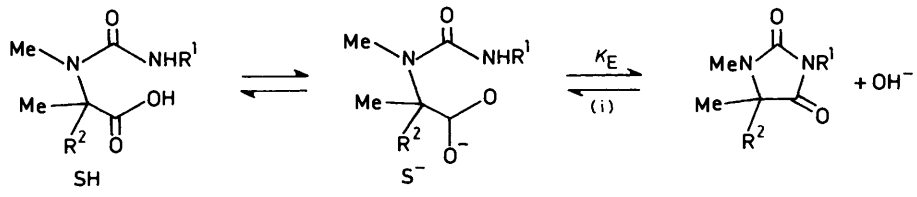
Ureas are very weakly basic nucleophiles (a pK_a of −3.9 has been estimated for *N*-protonated *N*-methylurea[3] and an *N*-phenylurea will be less basic still), and their kinetic behaviour may differ considerably from that of more basic amino-compounds. On the basis of ^{18}O exchange experiments Moodie *et al.* established that for nucleophiles with $pK_a < 0$, such as 2,4-dinitroaniline and the *N*-methylureido group, the rate-determining step (for the acid-catalysed cyclisation of 4-arylaminobutanoic acids[4] and of 5-methylhydantoic acid[5]) is the formation of the tetrahedral intermediate. For more basic anilino groups the elimination of OH from T° is rate determining, as found previously by Camilleri *et al.*[6] for the cyclisation of 3-(2-aminophenyl)propanoic acids. Güler and Moodie[5] also observed catalysis by methoxyacetic acid of the ring closure of 5-methylhydantoic acid, but did not study buffer catalysis in detail.

A problem with any nucleophilic reaction involving a urea (or amide) nitrogen is the timing of the deprotonation step. The neutral group is normally alkylated or protonated on oxygen, and attack on nitrogen requires prior deprotonation.[7] In fact all three pathways important for the cyclisation of the *N*-phenylhydantoic acid (**2**) above pH 3 involve deprotonation of the urea nitrogen either before or during the course of attack on the carboxy carbon.[2] There remains the general acid-catalysed reaction of the neutral compound (SH). From our results with (**2**) it was not possible to distinguish simple general acid catalysis (**A**) from the kinetically equivalent specific acid–general base mechanism (**B**, Scheme 1).

The reaction was too fast to follow for the tetramethylhydantoic acid (**1**), but so slow for a hydantoic acid lacking *C*-methyl groups that general acid catalysis could not be measured.[5] So we prepared the trimethyl compound (**3**), hoping that a comparison of Brønsted α-values for attack by *N*-methyl and *N*-phenyl ureido groups would allow us to resolve this question. To help resolve problems of kinetic ambiguity associated with the ionisation of the CO_2H group we also studied the ring-closure of the ethyl ester (**4**) of compound (**3**) under the same conditions.

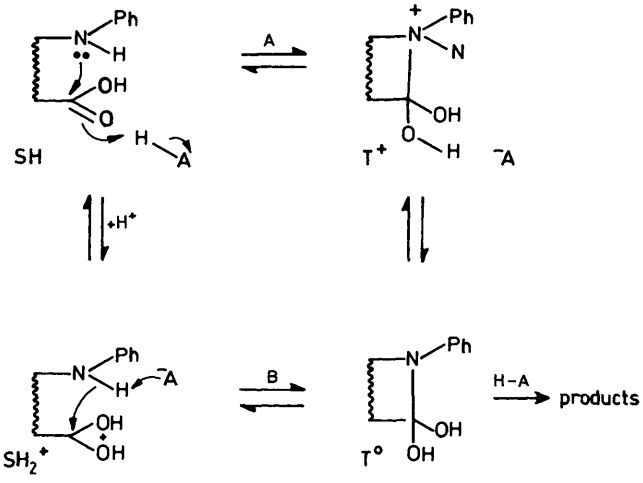
Experimental

Materials.—Inorganic reagents and buffer components were of analytical grade, and were used without further purification.



(**1**) $R^1 = R^2 = Me$
(**2**) $R^1 = Ph$, $R^2 = H$
(**3**) $R^1 = Me$, $R^2 = H$

$K_E > 10$ mol dm^{-3}
K_E $3{\cdot}6\times10^{-4}$ mol dm^{-3}



Scheme 1.

Potassium hydroxide and buffer solutions were prepared with CO_2-free distilled water.

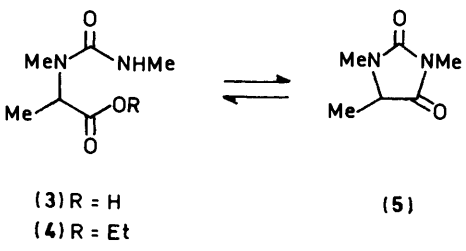
Potassium 2,3,5-*trimethylhydantoate* [the potassium salt of (**3**)] was obtained in solution (only) from the potassium salt of *N*-methylalanine and methyl isocyanate, as described for 2,2,3,5-tetramethylhydantoate.[1] Stock solutions used for the kinetic experiments were 0.1 mol dm^{-3} in 20% (v/v) aqueous ethanol. The stock solutions were stored frozen.

1,3,5-*Trimethylhydantoin* (**5**) was best prepared by cyclisation of potassium 2,3,5-hydantoate, according to Cortes and Cohn.[8] Our product had the same b.p. (68–69 °C at 0.1–0.2 mmHg) and a satisfactory elemental analysis.

Ethyl 2,3,5-*trimethylhydantoate* (**4**). Methyl isocyanate (70 mm^3, 1.1 mmol) was added to an ice-cooled solution of the ethyl ester of *N*-methylalanine (0.132 g, 1 mmol) in dry THF (1.5 cm^3). The mixture was stirred for 15 min at 0 °C, and then for 30 min at room temperature. The product cyclised in ethanol. Stock solutions, 0.1 mol dm^{-3} in (**4**), were prepared by diluting the mixture with dry THF.

pK_a *Measurements.*—The pK_a value for the dissociation of the carboxy group of (**3**) was determined under the conditions of the kinetic experiments (25 °C, ionic strength maintained at 1.0 mol dm^{-3} with KCl) by potentiometric titration, as described for 2,3-dimethyl-5-phenylhydantoic acid,[2] except that the concentration of the potassium salt was corrected for the 4% hydantoin present in the equilibrium mixture after hydrolysis in 1 mol dm^{-3} KOH. The value obtained was 3.93 ± 0.02.

Kinetic Measurements.—Rate constants were determined at 25.0 ± 0.01 °C under pseudo-first-order conditions in the thermostatted cell compartment of a Unicam SP-800 or Gilford 2600 spectrophotometer. The rate of the cyclisation of (**3**) and (**4**), and of the hydrolysis of (**5**), was followed by monitoring the change of absorbance at 243 nm due to (**5**). Reactions were initiated by injecting 40–50 mm^3 of 0.1 mol dm^{-3} stock solutions of (**3**), (**4**) or (**5**) into 2.7 cm^3 of preheated buffer solution. An aqueous stock solution of (**5**) was used for the hydrolysis experiments. Ionic strength was maintained constant (1.0 mol dm^{-3}) with KCl. Measurements of pH values, calculations of first-order rate constants (k_{obs}), and derived rate constants were as previously described.[2] In all cases good first-order plots ($r > 0.999$) were obtained over three half-lives. Infinity values of absorbance for the irreversible cyclisation of (**3**) and (**4**) corresponded over the whole pH-range studied to that for the product hydantoin, obtained by cyclisation in 1 mol dm^{-3} HCl. k_{obs} Values were reproducible to within ±3%, and were corrected for small variations in pH with changing buffer concentration.



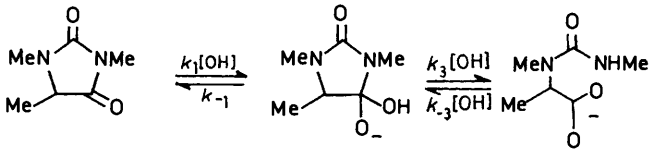
(**3**) R = H
(**4**) R = Et

(**5**)

Results

Reversible Alkaline Hydrolysis of 1,3,5-*Trimethylhydantoin.*—The hydrolysis of (**5**) is reversible, with the position of equilibrium shifting to favour the cyclic form at lower pH [reaction (i)]. The equilibrium constant K_E for (**3**) ⇌ (**5**) was calculated as 0.034 ± 0.006 mol dm^{-3} from 12 measurements in 0.1–1.0 mol dm^{-3} KOH. The concentration range could not be extended further since at long reaction times slow degradation of the hydantoic acid occurs, observed as a decrease in the final absorbance due to the hydantoin after recyclisation in 1 mol dm^{-3} HCl. Separate measurements on KOH solutions of 2,3,5-trimethylhydantoate showed that after 10 half-lives (when end-points were measured) the decrease in total absorbance after recyclisation did not exceed 3% even for the slowest runs.

The hydrolysis of (**5**) in this concentration range is second order in hydroxide; the slope of the linear plot of log k_{hyd} *versus* log [OH] being 2.05 ± 0.03. This is the well established hydroxide-catalysed decomposition of the tetrahedral intermediate in the hydrolysis of acylureas[9] (Scheme 2): the reverse reaction is observed, exceptionally, for compounds with strained ground states. The value of the third-order rate constant for hydrolysis, k_1k_3/k_{-1}, is 4.65 ± 0.25 × 10^{-2} dm^6 mol^{-2} s^{-1}, and the rate constant for the hydroxide-catalysed cyclisation of the anion of (**3**), k_{-3}, calculated from the equilibrium constant K_E, is 1.6 × 10^{-3} dm^3 mol^{-1} s^{-1}.



Scheme 2.

Irreversible Ring Closure of 2,3,5-*Trimethylhydantoic Acid* (**3**) *and Ethyl Trimethylhydantoate* (**4**).—Data for the cyclisations of (**3**) and (**4**) are presented graphically in Figure 1. Both reactions

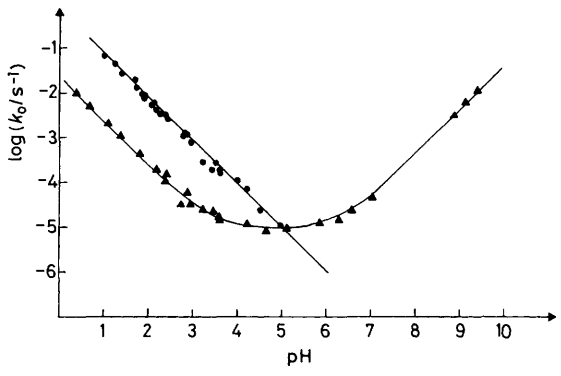


Figure 1. pH–Rate profiles for the cyclisations of hydantoic acid (**3**) (circles) and its ethyl ester (**4**) (triangles), at 25 °C and ionic strength 1.0 mol dm^{-3}

Table 1. Buffer catalysis data for the cyclisation of 2,3,5-trimethylhydantoic acid (**3**) at 25 °C and ionic strength 1.0 mol dm^{-3}

Buffer acid	pK_a [a]	Concn. range mol dm^{-3}	Runs	%A^-	pH	$10^3 k_{cat}$ [b]	$10^3 k_{HA}$/dm^3 mol^{-1} s^{-1}	$10^4 k_{A^-}$
H_3O^+	−1.74						830 ± 16 [c]	0.029 [d]
H_3PO_4	1.78	0.1–0.7	3	50	1.95	95.0 ± 1.7		
		0.1–0.7	3	70	2.28	66.0 ± 0.6		
		0.1–0.7	3	90	2.92	29.4 ± 1.8	177 ± 7 [e]	173 ± 32 [e,g]
$NCCH_2CO_2H$	2.38	0.1–0.5	3	20	1.94	29.5 ± 2.3		
		0.1–0.5	3	30	2.10	25.9 ± 0.9		
		0.1–0.5	3	50	2.43	18.2 ± 1.1		
		0.1–0.5	3	70	2.81	10.2 ± 0.5		
		0.1–0.5	3	90	3.44	3.07 ± 0.01	37.3 ± 0.3 [e]	1.3 ± 2.6 [g]
$H_3N^+CH_2CO_2H$	2.45	0.1–1.0	4	30	2.18	20.4 ± 0.9		
		0.4–1.0	3	50	2.41	12.7 ± 1.0		
		0.1–1.0	4	70	2.86	7.23 ± 0.58		
		0.1–1.0	4	90	3.53	2.21 ± 0.13	28.7 ± 1.5 [e]	*f*
HCO_2H	3.57	0.096–0.3	3	15	2.97	13.2 ± 0.1		
		0.1–0.28	3	30	3.25	10.1 ± 0.1		
		0.1–0.4	4	50	3.64	5.93 ± 0.03		
		0.1–0.5	4	70	4.01	2.54 ± 0.03	17.2 ± 0.1 [e]	6.83 ± 0.78 [e]
CH_3CO_2H	4.62	0.1–0.5	3	10	3.66	3.89 ± 0.02		
		0.1–0.5	3	30	4.24	1.59 ± 0.06		
		0.1–0.5	3	50	4.61	0.748 ± 0.010		
		0.1–0.5	3	70	5.00	0.328 ± 0.010	5.99 ± 0.37 [e]	31.2 ± 5.2 [e]
$H_2PO_4^-$	6.48	0.2–0.8	4	10	5.57	0.376 ± 0.025		
		0.1–0.7	4	20	5.96	0.237 ± 0.010		
		0.1–0.6	4	30	6.25	0.153 ± 0.002		
		0.1–0.5	4	50	6.63	0.110 ± 0.005		
		0.1–0.4	4	70	7.15	0.044 ± 0.0008	5.98 ± 1.90 [e]	1 020 ± 31 [e]

[a] pK_a Values from ref. 2. [b] Calculated from equation (ii). [c] Calculated from six values of k_{obs}, with $[H^+]$ in the range 0.08–0.01 mol dm^{-3}. [d] $k_{H_2O}/55.5$. [e] Values corrected for ionisation of the substrate. See text. [f] A negative intercept (4.7 ± 1.1) was obtained. [g] Data not included in the Brønsted correlations.

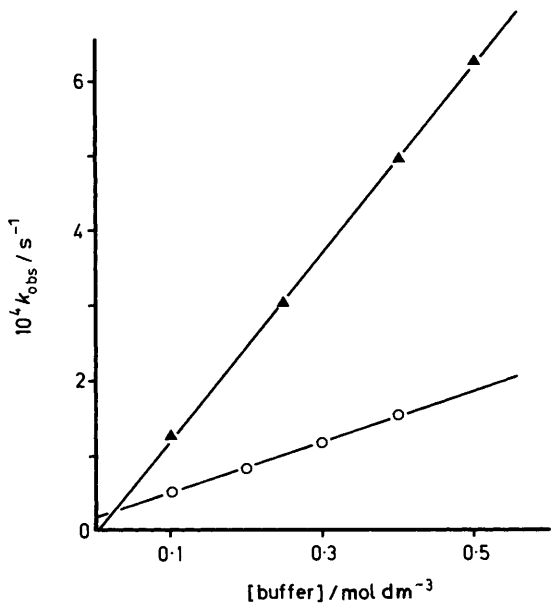


Figure 2. Buffer catalysis of the cyclisation of ester (**4**) in formate (open circles) and phosphate (mono/dianion, closed circles) buffers, both 50% free base

are subject to strong buffer catalysis. For the ester (**4**) this result (see representative data in Figure 2) differs from those of Kavalek *et al.*,[10] who did not detect buffer catalysis of the cyclisation of various *N*-methylhydantoate esters. This could be because the Czech authors were working in an unfavourable pH range. Rate constants k_o were obtained above pH 2 by extrapolation to zero buffer concentration of k_{obs} values, according to equation (i).

$$k_{obs} = k_o + k_{cat}[\text{buffer}]_{tot} \quad \text{(i)}$$

For the KH_2PO_4–K_2HPO_4 buffers listed in Tables 1 and 2, the extrapolations give small negative values of k_o for both (**3**) and (**4**). This may be the result of a specific salt effect of the doubly charged HPO_4^{2-} ion: we observed a 15% increase in the k_{obs} value for cyclisation of (**3**) when 0.27 mol dm^{-3} K_2SO_4 was used to raise the ionic strength of 0.1 mol dm^{-3} phosphate buffer, 50% free base. The data shown in Figure 1 for pH 5.8–7.04 represent values for k_{obs} measured in 0.005 mol dm^{-3} phosphate buffers, corrected for buffer catalysis using rate constants from Table 2.

The pH–rate profile for ring closure of (**3**) (Figure 1) is described by equation (ii), with pK_A 3.93, k_H 0.825 dm^3 mol^{-1} s^{-1}, and k_{H_2O} 1.4 × 10^{-4} s^{-1} [k_H and k_{H_2O} are the rate constants for the hydroxonium and water-catalysed reactions of the neutral form of (**3**), obtained as the slope and intercept of the linear plot of k_O values, corrected for substrate ionisation, against a_H].

$$k_O = \frac{a_H}{K_a + a_H}(k_{H_2O} + k_H a_H) \quad \text{(ii)}$$

The pH–rate profile for the cyclisation of the ester (**4**) (Figure 1) is described by equation (iv) (see text) k_H 2.64 × 10^{-2} dm^3 mol^{-1} s^{-1}, k_{H_2O} 1.06 × 10^{-5} s^{-1}, and k_{OH} 480 dm^3 mol^{-1} s^{-1}. k_H and k_{H_2O} were calculated from k_o values obtained for pH 2–4.2. The second-order rate constant (k_{OH}) for hydroxide ion catalysis was calculated from k_o values for cyclisation in carbonate–hydrogen carbonate buffers. The hydroxide catalysed cyclisation of the ester (**4**) was also studied in TRIS and glycine buffers (pH 8–9.8), but at higher concentrations of the free amines k_{obs}

Table 2. Buffer catalysis data for the cyclisation of ethyl 2,3,5-trimethylhydantoate (**4**) at 25 °C and ionic strength 1.0 mol dm^{-3}

Buffer acid	pK_a	Concn. range/ mol dm^{-3}	Runs	$\%A^-$	pH	$10^4 k_{cat}$ [a]	$10^4 k_{HA}$/dm^3 mol^{-1} s^{-1}	$10^4 k_{A^-}$
H_3O^+	−1.74						264 ± 2 [b]	(1.9 ± 0.2) × 10^{-3} [c]
H_3PO_4	1.78	0.1–0.7	3	10	1.52	55.8 ± 0.5		
		0.1–0.7	3	30	1.72	45.5 ± 1.1		
		0.1–0.7	3	50	1.97	29.1 ± 0.6		
		0.1–0.7	3	70	2.29	19.4 ± 0.2	62.6 ± 2.1	*d*
$NCCH_2CO_2H$	2.38	0.1–0.5	3	50	2.38	6.98 ± 1.20		
		0.1–0.5	3	70	2.74	4.72 ± 0.22		
		0.1–0.5	3	90	3.35	2.16 ± 0.08	13.1 ± 0.3	1.01 ± 0.15
$H_3N^+CH_2CO_2H$	2.45	0.1–1.0	4	30	2.19	7.45 ± 0.06		
		0.4–1.0	4	50	2.42	5.32 ± 0.09		
		0.1–1.0	4	70	2.88	3.98 ± 0.36		
		0.1–1.0	4	90	3.46	1.67 ± 0.05	10.2 ± 0.4	0.869 ± 0.292
HCO_2H	3.57	0.1–0.28	3	30	3.23	3.75 ± 0.12		
		0.1–0.4	4	50	3.62	3.35 ± 0.15		
		0.1–0.5	4	70	4.01	2.72 ± 0.05	4.56 ± 0.17	1.99 ± 0.17
CH_3CO_2H	4.62	0.1–0.5	3	10	3.65	1.78 ± 0.04		
		0.1–0.5	3	30	4.24	2.01 ± 0.01		
		0.1–0.5	3	50	4.64	2.49 ± 0.10		
		0.1–0.5	3	75	5.16	2.76 ± 0.13	1.61 ± 0.09	3.19 ± 0.11
$H_2PO_4^-$	6.48	0.2–0.6	3	10	5.58	6.70 ± 0.35		
		0.1–0.6	3	30	6.24	9.07 ± 0.04		
		0.1–0.4	3	50	6.64	11.7 ± 0.03		
		0.1–0.3	3	70	7.05	14.4 ± 0.1	5.32 ± 0.12	18.2 ± 0.17
HCO_3^-	9.69	0.1–0.8	4	10	8.84	8.95 ± 0.41		
		0.1–0.7	5	20	9.17	30.0 ± 0.1		
		0.1–0.6	4	30	9.40	49.2 ± 3.0	*d*	*e*
H_2O	15.74							4.8 × 10^6 [f]

[a] Calculated from equation (ii). [b] Calculated from six values of k_{obs}, with $[H^+]$ in the range 0.4–0.04 mol dm^{-3}. [c] $k_{H_2O}/55.5$. [d] Intercepts gave small negative values. [e] For carbonate–hydrogen carbonate buffers the increase in k_{obs} over the range of concentration used was not more than 20%. Since this is comparable with the (presumably specific salt) effect of added K_2SO_4, the k_{A^-} value obtained (1.9 × 10^{-3}) cannot be considered meaningful. [f] For calculation of k_{OH} see text.

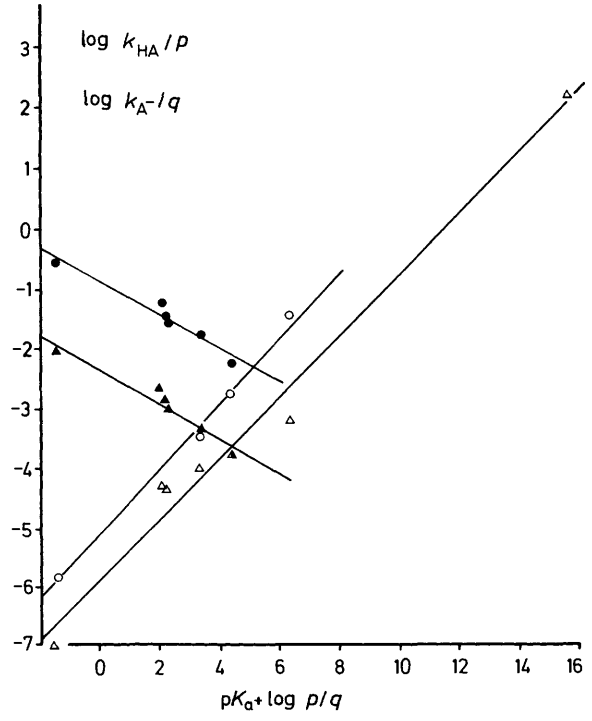


Figure 3. Brønsted plots for general acid (filled symbols) and general base catalysis (open symbols) of the cyclisations of (**3**) and (**4**). Other details as for Figure 1.

values were observed to decrease. A similar medium effect of free amines has been noted previously for the cyclisation of (**1**).[1]

The ring-closure of (**4**) was not investigated further in amine buffers.

Data for buffer catalysis of the ring-closure of the hydantoic acid (**3**) and the ester (**4**) are given in Tables 1 and 2, and those used for the Brønsted correlations plotted in Figure 3. The second-order rate constants for general acid (k_{HA}) and general base catalysis (k_{A^-}) were calculated according to equation (iii), where f_B is the fraction of the buffer free base.

$$k_{cat} = f_B \cdot k_{A^-} + k_{HA}(1 - f_B) \qquad \text{(iii)}$$

In the case of the hydantoic acid (**3**) all second-order rate constants are calculated in terms of the neutral form of the substrate, *i.e.* k_{cat} values are corrected where necessary for the ionisation of (**3**). The statistically corrected data for general acid catalysis give linear Brønsted plots (Figure 3), with identical slopes, $\alpha = 0.27 \pm 0.03$ and 0.29 ± 0.04 for the cyclisation of the hydantoic acid (**3**) and the ester (**4**), respectively.

General base catalysis of the ring closure of the neutral hydantoic acid (**3**) is the minor component of catalysis for all buffers studied, except for phosphate dianion. For more acidic buffers, cyanoacetic acid and glycine, k_{A^-} could not be obtained, and the value for catalysis by $H_2PO_4^-$ measured at lower pH values is three times larger than the value obtained at higher pH (Table 1), and is omitted from the correlation. The four available k_{A^-} values (including that for catalysis by water) give a linear Brønsted plot, with a slope β 0.55 ± 0.03 (Figure 3).

General base catalysis is relatively more important for ring closure of the ester (**4**), and more extensive data were obtained (k_{A^-}, Table 2). Nevertheless, an unambiguous interpretation is not possible. On the one hand, a good line of slope β 0.26 ± 0.01 can be drawn through five points, excluding H_2O and HO^-.

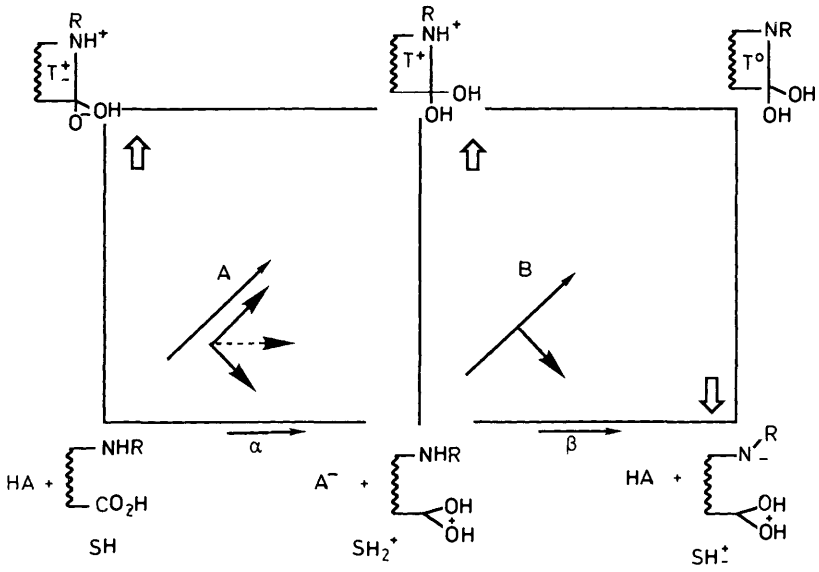


Figure 4. More O'Ferrall–Jencks diagrams (W. P. Jencks, *Chem. Rev.*, 1985, **85**, 511) for the alternative pathways (A and B) of Scheme 1. See text

(Phosphate monoanion shows a marked positive deviation, and was not included.) But this leaves the points for hydroxide and water showing large positive and negative deviations, respectively; this is not in itself unusual, but one then has the problem of explaining why β should be so different from that measured for the same reaction of the acid under the same conditions. If we include the water and hydroxide points the correlation is poorer (r falls from 0.996 to 0.990, see Figure 3), and the slope β increases to 0.51 ± 0.03. This is now identical within experimental error with the slopes measured for the corresponding reactions of the acid (**3**) and the *N*-phenyl compound (**4**), which include k_{H_2O} in both cases. [No hydroxide point is accessible for (**3**). That for (**2**) shows a large positive deviation, identified as a change of mechanism [2] to specific base catalysis for the more acidic *N*-phenyl compound.] That the three Brønsted exponents should be identical is doubtless coincidental. But the similarities are close enough to convince us that the second interpretation is likely to be correct. For these reasons our discussion is based on a β value of 0.5 for the general base-catalysed cyclisation of the neutral form (SH) of (**3**).

A possible complication in the study of reactivity–selectivity relationships involving cyclisation reactions, especially the formation of small rings as in this work, is that polar effects at the nucleophilic centre may affect the reactivity of the electrophilic group (CO_2H, CO_2^-) also. This effect appears not to be large: the pK_a values for the ionisation of the carboxy groups of the *N*-methyl- and *N*-phenyl-hydantoic acids (**2**) and (**3**) differ by only 0.22 units.

Discussion

General Acid-catalysed Ring Closure.—The *N*-methylureido group is more basic, and thus may be expected to act as a more effective nucleophile than the *N*-phenylureido group. This is confirmed by a comparison of the data for the general acid-catalysed ring closure of the *N*-methylureido acid (**3**) (Table 1) with data for the same reaction of the phenylureido acid (**2**).[2] The ratio k_{Me}/k_{Ph} of the corresponding second-order rate constants k_{HA} varies from 6 for catalysis by hydronium ion to 280 for formic acid. This variation reflects the considerable difference in the Brønsted α-values, 0.27 for the cyclisation of (**3**), and 0.60 for the reaction of the *N*-phenyl compound (**2**).

The general acid-catalysed cyclisation of the ester (**4**) is *ca.* 30 times slower than the corresponding reaction of the acid (**3**), most likely because of the increased steric requirements of the OEt *versus* the OH group in the tetrahedral intermediate. The Brønsted plot for cyclisation of the ester has the same slope (0.29)* as that for cyclisation of the neutral acid. As expected, OH and OEt are displaced by the same mechanism, which does not therefore involve the ionisation of the carboxy group of (**3**).

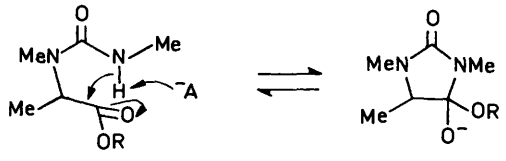
The expected change of transition-state structure for general acid-catalysed ring-closure, when the methylureido-group is replaced by the *N*-phenyl group, can best be visualised by means of More O'Ferrall reaction co-ordinate diagrams. The two alternative pathways A and B of Scheme 1 are represented as a pair of diagrams with a common edge in Figure 4.

The *N*-phenyl group will act predominantly on the stability of SH_2^+ and the *N*-protonated intermediates T^+ and $T^\pm$, and the resulting changes in the position of the transition state should lead to larger values for both α and β in both pathways A and B. A larger value of β corresponds to a smaller value of $\alpha = (1 - \beta)$ for the general acid-catalysed reaction of the *N*-phenylhydantoic acid (**2**), but this is the opposite of what we observe. The larger value (α 0.60) found for the reaction of the phenylureido derivative is consistent with the increase expected for direct general acid catalysis, with formation of T^+ rate determining (pathway A).

This mechanism requires that the reverse reaction (the acid hydrolysis of acyl ureas, or amides with weakly basic leaving groups) involve general base-assisted departure of the protonated leaving group. Presumably the partial positive charge on nitrogen required by pathway B does not by itself provide sufficient driving force for the reaction. We have proposed a similar mechanism (specific base–general acid catalysis) for the general acid-catalysed breakdown of T° in nucleophilic catalysis by neighbouring pyrimidine nitrogen of the hydrolysis of a *p*-nitroanilide.[11]

General Base-catalysed Ring Closure.—Similar Brønsted β values in the region of 0.5, indicating that proton transfer is concerted with heavy-atom bond formation, suggest similar

* This value compares well with Güler and Moodie's figure of 0.47, based on a two-point Brønsted plot, for the cyclisation of *N*-methyl-aminocarbonylglycine.[5]



(3) R = H
(4) R = Et

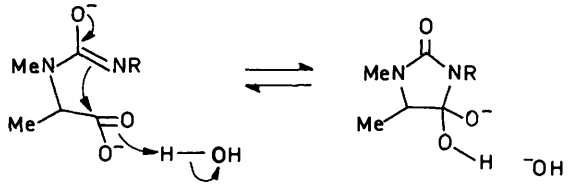
Scheme 3.

mechanisms for the general base-catalysed cyclisations of (2) (SH), (3) (SH), and of ester (4). The rate-determining step for the reaction of the *N*-phenyl compound was considered to be classical general base catalysis of the initial ring formation, and similar mechanisms are presumably involved in the cyclisations of (3) and (4) (Scheme 3).

In our previous paper[2] we suggested that the *N*-phenylureido anion, despite its lower basicity, is in fact a stronger nucleophile towards neighbouring carboxylate than *N*-methylureido anion. We can now compare data for the *N*-phenyl and *N*-methyl derivatives of the same hydantoic acid (Scheme 4), and here find a ratio of k_{-3} values (see Scheme 2), k_{Ph}/k_{Me} of 250. Using the pK_a values available for appropriately substituted ureas, of 18.3 for *N*-methylurea (3) and 16.6 for 3-methyl-5-phenylhydantoic acid,[12] the ratio of reactivities falls to 5. Although the pK_a values used do not correspond exactly to our compounds (2) and (3), this low ratio indicates at least a lack of sensitivity towards ureido-group basicity. The alkaline hydrolysis of hydantoins, by contrast, is highly sensitive to substitution in the ureido group, the k_1k_3/k_{-1} values (Scheme 2) giving a ratio k_{Ph}/k_{Me} of 2×10^4.

Data have recently become available for the hydroxide-catalysed cyclisation of a series of hydantoic acid esters.[10] For four pairs of 5-phenyl- and 5-methylhydantoate esters the ratio k_{Ph}/k_{Me} varied between 130 and 3 000 for cyclisation in water, and between 20 and 350 for reaction in methanol. These results weaken our previous explanation[2] of the greater nucleophilicity of the *N*-phenylureido anion towards the carboxylate group in terms of a reduced electrostatic barrier. However, the comparison (k_{OH} for *N*-phenyl *versus* *N*-methylureido ester cyclisation) is not a simple one. The reaction of the *N*-phenyl compounds is presumably specific-base catalysed,[2] whereas, insofar as the Brønsted line drawn (Figure 4) for the reaction of (4) is valid, the cyclisation of the *N*-methyl compounds appears to be general-base catalysed. [Consistent with this interpretation, a log–log plot of the second-order rate constants for general base catalysis of the cyclisations of neutral acid (2) and ester (4) is a good straight line, save for a positive deviation, of several orders of magnitude, for k_{OH} for the *N*-phenyl ester.] In any case, the greater nucleophilicity of the *N*-phenylureido group in water seems well established. The smaller ratios observed in methanol (in a few cases *N*-methyl esters actually cyclise more rapidly in MeOH[10]) suggest that differential solvation, specifically, tighter solvation of the *N*-methylureido anion in water, may be involved.

Stereoelectronic Factors.—The mechanisms proposed for the general acid and general base catalysed cyclisations of hydantoic acids and esters (path A of Scheme 1, and Scheme 3, respectively) both present significant stereoelectronic difficulties. The common fundamental problem is the timing of the deprotonation step, discussed briefly above. Both mechanisms involve sp^2 hybridised NH acting as a nucleophile, with deprotonation either concerted with C–N bond formation (Scheme 3), or a separate, subsequent step (Scheme 1A). In principle, solvent water could be involved in the latter mechanism as a general base, with deprotonation concerted



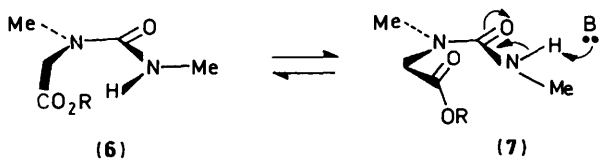
Scheme 4.

with heavy-atom bond formation here also, but this would involve an entropically unfavourable termolecular process.

Deprotonation of the urea cannot itself be a separate, rate-determining step: this would require reprotonation of the ureido anion, a base of $pK_a > 18$, to be slower than the nucleophilic addition of N^- to $CO_2H(Et)$. This latter reaction is certainly rapid: the data of Sterba and co-workers[10] allow us to estimate an upper limit of *ca.* 10^7 s^{-1} at 25 °C. But protonation of the ureido anion should proceed at the diffusion-controlled rate,[13] at least 100 times faster. Mechanisms involving the iminol tautomer of the urea can also be ruled out with some confidence. If the pK_a of the RN=C(OH)NHR form is in the region of 9, slightly more acidic than an enol, then the equilibrium constant for formation of the iminol form can be estimated, using the figure of 18.3 quoted above for the pK_a of the keto form, to be in the region of 10^{-10}. This is of the same order of magnitude as an estimate of $10^{-11.3}$ made by Finkel'shtein and Monclarzch[14] for urea itself. The observed rate constant for hydantoic acid formation from (3) in 1 mol dm^{-3} acid, *ca.* 1 s^{-1}, would then require a true rate constant for the reaction of the iminol tautomer in the region of 10^{10} s^{-1}, faster than all but the fastest proton-transfer processes.

If urea nitrogen does act as a nucleophile while the proton is still, if only partially, attached, it must do so through its π-delocalised lone pair. (It does not seem reasonable, on either orbital energy or stereoelectronic grounds, for the N–H σ-bonding orbital to act as the nucleophile towards such a weak electrophile as carboxylic acid or ester C=O). Challis *et al.*[15] have calculated charge distributions and atomic electron densities for the amide group, and find π and n_o orbitals close to degenerate, with π-electron density actually greater on nitrogen than oxygen. A urea is expected to be relatively more reactive at nitrogen, and cases are known where even a tertiary amide nitrogen appears to act as a nucleophile.[16,17]

In fact the geometry of the hydantoic acid cyclisation is such that this 'limiting' reactivity is unlikely to be involved. In the ground state conformation (6) only C(1) can be out of the plane defined by the urea group, and bond formation between C(1) and N(5) is clearly impossible. If C(1) and N(5) are to form a bond, there must be rotations about C(2)–N(3) *and* one of the urea C–N bonds. It is clearly more effective if this is C–N(5), thus (6) ⇌ (7), because this interrupts π-conjugation, and makes available a more or less localised lone pair on the nitrogen which must act as a nucleophile.



(6) (7)

It seems likely that both mechanisms (*i.e.* those in Schemes 1A and 3) involve this conformation (7). The general base in Scheme 3, shown also in (7), restores some of the lost delocalisation in the transition state for addition to CO_2R. The partially protonated CO_2R group (Scheme 1A) is more electrophilic, and can react without further assistance.

These mechanisms will be more favourable for ureas than for

amides, because N–C=O conjugation is retained across one C–N bond. (The barrier to rotation is correspondingly reduced, to 11–13 ± 4 kcal mol^{-1} in ureas,[18] too small to be kinetically significant in our reactions.) They are clearly not directly relevant to the mechanism of action of biotin, because the fused five-membered ring structure of the urea system of the coenzyme precludes significant rotation about the relevant C–N bond. Thus the coenzyme is forced to adopt a 'specific iminolate' strategy,[19] with deprotonation a separate, preliminary step.

Acknowledgements

We are grateful to the Bulgarian Academy of Sciences, and the Royal Society, London, for travel funds.

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Received 24*th May* 1988; *Paper* 8/02080I