Intramolecular Nucleophilic Attack on Carboxylate by Ureide Anion. General Acid–Base Catalysis of the Alkaline Cyclisation of 2,2,3,5-Tetramethylhydantoic Acid †

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The cyclisation of the title compound to the corresponding hydantoin is a model for the carboxylation of biotin by hydrogen carbonate. The reaction is rapid over the whole pH range, and is catalysed by both general acids and general bases. Above pH 9.2 the reaction is first order in hydroxide, which is shown to act as a general base. The preferred mechanism is specific base–general acid catalysis, involving nucleophilic attack by the ureide anion on the ionised carboxy group, assisted by proton transfer from the general acid. This defines also the mechanism of the reverse reaction, and clarifies for the first time the role of the second hydroxide ion in the $[HO^-]^2$ term for the hydrolysis of amides with good leaving groups.

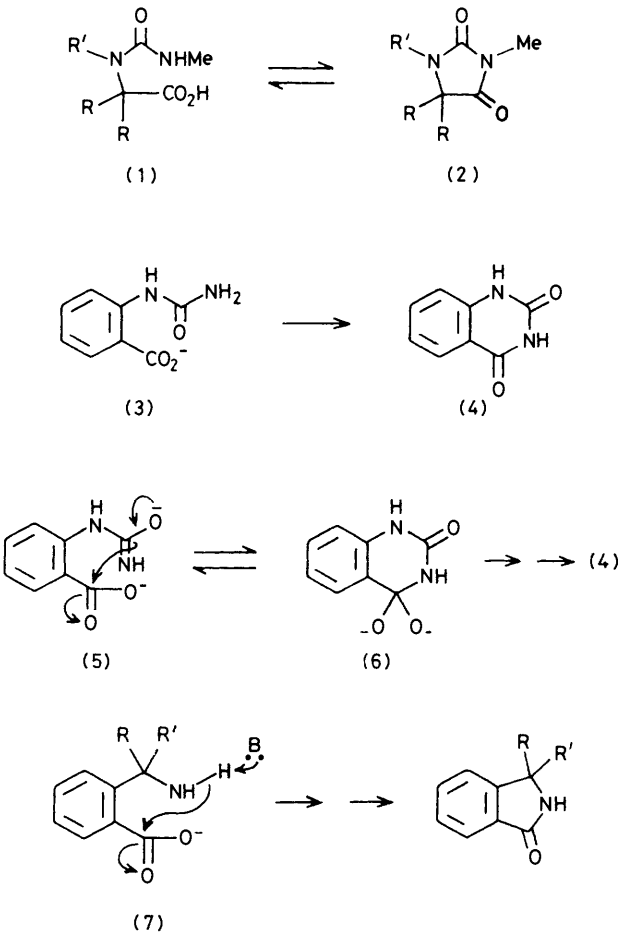
Several groups have studied the acid-catalysed cyclisation of hydantoic acids to hydantoins,[1] and of β-ureidopropionic acids to dihydrouracils,[2] reactions which involve intramolecular nucleophilic attack by urea nitrogen on the carboxylic acid group. These reactions have generally been considered to be specific acid catalysed, and Stella and Higuchi [1] actually looked, unsuccessfully, for evidence of general acid catalysis by acetic acid (at pH 1; not ideal conditions for the test). But recently Güler and Moodie [3] observed catalysis by methoxyacetic acid of the cyclisation of *N*-(methylcarbamoyl)glycine (1; R = R′ = H) to the hydantoin (2).

We have studied the much faster cyclisation of 2,2,3,5-tetramethylhydantoic acid (1; R = R′ = Me). As a result of the more favourable equilibrium constant for cyclisation (a manifestation of the Thorpe–Ingold, or *gem*-dialkyl effect[4]) the forward reaction is observed over the whole pH range, and we find it is subject to both general acid *and* general base catalysis.

This paper deals with the unusual reaction in base, where the starting material is present as the carboxylate anion. An apparent precedent is the cyclisation of 2-ureidobenzoate (3) studied by Hegarty and Bruice.[5] The formation of (4) was found to be catalysed by hydroxide ion, and the authors [5] suggested a mechanism (5) involving rate-determining attack on the carboxylate group by the ureide anion. If this mechanism is correct, it represents a unique example of nucleophilic attack on the carboxylate group by an anion. [Though we recently observed the general base catalysed lactamisation of (7; R,R′ = Me,Me or Me,H), which appears to involve attack on carboxylate by the developing amide anion.[6]]

The carboxylation of biotin by hydrogen carbonate also involves the reaction of a urea nitrogen with a carboxylate group, though an important additional factor may be the phosphorylation of the leaving group oxygen.[7] In the model (3) studied by Hegarty and Bruice, oxygen is displaced nominally as O^{2-}, though in practice assistance from general acid catalysis might be expected. General species catalysis of the cyclisation of (3) cannot be detected, possibly because the reaction is so slow below pH 11 (k_{OH} 5.6×10^{-4} dm^3 mol^{-1} s^{-1} at 30 °C [5]). The cyclisation of (1; R = R′ = Me) is some 10^3 times faster (k_{OH} 0.12 dm^3 mol^{-1} s^{-1} at 25 °C), and allows us to study the details of this intriguing reaction for the first time.

The results are also of interest for the light they may shed on the reverse reaction. The hydrolysis of acyl ureas, like that of many amides and related compounds with poor leaving groups attached to C=O, shows an important $[HO^-]^2$ term, which is generally taken as evidence for dianion intermediates such as (6).[8]



Experimental

Materials.—Inorganic reagents and tris(hydroxymethyl)-methylamine (Tris) were of analytical grade and used without further purification. β-Alanine and methylamine hydrochloride

† 2-(1,3-Dimethylureido)-2-methylpropionic acid.

were recrystallized twice before use. 2-Aminoethanol and propylamine were purified by distillation and subsequent recrystallization of their hydrochlorides. Potassium hydroxide and buffer solutions were prepared with CO_2-free distilled water. Deuterium oxide (99.9 atom % D) was purchased from Fluka.

Potassium 2,2,3,5-Tetramethylhydantoate (TMHA).—A solution of 2-methyl-2-(methylamino)propionic acid (0.117 g, 1 mmol) in an equivalent amount of aqueous potassium hydroxide was evaporated to dryness and the residue dissolved in 95% ethanol (2 ml). The solution was then cooled at 0 °C, and MeNCO (70 μl) was added. The reaction mixture was kept for 5 min at 0 °C then for 5—7 min at room temperature.

If at this stage acetone was added to the reaction mixture, a precipitate was formed. The potassium salt of TMHA isolated in this way can be stored in a vacuum desiccator over P_2O_5. It is very hygroscopic and if left for a short time in contact with air forms 1,3,5,5-tetramethylhydantoin. Satisfactory elemental analytical results could not be obtained.

Stock solutions of the substrate were prepared by adding 0.1M-Tris buffer [18 ml; pH 8.8; *I* 1.0 M (KCl)] to the reaction mixture (2 ml) prepared as just described. The stock solutions are best kept frozen.

Product Analysis: 1,3,5,5-Tetramethylhydantoin.—In order to identify the reaction products in acid and basic media, the potassium salt of TMHA was allowed to cyclise in water (A) or hydrochloric acid (B) immediately after its preparation.

Procedure A. An ethanolic solution (20 ml) containing the potassium salt of TMHA (10 mmol) was evaporated to dryness and water (15 ml) was added. After 15 min the potassium hydroxide released was neutralised with Dowex-50W resin (H^+). Crude tetramethylhydantoin (1.4 g, 90% yield) was obtained after evaporation of the filtrate.

Procedure B. A solution (20 ml) as used in procedure A was treated with hydrochloric acid (20 mmol) and evaporated to dryness. The residue was extracted by boiling with dry ethyl acetate (3 × 30 ml). Crude tetramethylhydantoin (1.5 g, 96% yield) was obtained after evaporation.

The products from procedures A and B were identical (i.r. spectra and mixed m.p.). After two recrystallizations from light petroleum, the pure 1,3,5,5-tetramethylhydantoin melted at 104—104.5 °C (lit.,[9] 105—106 °C).

1,3-Dimethylhydantoin was prepared by boiling for 15 min in 2M-HCl the product obtained from the potassium salt of sarcosine and MeNCO; m.p. 43—44 °C (from ether) (lit.,[10] 44—45 °C).

2-(3-Methylureido)benzoic acid was prepared from the potassium salt of anthranilic acid and MeNCO; m.p. 187—188 °C (from acetone) (lit.,[11] 187—189 °C).

Kinetic Measurements.—Rate constants were determined under pseudo-first-order conditions by use of tightly stoppered 1 cm cuvettes and a Unicam SP 800 spectrophotometer with a thermostatted cell holder.

The rate of the base-catalysed cyclisation of the potassium salt of TMHA was followed by monitoring the increase in absorbance at 240 nm after the addition of a 5×10^{-2}M-Tris-buffered solution (70—80 μl) of the substrate to thermostatted buffer solution (2.8 ml). Pseudo-first-order rate constants, k_{obs}, were calculated from plots against time of log $(A_\infty - A_t)$, where A_∞ is the final absorbance of the reaction mixture. For the slower reactions A_∞ was determined from parallel runs in 0.1M-hydrochloric acid. The ionic strength was maintained constant (1.0M) with potassium chloride. pH Values were measured directly after each kinetic run, using a Radiometer 26 pH meter with GK2301B electrode, standardized at pH 6.5 and 9.18 (25 °C). The observed rate constants were corrected for the small variations in pH with changing buffer concentrations. (The pD values of deuterium oxide solutions were obtained by adding 0.40 to the observed pH-meter readings.)[12] 2-Aminoethanol hydrochloride was not exchanged prior to use for the kinetic measurements in D_2O. For these experiments, the Tris-buffered stock solution of the substrate was prepared in D_2O.

Inhibition by free amines was determined in KOH solutions with ionic strength 1.0M (KCl) and amine concentrations varying from 0.1 to 1.0 mol dm^{-3}. The rate constants were corrected for the variations in pH.

The rate of hydrolysis of 1,3-dimethylhydantoin was followed at 240 nm after the addition of an aqueous 0.1M-solution of the substrate (40 μl) to potassium hydroxide solution [2.8 ml; *I* 1.0M (KCl)].

The rate of cyclisation of 2-(3-methylureido)benzoic acid was followed by monitoring the decrease in absorbance at 300 nm after the addition of a 1×10^{-2}M-solution of the substrate (80μl) in dioxane to 0.24M-potassium hydroxide solution [2.8 ml; *I* 1.0M (KCl)]. The propylamine concentrations were in the range 0.1—1.0 mol dm^{-3}.

Rate constants and derived rate constants were calculated by the least squares procedure. Rate constants were reproducible to within ±5%. Detailed kinetic data are available as Supplementary Publication no. SUP 23848 (20 pp.).*

Results

2,2,3,5-Tetramethylhydantoic acid could not be isolated, as it rapidly cyclises to the corresponding hydantoin ($t_{\frac{1}{2}}$ 78 s in water at 25 °C and pH 4.4). The potassium salt of TMHA also cyclised rapidly in water, the reaction being autocatalysed by the potassium hydroxide released. If the preparation of the potassium salt of TMHA was carried out in ethanol, as described in the Experimental section, a quantitative yield was obtained, as judged by u.v. estimation of the product 1,3,5,5-tetramethylhydantoin after cyclisation in both acid and alkali. The same results were obtained in preparative scale experiments. The potassium salt of TMHA could be isolated by precipitation with acetone, but is very hygroscopic and difficult to store. For this reason stock solutions of the substrate were prepared in Tris-buffers at a pH close to the minimum in the pH–rate profile for cyclisation (Figure 1) and stored frozen.

The pH–rate profile for cyclisation of TMHA, shown in Figure 1, was obtained in the region above pH 11.5 by measuring the rates in potassium hydroxide solutions. At lower pH the data represent extrapolations to zero buffer concentration [equation (i)]. The pH–rate profile can be satisfactorily

$$k_{obs} = k_0 + k_2[\text{buffer}_{tot}] \quad \text{(i)}$$

represented by a combination of two lines with slopes −1 and +1, corresponding to a formal rate equation (ii). The good fit of the experimental points to the theoretical curve, calculated

$$k_0 = k_{H^+}[H^+] + k_{OH^-}[OH^-] \quad \text{(ii)}$$

from equation (ii), indicates the absence of a significant pH-independent reaction.

When the data for k_2, calculated from equation (i) for the amine buffers in Table 1, are plotted against the fraction of free base, a non-linear decrease is observed at higher fractions of base (see Figure 2).

* For details of Supplementary Publications see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, 1984, Issue 1.

Table 1. Kinetic data for the buffer-catalysed cyclisation of 2,2,3,5-tetramethylhydantoic acid at 25 °C and ionic strength 1.0M

Buffer	Concn. range (mol dm^{-3})	No. of runs	pH	Fraction base	$10^6 k_2$ [a]	$10^6 k_2'$ [b] (dm^3 mol^{-1} s^{-1})
Tris	0.1—1.0	4	8.30	0.50	13.2	*c*
	0.1—1.0	4	8.79	0.75	8.20	*c*
	0.05—1.0	4	9.23	0.90	4.21	4.85
2-Aminoethanol	0.1—1.0	4	9.36	0.25	6.15	6.78
	0.1—1.0	4	9.76	0.50	9.00	11.3
	0.1—1.0	4	9.90	0.60	8.53	12.0
	0.1—1.0	4	10.22	0.75	9.40	16.4
	0.1—1.0	4	10.66	0.90	2.83	19.9
2-Aminoethanol in D_2O	0.1—1.0	4	9.93 [d]	0.25	3.17	3.33
	0.1—1.0	4	10.47 [d]	0.50	4.14	4.76
	0.1—1.0	4	10.97 [d]	0.75	6.27	8.07
Methylamine	0.1—1.0	4	10.58	0.25		54.4
	0.1—1.0	4	10.81	0.35		72.1
	0.1—1.0	4	11.06	0.50		92.0
	0.1—1.0	4	11.49	0.75		163
β-Alanine	0.1—0.7	4	10.03	0.37		9.20
	0.1—0.7	4	10.25	0.53		12.0
	0.1—0.6	4	10.55	0.63		15.2
Carbonate	0.12—0.6	4	9.21	0.25	69.9	
	0.1—0.5	4	9.64	0.46	51.8	
	0.1—0.4	4	10.02	0.69	36.3	
Phosphate	0.1—0.24	3	10.37	0.10	53.6	
	0.1—0.25	4	10.96	0.30	158	
2,2,2-Trifluoroethanol	0.1—1.0	4	12.08	0.5	−370 [e]	

[a] Data calculated according to equation (i). [b] Data calculated according to equation (i) with k_{obs} values corrected by means of equation (v). Thus $k_{corr} = k_0' + k_2'[\text{buffer}_{tot}]$. [c] k_{obs} was not corrected at the lowest pH values. [d] pD Values. [e] $k_1/k_0 = -0.27$.

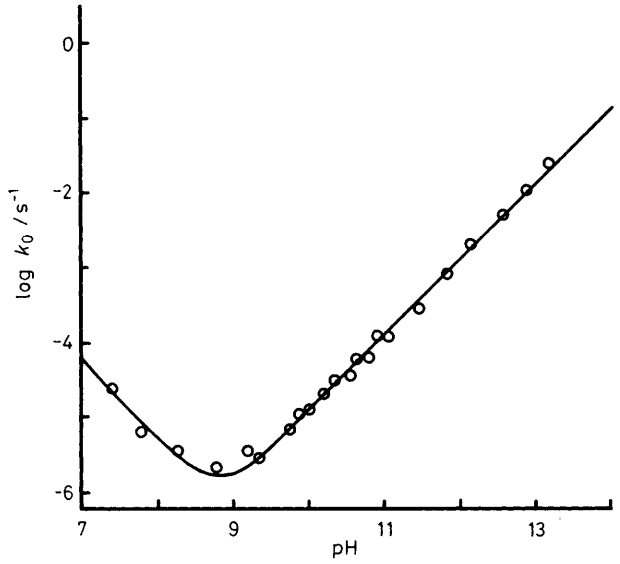


Figure 1. pH–Rate profile for the cyclisation of TMHA (1; R = R′ = Me), at 25 °C and ionic strength 1.0M (KCl); the points are experimental, and represent extrapolations to zero buffer concentration where appropriate; the curve is calculated, from the equation $k_{obs} = 540a_H + 0.118a_{OH}$

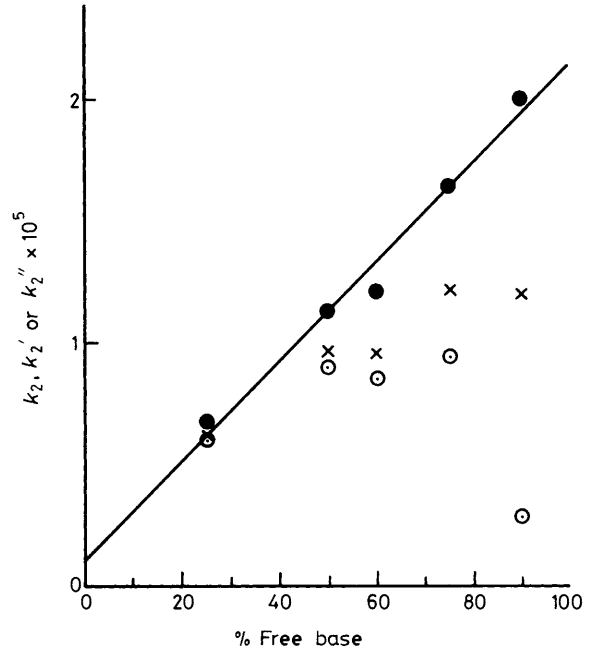


Figure 2. Catalysis of the cyclisation of TMHA by 2-aminoethanol buffers, as a function of the buffer ratio; the three sets of five points refer to the same set of data: ○, experimentally observed values of k_2; ×, values of (k_2'') corrected according to equation (iv) (see text); ●, values (of k_2') corrected according to equation (v)

With trifluoroethanol buffer (50% base) only inhibition is observed, and cyclisation is also inhibited by added dioxane ($k_1/k_0 = -0.36$). We therefore assumed that this curvature is due to a medium effect of the amine bases. By studying the effect of free amines on the rates of the faster potassium hydroxide-catalysed cyclisation we demonstrated that the k_{obs} values decrease with increasing amine concentration according to equation (iii). The inhibition constants k_i depend

$$k_{obs} = k_0 + k_i[\text{amine}] \quad \text{(iii)}$$

on [OH$^-$], and the data shown in Table 2 are mean values from 2—3 determinations at different hydroxide concentrations.

Table 2. Inhibition by amines of the hydroxide-catalysed cyclisation of 2,2,3,5-tetramethylhydantoic acid at 25 °C and ionic strength 1.0M

Amine	$-10^2k_1/a_{OH^-}$ [a,b] / s^{-1}	$-k_1/k_0$ [a,b] / $dm^3\ mol^{-1}$
Tris	0.80	0.082
2-Aminoethanol	2.2	0.24
2-Aminoethanol (in D_2O)	1.4	0.11
β-Alanine	4.2	0.30
Methylamine	3.0	0.27
Propylamine	3.4	0.35

[a] k_1 determined according to equation (iii) with 3—4 amine concentrations in the concentration range 0.1—1.0 mol dm^{-3}. [b] Mean values from 2—3 determinations of k_1 at different hydroxide concentrations.

Inhibition by free amines has been observed previously, for the hydroxide-catalysed cleavage of 1-phenylcyclopropanol.[13]

We applied the two alternative corrections for k_{obs} proposed by Thibblin and Jencks [13] to the data from Table 2. Equation (iv) is based on the assumption that only the k_0 term is inhibited (a'_{OH^-} corresponds to the pH value at which

$$k_{corr} = k_{obs} - (k_1/a_{OH^-})a'_{OH^-}[\text{amine}] \quad \text{(iv)}$$

$$k_{corr} = k_{obs}/(1 + k_1[\text{amine}]/k_0) \quad \text{(v)}$$

k_{obs} is measured); equation (v) is based on the assumption that both k_0 and k_2 terms are inhibited to the same extent, as a result of a medium effect on the ionisation of the substrate.

The results obtained, with k_{obs} corrected according to both equations (iv) and (v), are shown in Figure 2 for catalysis by 2-aminoethanol, which was studied in most detail. The best line is obtained using equation (v), which corresponds also to our preferred reaction mechanism (see Discussion). For this reason all values of k_2 were calculated with data corrected according to equation (v). These values (final column of Table 2) were used for the calculation of the catalytic constants k_B and k_{BH^+}. As can be seen from Table 3, the k_B values are much greater than the k_{BH^+} values, with the exception of Tris and carbonate buffers. The data for Tris catalysis correspond to the low pH region where acid catalysis dominates, and the k_{BH^+} term can probably be attributed to reaction of the neutral form of the substrate.

The solvent isotope effects, k_{H_2O}/k_{D_2O}, for cyclisation of TMHA, calculated from the data from Table 3, are 1.01 ± 0.04 for the hydroxide-catalysed reaction and 2.1 ± 0.2 for the reaction catalysed by 2-aminoethanol.

The k_B values for general catalysis of the cyclisation of TMHA give a linear Brønsted plot (Figure 3) with slope 0.64 ± 0.04 (Figure 3).

We also measured the rate of hydrolysis of 1,3-dimethylhydantoin (2; R′ = Me, R = H) at 25 °C and ionic strength 1.0M (KCl), at five different concentrations of KOH in the range 0.16—0.63 mol dm^{-3}. The reaction is clearly second order in [HO^-] (a plot of log k_{obs} *vs.* log [KOH] gave a good straight line of slope 2.05 ± 0.07). The third-order rate constant, k_1k_3/k_{-1}, calculated from equation (vi) was 0.286 ± 0.040 $dm^6\ mol^{-2}\ s^{-1}$.

$$k_{obs} = k_1(k_3/k_{-1})[HO^-]^2 \quad \text{(vi)}$$

The hydrolysis of 1,3-dimethylhydantoin in 0.24M-KOH is inhibited by n-propylamine, with $k_1/k_0 = 0.65$, and by 2,2,2-trifluoroethanol buffer (50% base) with k_1/k_0 −0.46.

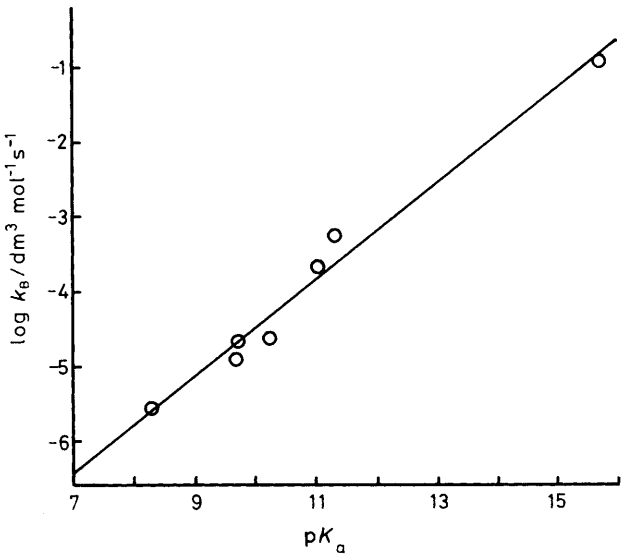
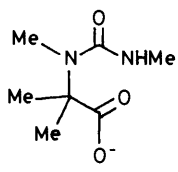
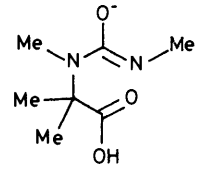


Figure 3. Brønsted plot for general base catalysis of the cyclisation of TMHA; the (least squares) line drawn has a slope of 0.64



(1a)



(1b)

The same strong inhibition by n-propylamine in 0.24M-KOH [I = 1.0 (KCl)] at 25 °C, $k_1/k_0 = -0.73$, is observed for the cyclisation of 2-(3-methylureido)benzoic acid.

Discussion

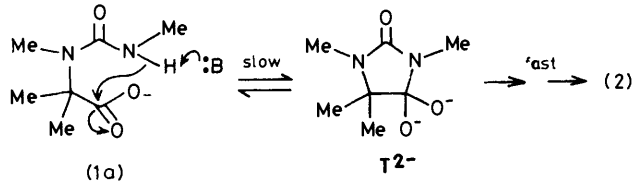
Above pH 9.2 the cyclisation of TMHA (1; R = R′ = Me) is first order in hydroxide concentration, and so represents the base-catalysed reaction of the carboxylate anion (1a). The alternative route *via* (1b) can readily be excluded. Assuming reasonable pK_a values for the carboxy and urea groups of (1a) (values of 4.46 and 18.3 have been measured for 2,2-dimethylhydantoic acid [14] and *N*-methylurea,[15] respectively) gives an equilibrium constant [(1b)]/[(1a)] of *ca.* 10^{-14}. Thus rate constants above the diffusion limit would be required to account for the observed rates of reaction. Furthermore, hydroxide appears to be acting mechanistically in the same way as general bases, since the point for catalysis by hydroxide falls on the Brønsted plot defined by the rate constants for other bases. And the Brønsted coefficient, β, of 0.64, is consistent with proton transfer in the rate-determining transition state, concerted with the making or breaking of bonds between heavy atom centres.

We consider two possible mechanisms (Schemes 1 and 2) for the cyclisation of (1a). Both involve rate-determining attack of urea nitrogen on the carboxylate group: all the evidence from hydrolysis studies of acyl ureas and anilides (see later) is consistent with breakdown of tetrahedral intermediates (C–N cleavage) being rate-determining in the reverse ([HO^-]^2) reaction: therefore the (presumed fast) steps involved in the breakdown of T^- or T^{2-} to hydantoin (2) are not specified.

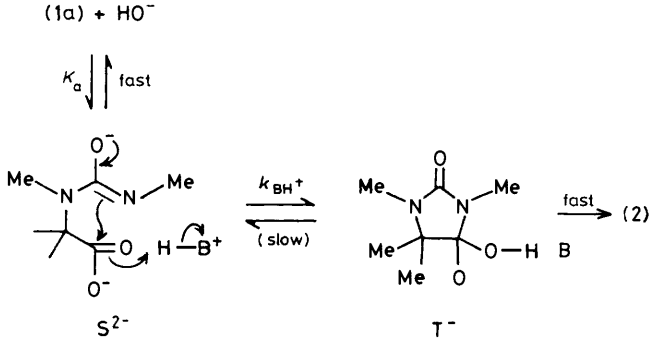
Table 3. Derived rate constants for the general base and general acid-catalysed cyclisation of 2,2,3,5-tetramethylhydantoic acid at 25 °C and ionic strength 1.0M

Catalyst	[pK_a [a]]	k_B [b]	k_{BH^+} [c]
		[(dm^3 mol^{-1} s^{-1})]	
Tris	8.30	(2.86 ± 0.14) × 10^{-6}	(23.6 ± 0.3) × 10^{-6}
2-Aminoethanol	9.75	(2.13 ± 0.07) × 10^{-5}	(0.121 ± 0.098) × 10^{-5}
2-Aminoethanol (in D_2O)	10.47	(1.01 ± 0.08) × 10^{-5}	(0.067 ± 0.076) × 10^{-5}
β-Alanine	10.26	(2.32 ± 0.14) × 10^{-5}	(0.062 ± 0.14) × 10^{-5}
Methylamine	11.06	(2.13 ± 0.12) × 10^{-4}	*d*
Carbonate	9.69	(1.20 ± 0.21) × 10^{-5}	(8.82 ± 0.19) × 10^{-5}
Phosphate	11.33	5.32 × 10^{-4}	
HO^-	15.75	0.118 ± 0.003 [e]	
DO^-		0.117 ± 0.002 [f]	

[a] From pH measurements at fraction base 0.50. [b] Intercept of plot of k_2' values against fraction acid. [c] Intercept of plot of k_2' values against fraction base. [d] A negative value of 0.05 × 10^{-4}. [e] Calculated from four k_{obs} values with [OH^-] in the range 0.030—0.31 mol dm^{-3}. [f] Calculated from four k_{obs} values with [OD^-] in the range 0.023—0.24 mol dm^{-3}.



Scheme 1.



Scheme 2.

The simpler mechanism (Scheme 1) involves general base catalysis of the formation of T^{2-}, as suggested for the lactamisation of (7).[6] The solvent deuterium isotope effect, k_{H_2O}/k_{D_2O} 2.1, is consistent with this mechanism for catalysis by 2-aminoethanol, but not for the hydroxide-catalysed reaction (k_{OH}/k_{OD} 1.01). [There is a clear difference here between the hydroxide-catalysed cyclisations of (1a) and (7), for which k_{OH}/k_{OD} = 2.44.[6] This is mechanistically reasonable in the light of Jencks' criteria [16] for concerted reactions, since the removal of the urea proton from (1a) (pK_a *ca.* 18) by hydroxide is thermodynamically not very unfavourable, whereas the formation of the amide anion from a primary amine (7) certainly is.]

Our preferred mechanism is the kinetically equivalent specific base–general acid-catalysed addition of the ureide anion to the carboxylate group (Scheme 2). The observed solvent deuterium isotope effects can then result from the complete or partial cancelling of the positive isotope effect on the rate-determining step and the inverse effect on the pre-equilibrium [equations (vii)]. The solvent deuterium isotope

$$v_{obs} = k_{H_2O}[S^{2-}][H_2O] + k_{BH^+}[S^{2-}][BH^+] \therefore k_{obs} = k_{H_2O}(K_a/K_w)[OH^-] + k_{BH^+}(K_a/K_{BH^+})[B] \quad \text{(vii)}$$

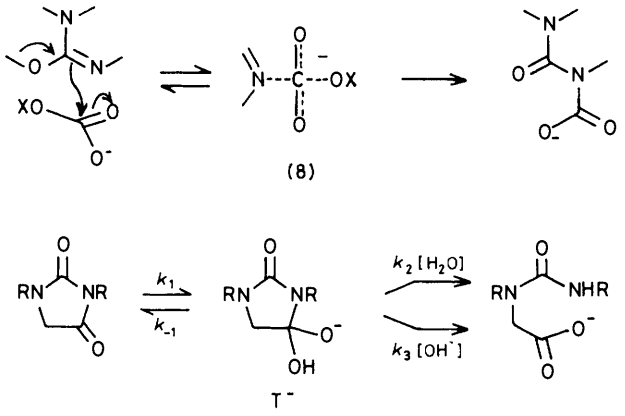
effect on K_w is 6.5, whereas values for the ionisation of most other OH and NH acids fall in the range 3—4.[17] Thus the expected kinetic solvent isotope effect of 2—3 on k_{H_2O} may be almost equal to the inverse effect on K_a/K_w, accounting for the absence of an observed effect on the hydroxide-catalysed reaction. The inverse effect on K_a/K_{BH^+}, on the other hand, is expected to be much smaller, so that the kinetic isotope effect dominates in the amine-catalysed reaction.

Presumably the ureide anion is not a strong enough nucleophile (too good a leaving group) to add to carboxylate directly to give T^{2-}. This is apparently not a problem for the amide anion derived from (7), though in that case electrostatic repulsion must make the anion–anion reaction unfavourable. In both reactions the initial approach of the nucleophile to CO_2^- can involve almost neutral nitrogen, with only the minimum amount of negative charge developing, as a result of electronic reorganisation in the case of (8), and of general base catalysis in the case of (7), before the transition state.

General acid catalysis of the cyclisation of the anion of (1a), by water in the case of the hydroxide-catalysed reaction, avoids the formation of the unstable species T^{2-} (Scheme 1). Almost identical considerations apply to the base-catalysed cyclisation of 2-ureidobenzoate (3) studied by Hegarty and Bruice,[5] so the mechanism of Scheme 2 may well hold for this reaction also,* as it probably does too for the recently observed cyclisation of the corresponding thiourea,[18] and for a number of similar reactions in which hydantoins are formed by the base-catalysed rearrangement of 1-alkyldihydro-orotic acids,[19] or orotic acids are formed from the rearrangement of 5-carboxymethylenehydantoins.[20]

It is a reasonable presumption that the urea nitrogen of biotin [7] is also deprotonated before carboxylation, and to that extent the cyclisation of S^{2-} is a valid model for the carboxylation of the coenzyme. It is a stronger presumption that high energy species like T^{2-} are avoided in the biological reaction; but this could be accomplished more efficiently than by the general acid catalysis mechanism of Scheme 2 if one of the hydrogen carbonate oxygens were already converted, for

* We could not detect buffer catalysis of the cyclisation of 2-(3-methylureido)benzoic acid, which becomes very slow below pH 11. The reaction in 0.24M-KOH is strongly *inhibited* by n-propylamine, as is that of (1a).



Scheme 3.

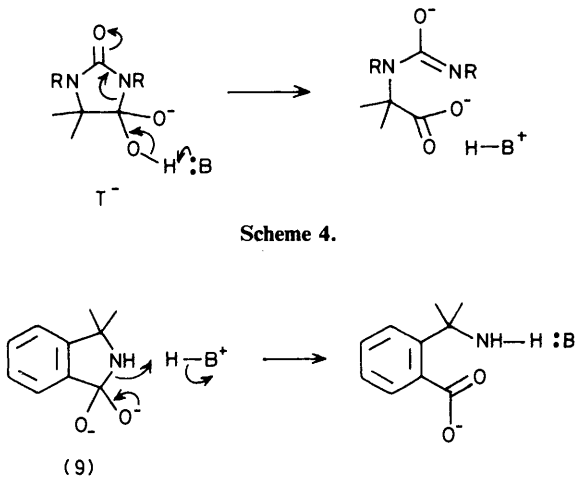
example by phosphorylation, into a good leaving group. Transfer of CO_2 could proceed smoothly by way of the sort of ' borderline S_N1–S_N2 ' transition state (8) apparently favoured for many phosphorylation reactions involving the transfer of the PO_3^- group.[21]

Implications for the Reverse Reaction.—It should be emphasised that the ready cyclisation of (1a) in base is unusual, and observed only because of the steric strain associated with the introduction of the three methyl groups at positions 2 and 3 of the hydantoic acid (1). Normally hydantoins, particularly *N*-alkyl derivatives, which cannot dissociate to unreactive anions, are hydrolysed rapidly in aqueous alkali [*cf.* the data for the hydrolysis of 1,3-dimethylhydantoin (2; R = H) already given].

Previous results for the alkaline hydrolysis of hydantoins,[22] and other acylureas,[8,23] have been interpreted in terms of Scheme 3, similar to that proposed for the hydrolysis of amides, with rate-determining breakdown of the tetrahedral intermediate catalysed by both water and hydroxide. The change to rate-determining addition of HO^- which is usually observed at high hydroxide concentrations is evidence for a kinetically significant tetrahedral intermediate (T^-), though the role of the second hydroxide ion (k_3 term) has never been clearly defined.

Buffer catalysis of these reactions has not been studied in any detail.[8,23] There is some evidence for general base catalysis of the hydroxide-catalysed reaction in a few cases, for the closely related hydrolysis of anilides.[24,25] But where buffer catalysis is firmly established, for reactions of acyl-activated compounds at low pH, it is primarily general acid catalysis, and the general base component is generally in the region of experimental error. We were unable to detect general base catalysis of the hydrolysis of 1,3-dimethylhydantoin in 0.24M-KOH because the reaction is *inhibited* by both trifluoroethanol and n-propylamine buffers.

Our results for the cyclisation of (1a) establish the mechanism of the reverse reaction clearly and unambiguously, as the general base-catalysed breakdown of the tetrahedral intermediate (T^-) (Scheme 4). General base catalysis is not normally observable because these reactions are almost invariably carried out in strong base. But transition state characteristics consistent with this mechanism, involving heavy atom reorganisation with the development of negative charge on the leaving group nitrogen, have been deduced from the non-linear Hammett plots and solvent isotope effects observed for the $[HO^-]^2$ reaction in the hydrolysis of amides with weakly basic leaving groups like *p*-nitro- and *p*-cyano-aniline.[26,27]



Scheme 4.

There is also some evidence that the elimination of poorer leaving groups from T^{2-} is general acid-catalysed (9),[26,28] consistent with the mechanism defined by the cyclisation of (7).[6] The clear implication is that the role of the second hydroxide ion in the $[HO^-]^2$ reactions of carbonyl compounds with poor leaving groups depends on just how poor the leaving group is. With relatively good leaving groups, like the delocalised ureide and *p*-nitroanilide anions, the breakdown of T^- (Scheme 3) is general base-catalysed, primarily because of the low stability of T^{2-}. For very poor leaving groups T^{2-} becomes a viable intermediate, and its formation from T^- specific base-catalysed. The breakdown of T^{2-} is then the (separate) rate-determining step, and may involve varying amounts of proton transfer to the leaving group nitrogen from solvent, or other general acid.

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