β-Ureido acids and dihydrouracils.[1] The kinetics and mechanism of the reversible ring closure of 3-(3′-methylureido)-propanoic acid and 3-(3[1]-phenylureido)-2-methylpropanoic acid in sulfuric acid solutions

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This paper is dedicated to Professor Ross Stewart on the occasion of his 65th birthday

VETKA RACHINA, IVA B. BLAGOEVA, IVAN G. POJARLIEFF, and KEITH YATES. Can. J. Chem. **68**, 1676 (1990).

The pK_{BH^+} values for protonation of the ureido groups of the title acids, and for protonation at the 2-carbonyl groups of the product hexahydropyrimidine-2,4-diones, have been determined by standard UV and NMR methods. A bell-shaped dependence of the observed rate constants on H_2SO_4 concentration was found for both the ring-closure and ring-opening directions. This medium dependence is satisfactorily reproduced by means of rate equations based on the excess acidity treatment, providing account is taken of unproductive protonation equilibria. The derived slope parameters (m^+) for the ring-closure direction indicate that the slow step involves proton transfer from nitrogen rather than to oxygen. For the ring-opening or hydrolysis reactions, the corresponding slope parameters (m^+m^*) are characteristic of similar reactions known to proceed with slow C—N scission concerted with proton transfer.

Key words: mechanism, hydrolysis, cyclization, acid catalysis.

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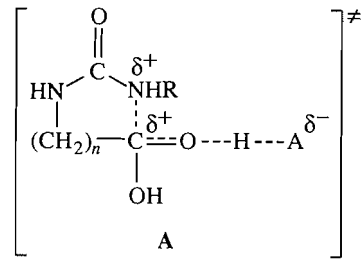
Faisant appel à des méthodes RMN et UV standard, on a déterminé les valeurs de pK_{BH^+} pour la protonation des groupements uréido des acides mentionnés dans le titre ainsi que pour la protonation des groupements carbonyles en position 2 des hexahydropyrimidine-2,4-diones. Tant pour la fermeture que pour l'ouverture du cycle, on a observé une relation en forme de cloche entre les constantes de vitesse et la concentration en H_2SO_4. Si on tient compte de l'équilibre de protonation qui n'est pas productif, on peut assez bien reproduire cette relation avec le milieu à l'aide d'équations de vitesse basées sur un d'excès d'acidité. Les paramètres de pente (m^+) que l'on dérive pour la direction de la fermeture de cycle indiquent que l'étape lente implique un transfert de proton à partir de l'azote plutôt qu'à l'oxygène. Pour les réactions d'hydrolyse ou d'ouverture de cycle, les paramètres de pente correspondants (m^+m) sont caractéristiques de réactions semblables qui sont connues et qui procèdent avec une scission lente de la liaison C—N, concertée avec un transfert de proton.

Mots clés : mécanisme, hydrolyse, cyclisation, catalyse acide.

[Traduit par la revue]

Introduction

The ring closure of 3-ureidopropanoic acid to dihydrouracil was found previously (2) to be reversible to aqueous HCl solutions, and from acidity function criteria (3) and other evidence it was concluded that the reverse, ring-opening reaction proceeds with slow attack of water on the protonated form of the dihydrouracil. This is analogous to the currently accepted mechanism of acid-catalyzed amide hydrolysis (4). Subsequently, a similar conclusion was drawn for the closely related reactions of acetylthiourea and thiohydantoin (4). More recently, however, Guler and Moodie (5), on the basis of ^{18}O-exchange experiments, have shown that the slow step in the cyclization of 5-methylhydantoic acid to the corresponding hydantoin is the formation of the C—N bond and not the breakdown of the tetrahedral intermediate, which is inconsistent with the above conclusions with respect to the ring-opening step in related systems. In the pH region, these authors (5) observed general acid catalysis and proposed a concerted mechanism, illustrated by the transition state **A**.



A

Subsequent studies (6) with strained hydantoic acids, which react rapidly at room temperature, also demonstrated general acid catalysis with Brønsted α values of 0.3 and 0.6 for 5-methyl and 5-phenyl substitution respectively, thus confirming the concertedness of heavy atom reorganization with proton transfer. Considerations of the effect of structure on the basicity of the nitrogen atom, in terms of its effect on Jencks – More O'Ferrall type diagrams (7), were all in agreement with the direction of change of α with structure expected for transition state **A**, and that which was observed experimentally (6).

However, for cyclization reactions in H_2SO_4 solutions, where a similar mechanism presumably operates, the m^+m^*

[1]Part XXI. For Part XX, see ref. 1.

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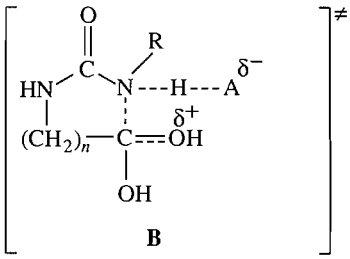
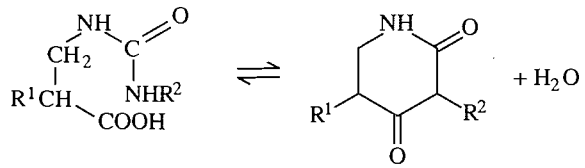
values obtained from an X-function treatment (5, 8) were 0.64 and 0.4 for the 5-methyl- and 5-phenylhydantoic acids respectively. If these parameters are interpreted in a similar way to Brønsted α values, this indicates the alternative and kinetically equivalent process of specific acid – general base catalysis, going through the more likely transition state **B**, especially where a very weakly basic ureido nucleophile is involved.



B

The above discrepancy posed a number of questions as to its origin, particularly: is the same mechanism operative in moderately concentrated H_2SO_4 solutions as in HCl, and can acidity function treatments be successfully applied to differentiate between possible concerted reactions where slow proton transfers between heteroatoms are involved? We now wish to report on ring-closure reactions of β-ureido acids in dilute to 70% sulfuric acid solutions, as shown in Scheme 1. The ring



1,3 **2,4**

1 R^1 = H, R^2 = Me; **3** R^1 = Me, R^2 = Ph

1 R^1 = H, R^2 = Me; **3** R^1 = Me, R^2 = Ph

SCHEME 1

closures of 3-ureidopropanoic acids such as **1** and **3** have the advantage of being measurably reversible, unlike hydantoic acids where the equilibria lie far on the hydantoin side, and hence can be studied kinetically in both directions. Also the hydrolysis reactions of **2** and **4** can be compared with the better

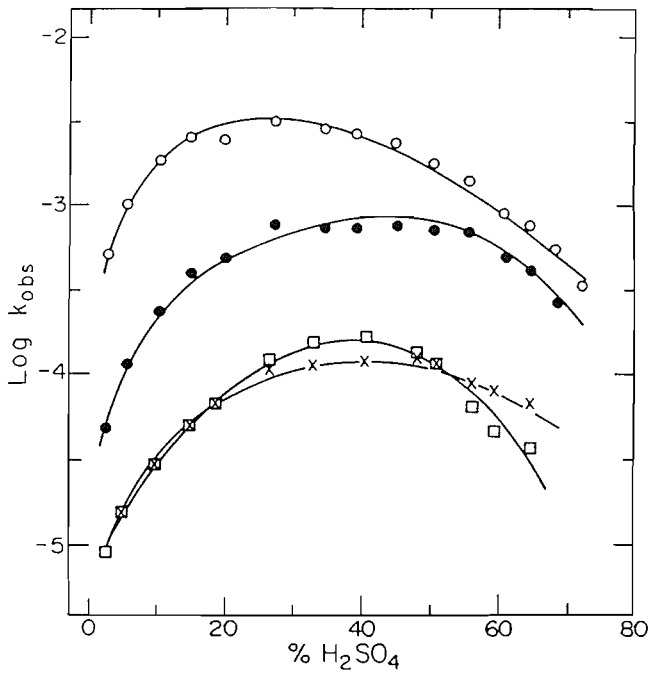


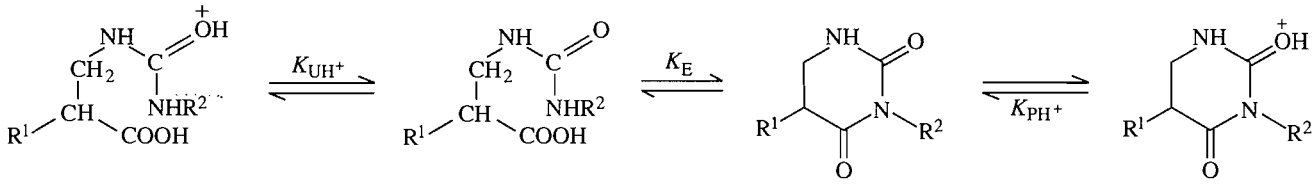
FIG. 1. Rate profiles for ring closure of **1** (○) and **3** (●) and for ring opening of **2** (□) and **4** (×) in H_2SO_4 solutions at 70°C. The points are experimental values of log k_{obs} and the solid curves are calculated (see text).

known amide hydrolysis mechanism. The effect of changing the N-substitution from methyl to phenyl was again intended to give information on the effect of N-basicity on transition-state structure. The 2-methyl derivatives **3** and **4** were chosen because the apparent equilibrium constant for this reaction is close to unity.

Results

Rate measurements

Plots of the observed first-order rate constants for both ring closure (k_f) and ring opening (k_r) versus % H_2SO_4 (w/w) are shown in Fig. 1. In the acidity range studied (0–70% H_2SO_4), both reactions are accompanied by the unproductive (and thermodynamically favoured) protonations shown in Scheme 2.



UH^+ U P PH^+

SCHEME 2

Therefore the observed rates of cyclization (V_f) and ring opening (V_r), and overall equilibrium constant are given by

$$V_f = k_f^{obs}([U] + [UH^+])$$

$$V_r = k_r^{obs}([P] + [PH^+])$$

$$K_e^{obs} = \frac{([P] + [PH^+])}{([U] + [UH^+])}$$

Thus corrections are needed for these unproductive ionizations.

pK determinations

The pK values of **1**–**4** listed in Table 1 were obtained using the excess acidity treatment of Cox and Yates (9). This has recently been shown (10) to be equivalent to the Bunnett–Olsen method (11), provided correct values of C_{H^+} are used in the latter treatment. The pK values are the thermodynamic values extrapolated to $X = 0$, obtained from the expression

$$\log [BH^+]/[B] - \log C_{H^+} = m^*X + pK_{BH^+}$$

TABLE 1. Protonation equilibrium constants and statistical parameters from excess acidity treatment

Compound	T(K)	pK_{BH^+}	pK^a	m^*	δ^a	r^b	δy^c
1	292	−0.85	0.01	1.02	0.02	0.998	0.019
2	303	−2.60	0.004	0.48	0.003	0.999	0.028
3	298	−1.83	0.01	0.73	0.008	0.994	0.048
4	298	−3.56	0.003	0.57	0.003	0.996	0.058

[a]Standard deviations of quantities indicated.
[b]Least-squares correlation coefficient.
[c]Standard deviation on y-axis (log K_{BH^+} axis).

These pK values, because of the extrapolation involved, are frequently sensitive to errors in determining m^* and the ionization ratio terms $[BH^+]/[B]$. However, the bases studied here are not very weak, so that the extrapolations involved are not that long. The *N*-methyl compounds **1** and **2** were studied via ^1H and ^{13}C NMR spectroscopy since the only changes observed in UV spectra with acidity were at the short wavelength (ca. 200 nm) end of the spectrum where accurate measurements are difficult. The variation in ^{13}C chemical shift of the 2-carbon gave reasonable sigmoidal behaviour with acidity, and thus was used to determine pK (see experimental section).

The *N*-phenyl compounds **3** and **4** were studied by standard UV measurements (see experimental section), using the procedure of Katritzky *et al.* (12) to account for spectral solvent dependencies, as described in detail in ref. 8.

We have used three criteria for the reliability of the pK values obtained: linearity of the Cox–Yates plots; the derived statistical parameters for m^*; and the fit of the recalculated to the observed spectral changes with acidity. In addition, the changes in basicity shown in Table 1 as a function of structure are very reasonable, either in terms of *N*-methyl versus *N*-phenyl substitution, or acyclic urea versus uracil formation.

Acidity dependence of the rate constants

The reactions (cyclization and ring opening) were sufficiently slow that they could be conveniently followed kinetically at 70°C. The observed rate constants were corrected for the unproductive ionizations discussed in the previous section, as in

$$k_{corr} = k_{obs}(1 + [BH^+]/[B])$$

where

$$[BH^+]/[B] = \text{antilog}\,(m^*X + pK_{BH^+} + \log C_{H^+})$$

The X-function and pK_{BH^+} values were temperature corrected to 70°C as recommended by Cox *et al.* (13). Values of log C_{H^+} at 25°C were used unchanged, since it has been shown that temperature corrections over the range studied would be very small or negligible (9).

The rate constants for the cyclization direction (k_f), which are the more important in terms of the present mechanistic comparisons, were treated by both the Cox–Yates (C–Y) (14) and Bunnett–Olsen (B—O) (15) treatments, as in eqs. [1] and [2] respectively.

[1] $\log k_f^{corr} - \log C_{H^+}$

[2] $\log k_f^{corr} + H_0 = \phi(H_0 + \log C_{H^+})$

In both cases linear plots were obtained (see Fig. 2), without including any water activity terms as is reasonable in terms of

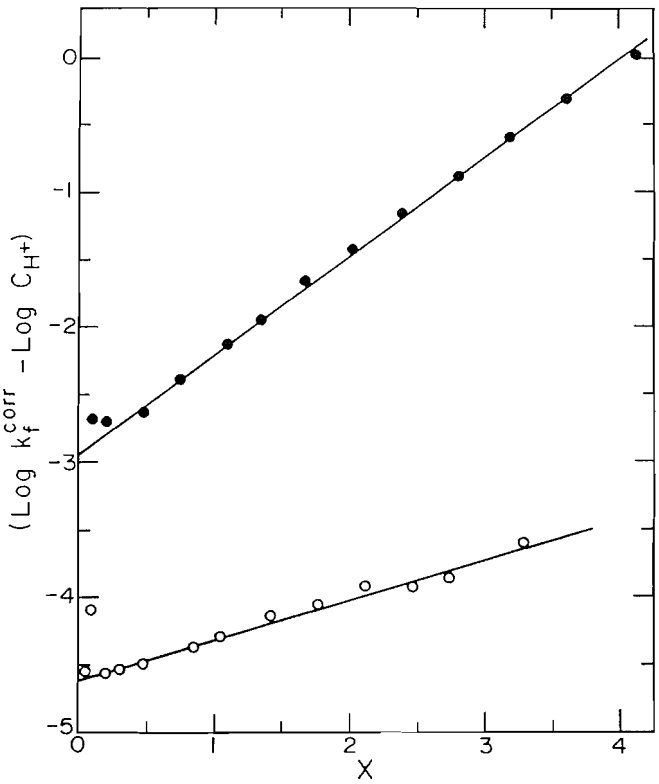


FIG. 2. Plots of (log k_f^{corr} − log C_{H^+}) versus the X-function for the ring closure of **1** (●) and **3** (○).

Scheme 1 for reaction in the forward direction. The medium-independent rate constants k_2^0 and the slope parameters ($m^*m^\ddagger$ or ϕ) are given in Table 2, along with the appropriate statistical parameters. Given the previously demonstrated (14) equivalence between $m^*m^\ddagger$ and $(1 - \phi)$, the two kinetic treatments give essentially the same results for both k_f and k_r. Since the former is somewhat easier to interpret mechanistically, only $m^*m^\ddagger$ will be used in subsequent discussion.

The rate constants in the ring-opening direction (k_r) were also treated by both the C–Y and B–O approaches, but the correlations were less clear-cut. The unmodified eqs. [1] and [2] led to downward curving plots, which is not reasonable either in terms of the negative $m^*m^\ddagger$ values implied or in terms of the stoichiometry of Scheme 1. Incorporation of explicit water activity terms as in eqs. [3] or [4]

[3] $\log k_+^{corr} - \log C_{H^+} + n \log aH_2O = m^*m^\ddagger X$

[4] $\log k_r^{corr} + H_0 + n \log aH_2O = \phi(H_0 + \log C_{H^+})$

improved the fit in some, but not all, cases. Also, although the

TABLE 2. Rate constants and associated parameters from acidity function treatment

Treatment	Rate constant	n^a	log $k_2^{0\,b}$	Slope parameter^c	r^d	δy^e
	3-(3′-Methylureido)-propanoic acid (**1**)					
C–Y^f	log k_f^{corr}	0	−2.851	0.70	0.998	0.06
	log k_f^{corr}	0	−3.702	−0.10	0.915	0.06
		1	−3.809	0.196	0.949	0.088
		2	−3.916	0.422	0.968	0.172
B–O^g	log k_f^{corr}	0	−2.808	0.35	0.987	0.082
	log k_f^{corr}	0	−3.707	0.09	0.999	0.059
		1	−3.800	0.82	0.998	0.075
		2	−3.893	0.54	0.982	0.151
	3-(3′-Phenyl)-2-methylpropanoic acid (**3**)					
C–Y	log k_f^{corr}	0	−4.616	0.29	0.992	0.041
	log k_f^{corr}	0	−4.526	−0.16	0.974	0.041
		1	−4.588	0.09	0.927	0.038
		2	−4.649	0.336	0.977	0.080
B–O	log k_f^{corr}	0	−4.609	0.72	0.999	0.043
	log k_f^{corr}	0	−4.528	1.16	0.999	0.072
		1	−4.584	0.92	0.999	0.048
		2	−4.641	0.68	0.994	0.085

[a]Number of log aH_2O included in eqs. [3] and [4].
[b]Medium-independent bimolecular rate constant from extrapolation to $X = 0$ or $(H_0 + \log C_{H^+}) = 0$.
[c]$m^*m^{\neq}$ (C–Y) or ϕ (B–O).
[d]Correlation coefficient.
[e]Standard deviation on y-axis (log k axis).
[f]Cox–Yates treatment, eqs. [1] or [3].
[g]Bunnett–Olsen treatment, eqs. [2] or [4].

slope parameters $m^*m^{\neq}$ became positive using eq. [3], there was no significant difference in linearity[2] between the cases of $n = 1$ and $n = 2$, as shown in Table 2. It therefore seems to be the case that, although a water activity term should be included, there is no clear-cut answer as to the molecularity of the ring-opening reaction in terms of water, unlike the situation found with ester and related hydrolysis reactions. The problem can be illustrated using the Yates r-parameter (17) modification of the original Bunnett w-parameter treatment (18) as shown in Fig. 3, where (log $k_r - H_s$) is plotted against log α_{H_2O}. The plots are again curved, as found in r-plots for amide hydrolysis (17*b*, 19), and there is a clear indication of a sharp break in water–activity dependence between reactions in dilute ($r \sim 4$) and more concentrated ($r \sim 1.5$) acid solutions. This again is reminiscent of amide hydrolysis, where, as the availability of water is strongly decreased in more concentrated acids, the mechanism changes from $r = 3$ to $r = 1$ in terms of its water dependence. Since the emphasis in the present paper is on comparisons of five- and six-membered ureido derivatives, and k_r cannot be studied kinetically in the former case, the kinetic treatment of these hydrolysis rate constants was not pursued further.

Acidity dependence of the equilibrium constants

The effect of changing acidity on the observed equilibrium constants is not very pronounced, as shown in Fig. 4. The equilibrium between the *N*-methyl compounds (**1** ⇄ **2**) shifts towards **1** with increasing acid concentration, as observed previously for dihydrouracil itself (2), and is explainable in terms of the protonation of the relatively basic methylureido group. A similar effect is observed for the equilibrium **3** ⇄ **4**, but is only exhibited at higher acidity because of the weaker basicity of the phenyl-ureido group. However, in both cases log K_{obs} changes by less than one unit over the entire range 0–70% H_2SO_4. The problem is that the equilibria of interest (Scheme 1) are complicated by the two unproductive protonations of Scheme 2. Taking these into account leads to the following expression for K_{obs}:

[2]This is due in part to the approximate linearity of the excess acidity function, X, with log aH_2O (slope ca. 0.3) in the region of acidities studied.

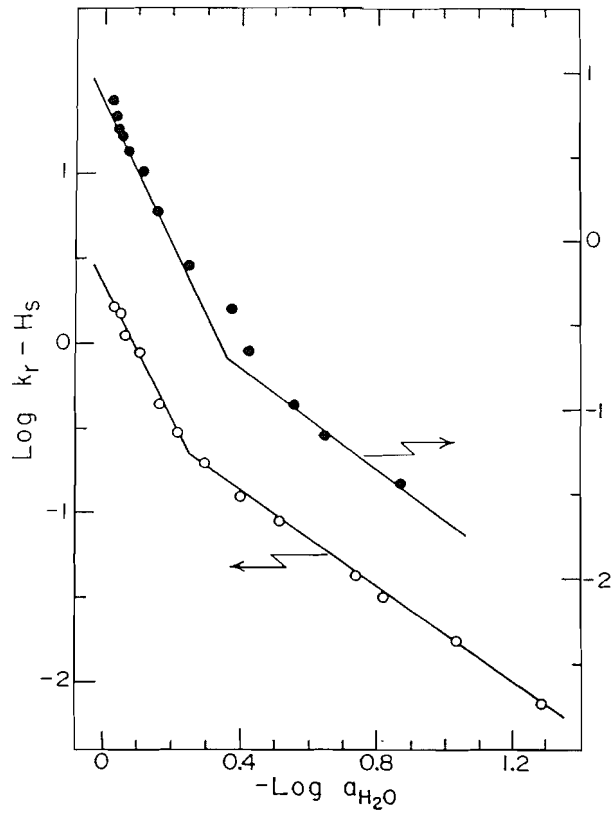


FIG. 3. Yates r-plots for the hydrolysis of **2** (●) and **4** (○).

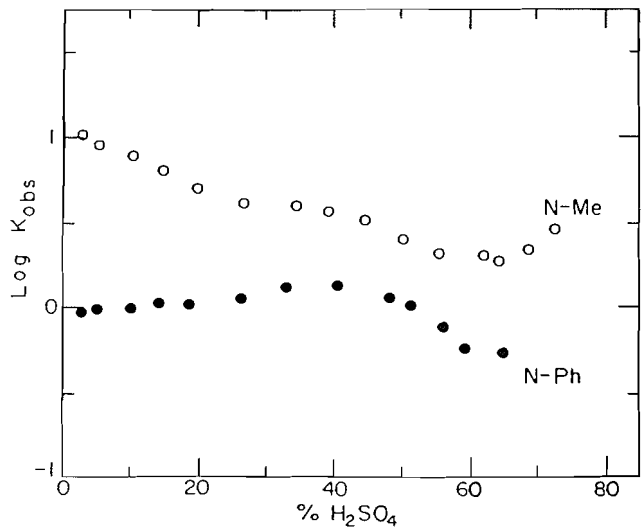


FIG. 4. Medium dependence of the equilibrium constants (log k_{obs}) on acid concentration. **1** ⇄ **2** (○); **3** ⇄ **4** (●).

$$[5] \quad K_{obs} = \left(\frac{(h_3{}^{P} + K_{PH^+})K_{UH^+}}{(h_s{}^{u} + K_{UH^+})K_{PH^+}}\right) \cdot \left(\frac{K_e f_u}{f_p a_{H_2O}}\right)$$

where the h and f terms refer to the relevant acidity functions and activity coefficients for the neutral species. The last term on the right of eq. [5] is the apparent equilibrium constant for the unprotonated species (as shown in Scheme 1), i.e., U ⇄ P, as given by eq. [6].

$$[6] \quad K_{app} = K_{obs}\frac{(1 + I_p)}{(1 + I_u)} = \frac{K_e f_u}{f_p a_{H_2O}}$$

Thus a plot of (log K_{app} + log aH_2O) versus X should give as slope the acidity dependence of log f_u/f_p and as intercept log K_e. The correlations are reasonable, as shown in Table 3. The slopes, which are equal to m_e, are positive in both cases, as expected because of the greater hydration requirements of the ureido acids than the uracils. The m_e values obtained should be equal to the difference between the kinetic $m^*m^{\ddagger}$ values for k_f and k_r given in Table 1, which is found to be the case.

TABLE 3. Equilibrium constants and associated parameters from acidity function treatment

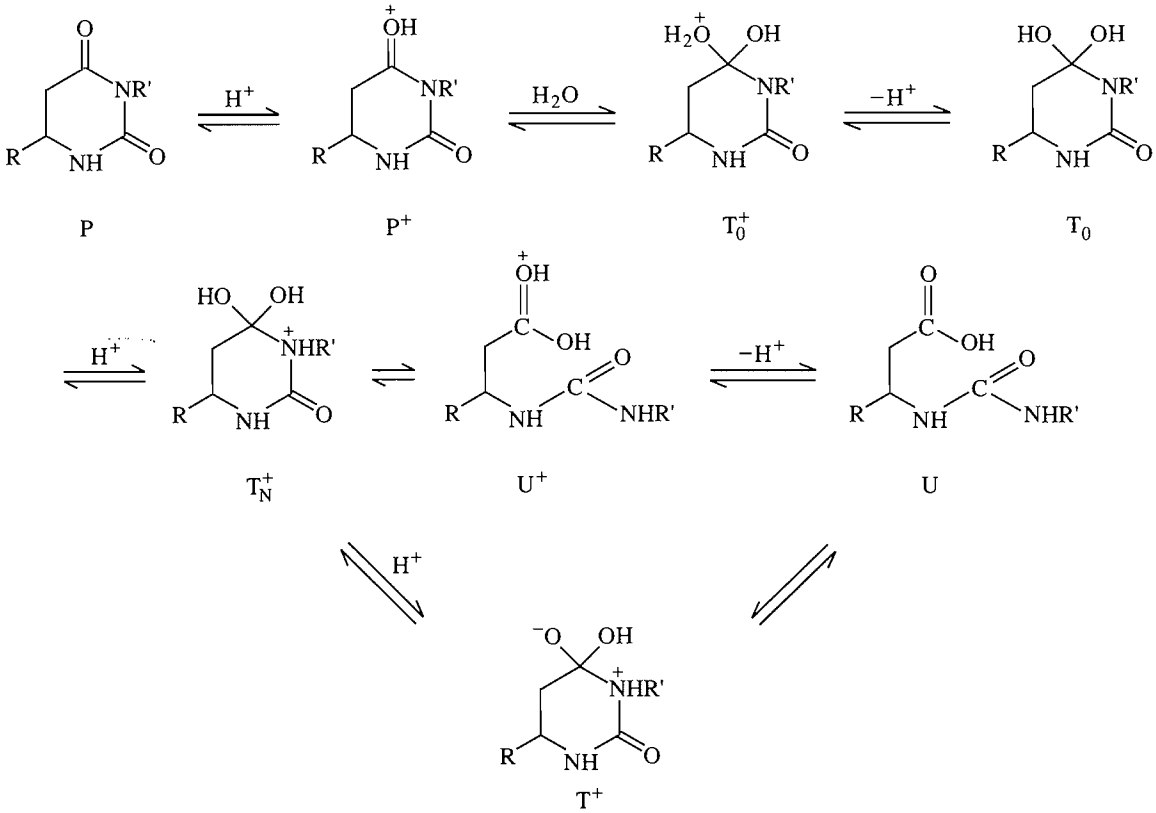
Equilibrium[a]	log K_c[b]	m_c[c]	r[d]	δy[e]
1 ⇄ **2**	0.96	0.51	0.987	0.114
3 ⇄ **4**	−0.04	0.20	0.991	0.029

[a]Equilibrium of unprotonated species, as in Scheme 1.
[b]Based on eq. [6] and plot of (log K_{app} + log aH_2O) versus X-function.
[c]Medium-dependent slope parameter from Cox–Yates treatment.
[d]Correlation coefficient.
[e]Standard deviation on y-axis (log K_{app} + log aH_2O).

Discussion

The pK_{BH^+} value of **1** (−0.85) is close to that reported for 5-methylhydantoic acid (5), if the latter is corrected by 0.3 units because of the mis-anchoring of the original H_A scale (20) (−1.06). Both values are significantly lower than the kinetically determined pK value of −0.25 reported for 3-ureidopropanoic acid (2), which is probably due to some loss of planarity in 1,3-disubstituted ureas. A similar effect is found when the pK_{BH^+} of the phenylureido acid **3** (−1.83) is compared with that for phenylurea (−1.22) (21). No reliable pK_{BH^+} values have been reported for the corresponding uracil derivatives. An H_0 value of −4.7 for the half-protonation of dihydrouracil has been reported (26) in $HClO_4$, and from somewhat uncertain ionization ratio determinations the Bunnett–Olsen treatment had given a pK_{BH^+} value of −2.54 (ϕ = 0.55) (2). The latter values are close to the values obtained in this work for **2** (pK_{BH^+} = −2.6, ϕ = 0.48). The value for **4** is significantly more negative (pK_{BH^+} = −3.56), as expected for the base-weakening effect of *N*-phenyl, rather than *N*-methyl substitution. It is interesting that effects of ring closure on the basicity of **1** and **3** are practically identical, as shown in Table 1. In addition, the decreases in $m^{\ddagger}$ for both **1** → **2** and **3** → **4** are in the expected direction, because of the higher hydration requirements of the ureido acid form. The m^* values for the protonation of the pyrimidinediones **2** and **4** fall in the usual range observed for amides (22).

Because of their structural similarities to amides and ureas, it is instructive first to consider possible hydrolysis mechanisms for pyrimidinediones (such as **2** and **4**) before examining the reaction in the ring-closure direction. The overall scheme including all reasonable intermediates is shown in Scheme 3.



SCHEME 3

Currently it is considered that in $A_{AC}2$ type ester (13) and amide hydrolysis (3), although T_0^+ can be formed by rate-determining attack of water on the protonated substrate, its presence can be avoided in dilute to moderately concentrated acids by the further participation of water (as a base) in a one-step process leading directly to T_0.

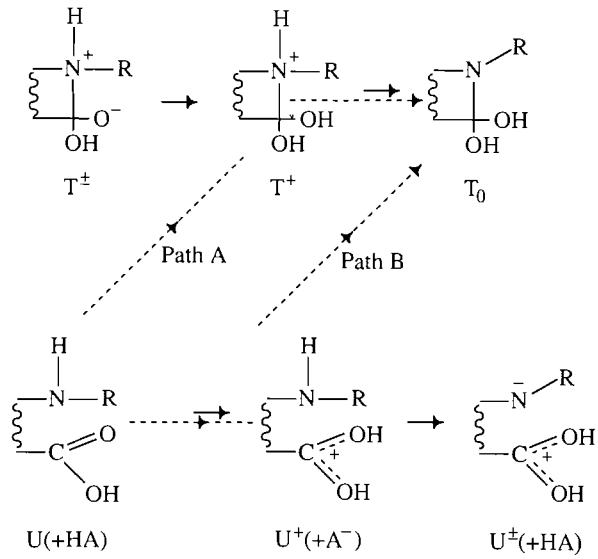
The parameters obtained from acidity function treatment of **2** and **4** are not very different from those observed for acid-catalyzed amide hydrolysis ($A_{AC}2$) (3) and, as previously mentioned, dihydrouracil (2) and acylthiourea (4) hydrolyses also behave similarly: with the latter, the interpretation of rate-determining water attack on the protonated substrate was consistent with other evidence, such as high negative $\Delta S^{\neq}$ values, inverse solvent isotope effect, and substituent effects in the acyl moiety (2, 4).

However, there is evidence for an alternate mechanism in the case of 3-methylhydantoin, where Guler and Moodie (5) observed that ^{18}O-exchange is at least 10 times faster than ring opening.[3] This strongly supports the idea that C—N bond breaking or formation is involved in the rate-determining steps of acid-catalyzed ring opening and ring closing. Furthermore, the same authors (5) observed general acid catalysis, whereas typical $A_{AC}2$ amide hydrolysis is specific acid catalyzed (3). In addition, one of us (2) has found that cyclization of sterically strained hydantoic acids showed general acid catalysis with Brønsted coefficients $0 < \alpha < 1$. This is generally believed to indicate proton transfer concerted with heavy atom reorganization.

An important question at this point is, how likely is it that the above five-membered ring compounds (hydantoins) hydrolyse by a different mechanism from the six-membered rings (uracils) of the present study? Five-membered rings are usually more difficult to open, and this can make ring formation rate determining on changing from six- to five-membered ring compounds, as shown previously for 3-(2′-aminophenyl) propanoic (24) and 2-aminophenylacetic acids (25). However, decreased basicity of the amino group in the hydrolysis direction tends to shift the rate-determining step in Scheme 3 from formation of T_0 or T_0^+ to one of the subsequent steps. Since anilines are a borderline case (26), then the much more weakly basic amino group of the present ureido systems is most unlikely to be affected by ring size.

Hydrolysis of **2** in ^{18}O-enriched 0.5 M HCl solutions showed that its rate of ^{18}O-exchange is 7.85 times faster than the rate of hydrolysis (**2** → **1**). This demonstrates that the process T → U occurs about 16 times faster than T → P, thus proving that C—N bond scission is also rate determining for the six-membered ring compounds.

Since the mechanism of hydrolysis of both hydantoin and uracil derivatives involves rate-determining C—N bond breaking, as opposed to the standard $A_{AC}2$ mechanism for amide hydrolysis, then are the acidity function parameters $m^*m^{\neq}$ or ϕ able to distinguish between such processes? The answer is certainly no, since the $m^*m^{\neq}$ or ϕ parameters listed in Table 2 fall within the range observed (3) for various types of amide hydrolysis, as do the m^* for the protonation step itself (see Table 1). A major problem, alluded to earlier, is that amide-type hydrolyses are more complex in terms of their medium dependence than other types of hydrolysis, as shown earlier by Cox and Yates (3*a*), and as illustrated by Fig. 3. One thing seems clear, however, from all the evidence; that is, in Scheme 3 the transition state in the ring-opening direction is almost certainly at T_0 or to the right of T_0. Therefore the transition state in the ring-closure direction must lie between T_0 and the starting ureido acid.



SCHEME 4

The possible pathways for ring closure are as shown in Scheme 4, since this approach will allow clearer consideration of alternate route diagrams of the Albery–Jencks – More O'Ferrall type (7).

First of all, pathways leading through $T^{\pm}$ can be neglected. Since the ureido nitrogen is very weakly, and the O^- group very strongly basic, this will represent a very high energy species. Similarly, the species $U^{\pm}$ will probably be even higher in energy than $T^{\pm}$ and can also be neglected. This means that the only two viable pathways will be paths A and B (see Scheme 4). Path A represents true general acid catalysis, and path B specific acid – general base catalysis, both being concerted with C—N bond formation. Since these two pathways are kinetically indistinguishable, there are two approaches to try to resolve the problem. One is to consider the effects of N-substitution on the basicity or acidity of the various intermediates. It is clear from Fig. 2 that the ring closure of the *N*-methyl derivative **1** has a substantially higher value of $m^*m^{\neq}$ than that of the *N*-phenyl derivative **3** (0.7 versus 0.3), similar to the situation reported (8) for five-membered ring analogues. On the highly probable assumption that N-substitution will have very little effect on the m^* value for proton transfer to the remote carboxyl group, this means that the $m^{\neq}$ value for proton transfer, following Kresge's interpretation (29) of the slope parameters obtained from the rate–acidity profiles, corresponds to the Brønsted α. This means that **1** will have a higher α, or later transition state, than **3**. As can be seen from Scheme 4 for path A, decreased basicity of N-Ph versus N-Me will increase the degree of proton transfer to nitrogen at the transition state and hence increase α, which is opposite to what is observed. For path B, a similar decrease of N-basicity (or increase of NH-acidity) will increase proton transfer from nitrogen to H_2O at the transition state and hence increase β for this step. Experimentally, this will be detected as a decrease in the observed α, which is what is observed experimentally. Thus path B is clearly favoured by this argument.

A second approach is to construct a three-dimensional Albery–Jencks – More O'Ferrall diagram (7) as shown in Fig. 5. This shows both pathways A and B as in Scheme 4, with the

[3]Dr. Moodie has kindly drawn attention to an error of 4 in the published estimate.

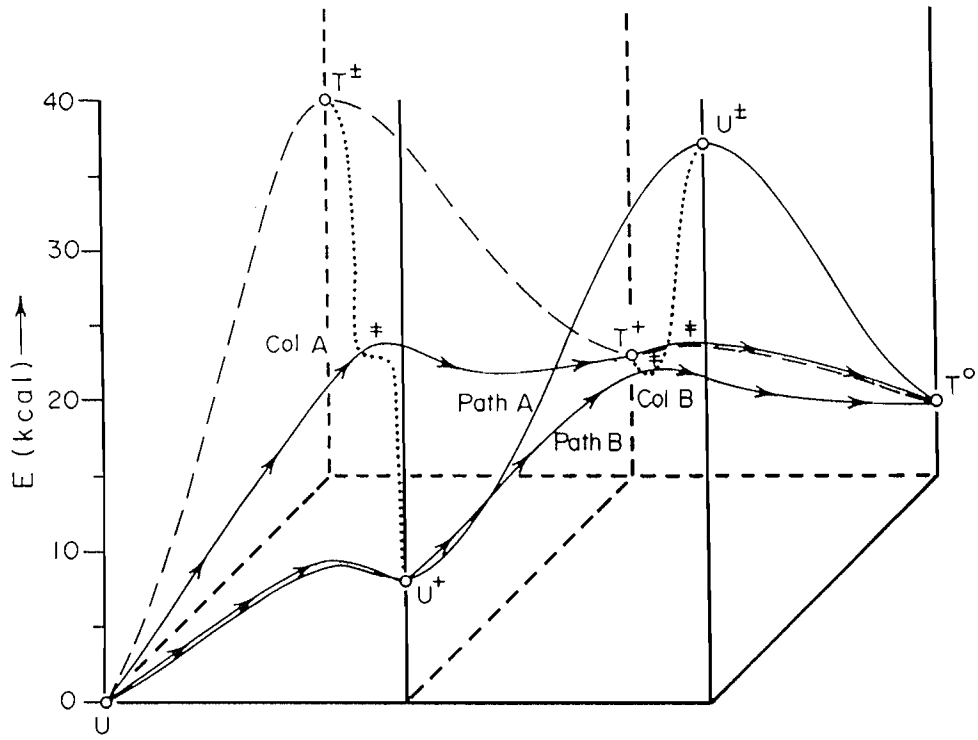


FIG. 5. Energy–reaction coordinate profiles for the ring closure of ureido acid (**U**) to form the neutral tetrahedral intermediate ($\mathbf{T}_0$). See text for description of intermediates and pathways.

heights of the various intermediates in energy terms, relative to that of the substrate, taken as the zero reference point. Estimates of these relative energies were based on p*K* values for related model compounds and on standard bond energy values, as described in the experimental section. It seems clear from the diagram that the saddle-point for path B (denoted Col. B) will be close in energy to, and probably lower than, that of the intermediate T^+, which lies on path A. As far as the saddle-point on path A is concerned (denoted by Col. A), this will either be higher than T^+ (and hence higher than Col. B), which would mean simple general acid catalysis, or it is lower than T^+, which would mean that the transition state for path A would lie between T^+ and T_0. The latter would imply that proton transfer from nitrogen would be rate determining, *after* the acid-catalyzed formation of the C—N bond, which seems most improbable, although it would lead to observed general acid catalysis. In the former, more probable case, if Col. A is higher than T^+, which in turn is equal to or higher in energy than Col. B, this indicates that path B would be the favoured mechanism, as already concluded from comparison of the *N*-methyl and *N*-phenyl derivatives' response to changing acidity. It should be emphasized that the conclusions based on Fig. 5 do not depend on the precise energy values calculated for the various intermediates, but only on the general features of the diagram.

Thus, overall, it seems probable that both six- and five-membered ring formation take place by rate-determining proton transfer from nitrogen, concerted with C—N bond formation, and not slow proton transfer to oxygen as previously assumed. As already mentioned, the variation of Brønsted α values observed for buffer catalysis with strained hydantoic acids, upon replacing N-Me for N-Ph, favour the alternate mechanism, path A. The reasons for this difference are at the present not clearly understood.

Experimental

Spectra

UV spectra were taken on a Carl Zeiss, Jena, Specord UV–VIS spectrophotometer and the NMR spectra on a Bruker WM 250 instrument.

Materials

3-(3[1]-Methylureido)-propanoic acid, **1**, was prepared by adding 0.033 mol of methyl isocyanate to an ice-cooled solution of 0.03 mol of 3-aminopropanoic acid in 15 mL of 2 M NaOH under vigorous stirring. The mixture was heated to ambient temperature for 5–10 min and, after a further 5 min, the pH of the solution was brought to 2 by adding cation-exchanger Dowex W in H^+-form. The resin was filtered and the filtrate evaporated to dryness to yield 1.68 g (38%) of **1**. The pure compound was obtained after repeated crystallization from acetone, mp 132–134°C (dec.). Anal. calcd. for $C_5H_8N_2O_2$: C 41.69, H 6.90, N 19.17; found: C 40.86, H 6.64, N 18.87%. 3-Methylhexahydropyrimidine-2,4-dione was obtained by evaporating to dryness a solution of **1** in 1:1 HCl at 100°C, extracting the residue with hot dioxane, and recrystallizing from ethanol; mp 128.5–129°C (lit. (30) mp 128–129°C). 3-(Phenylureido)-2-methylpropanoic acid, **3**, and 5-methyl-3-phenylhexahydropyrimidine-2,4-dione have been described previously (31).

Sulfuric acid solutions were prepared from analytical grade H_2SO_4 (Riedel de Haen) and distilled water, and the concentrations determined by titration.

pK_{BH^+} determinations; NMR measurements

These were carried out at 19°C and 30°C for **1** and **2** respectively. The p*K* value of **1** was determined from the changes in the ^1H chemical shifts at 250 MHz of the methyl protons with the concentration of the sulfuric acid. The shifts varied from 1.917 to 2.013 ppm for the unprotonated and protonated form respectively. Solutions (2%) of **1** in aqueous H_2SO_4 were used with acetone-d_6 and TMS as external lock and standard respectively. Care was taken to use the same capillaries throughout the series of measurements. The p*K* value of **2** was determined from the changes in the ^{13}C chemical shifts of the 2-CO carbon at 62.7 MHz, using 2% (w/v) solutions of **2** in aqueous H_2SO_4

and D_2O and TMS as external lock and standard respectively. The shifts varied from 135.7 for the unprotonated form to 159.3 for the protonated form.

UV measurements

The pK values of **3** and **4** were determined from the changes in absorbance at 238 nm with sulfuric acid concentration (24 solutions from 2.5 to 78%) at 25.0°C in a temperature controlled cell holder. Stock solutions of **3** and **4** (2×10^{-3} M) in ethanol were used and the final solutions prepared by adding 0.085 mL of **3** or 0.17 mL of **4** to 2.75 mL of the sulfuric acid solution. The changes in the total spectra did not show isosbestic points and were treated as described in Calculations.

Kinetic runs

In the case of **1** and **2** these were carried out in the temperature-controlled cell holder of the spectrometer at 70.0 ± 0.1°C in 10-nm stoppered cells. The reaction was initiated by adding 0.05–0.1 mL of a 2.2×10^{-2} M ethanolic solution of **1** or **2** to 2.75 mL of the H_2SO_4 solution at 70.0°C and monitored at 232 nm where **2** has a higher absorbance than **1**. The reaction of **3** or **4** was carried out in sealed ampoules in a thermostat bath at 70.0°C. The solutions were prepared by making up to 100 mL, 3 mL of an ethanolic 2×10^{-3} M solution of the substrate, with the sulfuric acid solution. The reaction was monitored at 238 nm by the decrease of the absorbance of **3** or the increase of that of **4**. In all cases good isosbestic points were obtained. With all sulfuric acid concentrations the reactions were carried out in both directions and the spectra obtained at $10t_{1/2}$, A_∞, were found to be identical within experimental error. The observed first-order rate constants $k^{obs} = k_f + k_r$, where k_f and k_r are the rate constants for the forward and reverse reactions, were calculated by the least-squares procedure from the linear dependence of $\ln(A_t - A_\infty)$ or $\ln(A_\infty - A_t)$ against time. The apparent equilibrium constant, $K_e^{obs} = k_f/k_r$ was obtained from

$$K_e^{obs} = \frac{A_\infty - A^0_u}{A^0_p - A_\infty}$$

where A^0_u and A^0_p are the initial absorbances of the ureido acid or pyrimidine, respectively, at a particular sulfuric acid concentration. The rate and equilibrium constants were obtained as averages from 2–3 runs. The differences between separate determinations did not exceed 5%. k_f and k_r were derived from the two equations above.

Kinetics of ^{18}O-exchange of 2

These were carried out in 0.5 M HCl at 50.0°C. In a separate experiment, K_e^{obs} and k^{obs} were determined as described above, to be 15.3 and 2.20×10^{-4} s^{-1}, respectively, yielding $k_f = 2.06 \times 10^{-4}$ s^{-1} and $k_r = 1.35 \times 10^{-5}$ s^{-1}.

A 0.5 M solution of HCl in water 20% enriched in ^{18}O was prepared by volume with concentrated HCl and the concentration checked by titration; 11.6 mg (10^{-4} mol) of **2** was dissolved in 0.9 mL of the HCl solution in a stoppered UV cell at 50.0°C in the temperature controlled cell holder. Aliquots of 0.1 or 0.05 mL were withdrawn and quenched in a small flask containing 0.5 mL of water and 0.4 (or 0.2) mL of 0.1 M KOH. The pH was adjusted to 7 with KOH solution and the contents evaporated to dryness. The residue was extracted three times with a total of 4 mL of methylene chloride. The extract was filtered and evaporated and the dry residue analysed on a JEOL JMS-D300 mass spectrometer, electron impact mode, ionization potential 70 eV, ionization current 300 μA, and ion source temperature 170°C. A separate experiment showed that no ureido acid is extracted under these conditions. The extent of exchange was monitored by the ratio of the M^+ to ($M^+ + 2$) peaks, averaged from several determinations and corrected for the natural content of ^{18}O. The rate constant of exchange, $k = 1.06 \times 10^{-4}$ s^{-1}, was calculated from the integrated first-order rate equation after accounting for rapid exchange via the ureido acid.[4]

[4]The hydrolysis of **2** is appreciably reversible, $K_e = 15.3$, so that the exchange can occur via the free acid. From the data in ref. 28 on ^{18}O-exchange in acetic acid, a rate of 0.002 s^{-1} can be calculated at the temperature at which the exchange rate of **2** was measured. Because of this rather high estimate for the exchange of the free carboxy group, the exchange data for **2** were corrected by assuming that every molecule of **1** exchanged before recycling. The ratio P*/P, for the exchange along this pathway, was found by means of the integrated rate equation for consecutive irreversible first-order reactions. The results obtained indicated that this was probably an "over-correction"; plots of ln (% of exchange) against time of the uncorrected data were linear for ca. 70% conversion; however, the rate constants before and after correction differed by less than 20%.

Calculations

*p*K *values*

These were obtained using the Cox–Yates (9) treatment outlined in the results section. In the case of **1** this method was applied in a straightforward fashion to the variation of ^1H chemical shift of the *N*-methyl group with acidity. For compound **2** the ^{13}C chemical shifts of the 2-CO group varied in the expected way up to 79% H_2SO_4, then decreased slightly (i.e., points at 83.5 and 88% H_2SO_4). That this is not due to a medium effect but rather is due to the onset of a second protonation at 4-CO was evidenced by the chemical shift behavior of the latter carbon. The chemical shifts decreased in parallel to the protonation of 2-CO (ca. 70 Hz up to $H_A = -3.5$), and then increased rapidly (by ca. 110 Hz up to $H_A = -5$). Since too few data were available in the high acidity region, no quantitative treatment of this second protonation was attempted. The ionization ratios for the first protonation were obtained by assuring that the maximum chemical shift is ΔBH^+. For compound **3**, the variation in UV spectra with acidity showed no isosbestic point, similar to the cases of arylureas (21, 32) and 5-arylhydantoic acids (8). Following previous experience the ionization ratios were obtained by assuming (12, 33) linear dependence of A(B) and $A(BH^+)$ on H_A. The latter values were obtained by plotting the absorbance (A) at 238 nm versus H_A, and extrapolating the linear portions of each end of the sigmoid curve obtained.

The 3-phenyldihydrouracil **4** showed only end UV absorption, which increased with acid concentration, but did not level off at high acidity. When plotted against H_0, however, an inflection point around $H_0 = -7$ was observed, indicating the completion of the first protonation and beginning of the second, as indicated by the ^{13}C NMR spectra of **2**. Usually with weaker bases, only A(B) is significantly medium dependent (33), and thus the ionization ratios for **4** were calculated by assuming linear dependence of A(B) on H_0 and by adjusting $A(BH^+)$ iteratively until the best fit was obtained for the total variation of A.

Rate constants

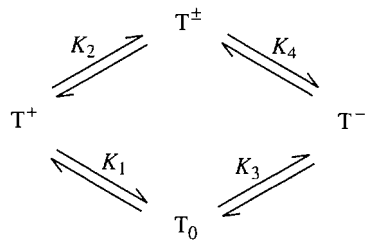
The medium independent bimolecular rate constants and equilibrium constants were obtained by means of eqs. [1]–[6] (see Results). The values for X and pK were corrected as recommended (13); log C_{H^+} values for 25°C were used. In the Bunnett–Olsen treatment H_0 values interpolated for 70°C from the data in ref. 34 were used together with log C_{H^+} instead of the acid molarity. The log aH_2O values at 70°C are from ref. 35; values for solutions more concentrated than 63% H_2SO_4 were obtained by extrapolation of a plot log aH_2O^{25} vs. log aH_2O^{70} (36).

Energy–reaction coordinate profiles

For the change in free energy for $U^+ \rightarrow U$, a pK value of approximately −4 was used, based on values obtained (37) for aromatic and α,β-unsaturated acids, using the Bunnett–Olsen

treatment. To the best of our knowledge, no pK values have been reported for simple aliphatic carboxylic acids. Recently, however, Edward and Wong (38) have determined $pK_{BH^+} = -4.7$ ($m^* = 0.56$) for benzoic acid. For the change $U^+ \rightarrow U^{\pm}$, we have used the reported pK values of 18.3 (39) for the equilibrium $H_2NCONHCH_3 \rightleftarrows H_2NCON^- CH_3 + H^+$, and 16.3 and 16.6 for the ionizations of $PhNHCONHCH_2COO^-$ and $PhNHCON(CH_3)CH_2COO^-$ respectively (40).

For the tetrahedral intermediates shown below, the following pK values are estimated using the approach of Fox and Jencks (41): $pK_1 = -8.1$, $pK_2 = 8.2$, $pK_3 = 12.8$, $pK_4 = -3.3$. These are based on a pK_{BH^+} of -3.9 reported (39) for the *N*-methyl nitrogen in methylurea and a suitable LFER recommended by Fox and Jencks (41), assuming that a unit charge changes the pK by 4.8 units.



The most difficult term to estimate reliably was the energy difference between U and T_0. Using representative average bond energies (16), T_0 was estimated to be only 2 kcal higher in energy than U. However, using group contributions from two sources (16, 23), based on somewhat dubious analogies, higher values of 9.5–11.8 kcal were obtained. Finally, heats of formation for U and T_0 based on AM1 calculations (27) gave $\Delta\Delta H_f$ of 7.2 kcal. We have therefore used an average value of ~6 kcal for this difference. The absolute accuracy is not, however, critical in comparing the relative energy changes of paths A and B from U to T_0.

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