Kinetics and Mechanism of Cyclisation of *N*-(Methylaminocarbonyl)-glycine to 3-Methylimidazolidine-2,4-dione

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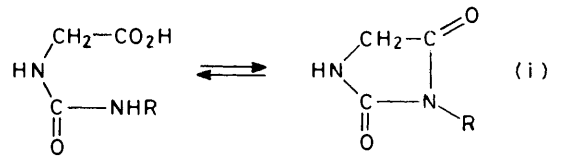
The dependence of rate coefficients for cyclisation upon acidity, solvent isotope effects, and the kinetics of oxygen exchange of the product, support the view that in the acid catalysed cyclisation there is rate-determining ring closure of the neutral substrate synchronous with protonation of the carboxy oxygen. This is contrary to what current views of the mechanism of acid-catalysed amide hydrolysis would lead one to expect; reasons for this are discussed. The kinetics of the uncatalysed cyclisation and of the reverse ring opening reaction in alkali are reported, and a mechanistic scheme for the whole pH range is presented. The equilibrium constant of the title reaction in water at 25 °C is shown to lie between 10^3 and 10^6; the slowness of the reaction at central values of pH prevents a closer estimate.

RING closure of hydantoic acids to hydantoins (of which the title reaction is an example) is reversible,[1] the forward reaction being favoured in acid and the reverse in alkali [equation (i)]. The kinetics of the forward



(1) (2) (i)

reactions for several 2-substituted hydantoic acids have been studied by Stella and Higuchi;[2] both an acid- and a water-catalysed reaction were disclosed [equation (ii), a is the fraction of hydantoic acid not dissociated]. The

$$k_{obs.}/\alpha = k_1 + k_2[H^+] \qquad (ii)$$

cyclisation reaction offers the unusual possibility of studying acid catalysed amide hydrolysis in reverse. We report here a study of the kinetics of reaction (i; R = Me) both in acid and in alkali. The reaction in alkali has previously been studied[3] and our results are in qualitative agreement. Related studies of protonation equilibria are also reported. The combined results permit some conclusions to be drawn regarding the mechanisms of, and set limits on the equilibrium constant for, reaction (i).

RESULTS

Protonation Equilibria.—Values of pK_a for *N*-(methylaminocarbonyl)glycine at 25 and 50 °C were found to be 3.80 (±0.01) and 3.78 (±0.01), respectively. That of methoxyacetic acid at 50 °C is 3.50 (±0.01). These values relate to an ionic strength of 0.2M; for thermodynamic values add 0.14.

A sigmoidal increase with the acidity function[4] H_A of the molar absorption coefficient at 220 nm of *N*-(methylaminocarbonyl)glycine in aqueous sulphuric acid showed that protonation was occurring. Ionisation ratios I deduced as before[5] fitted equation (iii).

$$\log I = -1.16H_A - 1.36 \qquad (iii)$$

The site of predominant protonation is uncertain but is probably the urea oxygen.[6] The protonation of 3-methylimidazolidine-2,4-dione could not be studied quantitatively; the molar absorption coefficient at each of several wavelengths in the range 210—230 nm increased steadily with acidity only above that represented by 55% H_2SO_4 and it is likely that the extent of protonation below that acidity is negligible. There was no levelling off of the molar absorption coefficient up to 98% H_2SO_4. The change of absorbance with acidity is similar to that reported for the related six-membered ring compound, dihydrouracil.[7]

The ionisation of 3-methylimidazolidine-2,4-dione in alkali was studied; concurrent hydrolysis led us to extrapolate absorbances A at 240 nm to zero time. The slope of the plot of $(A - A_0)/[OH^-]$ against A is[3] K_a/K_ω (A_0 is the absorbance in water). In the least squares analysis we assigned weights proportional to $[OH^-]^2$ since errors are proportional to $[OH^-]^{-1}$. We obtained pK_a 13.14 (±0.15) (lit.,[3] 13.06).

TABLE 1

Rate coefficients for cyclisation of *N*-(methylaminocarbonyl)glycine in aqueous sulphuric acid at 298 K unless stated otherwise

H_2SO_4 (%)	5.1	9.8	14.4	20.4	28.0	31.8	35.7	40.1	40.1	40.1	40.1	40.1	45.3	55.0
$10^5 k_{obs.}$ [a]/s^{-1}	3.2	6.6	11.3	17.5	26	30	30	30 [c]	56 [c,d]	90 [c,e]	220 [e,f]	346 [c,g]	29	21
$10^5 k_{up.}$ [b]/s^{-1}	3.3	7.3	14.3	29	74	120	180	300					*h*	*h*

[a] Observed rate coefficient. [b] Specific rate coefficient for reaction of the unprotonated substrate. [c] Activation parameters derived from these results are $\Delta H^\ddagger$ 74 (±2) kJ mol^{-1}, $\Delta S^\ddagger$ −64 (±6) J mol^{-1} K^{-1}. [d] *T* 303 K. [e] *T* 308 K. [f] *T* 318 K. [g] *T* 323 K. [h] Not calculated; see text.

Kinetics in Aqueous Sulphuric Acid.—Observed first-order rate coefficients are in Table 1. Using ionisation ratios derived by interpolation of the plot of log I *versus* H_A (extrapolation was judged to lead to uncertainties) values of the specific rate coefficients for reaction of the unprotonated substrate, k_{up}, were derived using equation (iv). The plot of k_{up} *versus* $-H_0$ is a straight line of slope 0.87.

$$k_{up} = k_{obs.}(1 + I) \qquad (iv)$$

Kinetics in Dilute Aqueous Hydrochloric Acid.—Observed first-order rate coefficients, $k_{obs.}$, are in Table 2. The ionic strength for the runs at 50 °C was adjusted to 1M in order that the results could be compared directly with those of

TABLE 2

Rate coefficients for cyclisation of *N*-(methylaminocarbonyl)glycine in dilute aqueous HCl

T/K [a]	[H$^+$]/M	$10^6 k_{obs.}$/s^{-1}	$10^6(k_{obs.}/\alpha)$ [b]/s^{-1}
323	1.50×10^{-3}	1.79 [f]	2.1
323	1.74×10^{-3}	2.2 [f]	2.5
323	2.06×10^{-3}	1.79 [f]	2.0
323	5.44×10^{-3}	6.7 [f]	7.0
323	1.01×10^{-2}	10.4	10.7
323	0.100	86	86
323	0.300	260	260
323	0.600	450	450
323	1.00	670	670 [d]
323	1.00	770 [e]	770 [d]
313	1.00	420	420 [d]
308	1.00	157	157 [d]
303	1.00	96	96 [d]
298 [c]	1.00	43 [f,g]	43 [d]
298 [c]	0.50	19.7 [f]	19.7
298	1.34×10^{-3}	0.073 [f]	0.085
298	1.46×10^{-3}	0.089 [f]	0.102
298	1.72×10^{-3}	0.102 [f]	0.149
298	3.44×10^{-3}	0.164 [f]	0.174
298	5.29×10^{-3}	0.26 [f]	0.27
298	1.01×10^{-2}	0.39 [f]	0.40
298	0.040	1.77 [f]	1.78
298	0.070	2.9 [f]	2.9
298	0.100	4.2 [f]	4.2
298	0.200	8.8 [f]	8.8

[a] The ionic strength was 0.2M for runs at 298 K and 1.0M for runs at other temperatures except where indicated. [b] Specific rate coefficients for reaction of the undissociated acid. [c] Ionic strength 1.0M. Not included in the correlation of $(k_{obs.}/\alpha)$ with [H$^+$]. [d] Activation parameters derived from these results are $\Delta H^‡$ 85 (±4) kJ mol^{-1} and $\Delta S^‡$ −45 (±13) J mol^{-1} K^{-1}. [e] In DCl–D_2O. [f] Initial rate method used; see Experimental section. [g] Both methods used.

Stella and Higuchi.[2] For the runs at 25 °C the ionic strength was 0.2M. The concentration of hydrogen ions, [H$^+$], and the fraction of *N*-(methylaminocarbonyl)-glycine remaining undissociated, a, were calculated using the measured acidity constant of *N*-(methylaminocarbonyl)-glycine with activity coefficients estimated using the Davies equation.[8] Following Higuchi we plotted the quantity on the left of equation (ii) against [H$^+$]. The slope is the rate constant for the acid-catalysed ring closure, k_2, and the intercept that for the uncatalysed ring closure, k_1, both relating to the undissociated acid. These were obtained by weighted least squares analysis, with weights assigned [9] as

TABLE 3

Rate constants for acid catalysed (k_2) and uncatalysed (k_1) cyclisation of *N*-(methylaminocarbonyl)glycine in dilute aqueous HCl

T/K	k_1/s^{-1}	k_2/l mol^{-1} s^{-1}
298	$4.0\ (\pm 0.8) \times 10^{-8}$	$4.1\ (\pm 0.2) \times 10^{-5}$
323	$8.0\ (\pm 2.0) \times 10^{-7}$	$8.0\ (\pm 0.6) \times 10^{-4}$

$1/k_{obs}$[2] in order to allow for the approximately constant percentage error of observed rate coefficients.

Values of k_1 and k_2 are in Table 3. The extreme slowness of the runs prevented studies at lower acidities. The errors in the rate constants k_1 (all reported errors are standard errors [10]) are therefore relatively high. Activation parameters relating to rate constant k_2 are in footnote *d*, Table 2.

The dependence of the specific rate coefficient for ring closure of the unprotonated substrate, k_{up}, upon acidity in aqueous sulphuric acid (Table 1) leads to a second estimate of k_2 at 298 K (Table 3). Extrapolation to dilute aqueous solution is possible using the Marziano function,[10] renamed X and recalculated by Cox and Yates.[11] The intercept of the plot (correlation coefficient 0.999) of $\log k_{up} - \log$ [H$^+$] *versus* X is [12] $\log k_2$. This gives $k_2 = 4.2\ (\pm 0.1) \times 10^{-5}$ l mol^{-1} s^{-1}, in agreement with the value in Table 3. (The slope of the plot is 0.64; lack of data for reactions of comparable mechanism precludes discussion now).

General Acid Catalysis.—From the data in Table 3 it follows that the uncatalysed and acid-catalysed reaction contribute equally to the overall reactions at pH 3.1. It can be shown that general acid catalysts with values of pK_a as close as possible to 3.1 will be (for a given stoicheiometric concentration) the most effective in enhancing the observed rate constant, and that such enhancement will be greatest at a pH intermediate between pH 3.1 and pH = pK_a of catalyst. We chose methoxyacetic acid (pK_a 3.50 at 50 °C) buffer solutions of which do not absorb strongly at 220 nm, the wavelength used for measurement. Rate coefficients for runs at pH 3.25 are in Table 4. Runs at higher pH were

TABLE 4

Rate coefficients for cyclisation of *N*-(methylaminocarbonyl)glycine in methoxyacetic acid buffers at 50 °C. Ionic strength 0.2M, pH 3.25

[HA] [a]/M	0	0.05	0.1	0.15	0.18	0.20	0.22	0.25
$10^7 k_{obs.}$/s^{-1}	4.0	5.2	5.6	6.8	7.2	7.5	7.7	7.6

[a] Total concentration of methoxyacetic acid.

precluded by the slowness of the reaction, and at lower pH the enhancement of the observed rate coefficient above the background reaction would have been even less. The catalytic constant is 2.7 (±0.2) × 10^{-6} l mol^{-1} s^{-1}. Together with the rate constant k_2 for hydrogen ion catalysis (Table 3) it leads to a Brønsted exponent α 0.47 for the reaction. The severe constraints on suitable catalysts and conditions limited us to this one study, and the Brønsted exponent is therefore highly approximate. The failure of Stella and Higuchi [2] to observe general acid catalysis in similar reactions can be attributed to the choice of non-optimum conditions.

The substrate itself probably acts as a general acid catalyst, but this is unlikely at the concentrations employed to contribute significantly to the overall reaction, and should not affect the deduced catalytic constant for methoxyacetic acid because initial rates were studied, and the catalytic constant comes from the enhancement over the background section in the absence of catalyst under the same conditions.

The Kinetics of Oxygen Exchange of 3-Methylimidazolidine-2,4-dione with Solvent Water.—Mass spectrometric analysis of 3-methylimidazolidine-2,4-dione extracted from solutions containing excess $H_2{}^{18}O$ showed substantial increase with time of the ($M^+ + 2$) peak, but not of the ($M^+ + 4$) peak, relative to the molecular ion peak (M^+): thus only one oxygen atom was exchanging. This was assumed to be the amide oxygen rather than the urea oxygen because urea does not exchange under similar conditions [13] and because *N*-methylsuccinimide exchanges both its oxygens at a similar rate to the present substrate under identical conditions.[14]

First-order rate coefficients for oxygen exchange deduced from the $(M^+ + 2)/[(M^+) + (M^+ + 2)]$ peak area ratio of each of 2—4 samples taken after 0.2—2 half-lives for exchange were in satisfactory agreement; details are in Table 5. The oxygen exchange is clearly acid catalysed.

TABLE 5

Rate constants for oxygen exchange of 3-methylimidazolidine-2,4-dione in aqueous acid

Acid	Atom % $H_2{}^{18}O$	n [a]	T/K	$(10^6\ k/s^{-1})$ [b]
40% H_2SO_4	19.8	4	298	3.9 (±0.6)
1M-HCl	18.8	2	298	0.73 (±0.1) [c]
1M-HCl	19.1	2	323	9.0 (±0.4) [c]

[a] Number of samples. [b] Observed first-order rate constants for ^{18}O exchange. [c] Activation parameters derived from these results are $\Delta H^{\ddagger}$ 78 (±4) kJ mol^{-1} and $\Delta S^{\ddagger}$ −100 (±12) J mol^{-1} K^{-1}.

Attempt to detect Any N-(*Methylaminocarbonyl*)*glycine when Equilibrium with* 3-*Methylimidazolidine*-2,4-*dione has been reached.*—A solution containing 3-methylimidazolidine-2,4-dione (1M) in HCl (1M), left for 10 half-lives for the ring closure reaction at 25 °C was titrated with standard alkali. The acid concentration was found to be 1.000 (±0.001)M. It follows that the equilibrium constant for reaction (i) is $>10^3$ in 1M-HCl.

Solvent Isotope Effect.—The rate constants (Table 2) for hydrolysis in 1M-HCl in H_2O (mean of four determinations) and in 1M-DCl in D_2O (mean of two determinations) lead to the ratio k_{H_2O}/k_{D_2O} 0.87.

Kinetics of Alkaline Hydrolysis of 3-*Methylimidazolidine*-2,4-*dione.*—There is a change from a second-order to a zeroth-order dependence of k_{obs} on $[OH^-]$ as the pH increases, at pH *ca.* 13 as found by others and attributable [7] to the fortuitous near coincidence of the pH at which occurs a change in rate-determining step (from breakdown of the dianionic tetrahedral intermediate to hydroxide ion attack on the neutral substrate) and pre-equilibrium ionisation of the substrate. Such a mechanism leads [7] to equation (v).

TABLE 6

Rate coefficients for alkaline hydrolysis of 3-methylimidazolidine-2,4-dione at 298 K. Ionic strength 0.2M

$[OH^-]$/M	$k_{obs.}$/s^{-1}	$k_{calc.}$/s^{-1} [a]
2.0×10^{-3}	7.0×10^{-6}	7.2×10^{-6}
5.0×10^{-3}	3.6×10^{-5}	4.3×10^{-5}
7.0×10^{-3}	8.4×10^{-5}	8.2×10^{-5}
1.0×10^{-2}	1.64×10^{-4}	1.61×10^{-4}
3.0×10^{-2}	1.20×10^{-3}	1.12×10^{-3}
5.0×10^{-2}	2.5×10^{-3}	2.5×10^{-3}
7.0×10^{-2}	4.2×10^{-3}	3.9×10^{-3}
9.0×10^{-2}	6.1×10^{-3}	5.4×10^{-3}
0.10	6.5×10^{-3}	6.1×10^{-3}
0.11	7.4×10^{-3}	6.8×10^{-3}
0.13	8.0×10^{-3}	8.1×10^{-3}
0.16	1.03×10^{-2}	0.99×10^{-2}
0.19	1.07×10^{-2}	1.15×10^{-2}
0.20	1.33×10^{-2}	1.20×10^{-2}

[a] Calculated as described in the text.

$$k_{obs.} = \frac{a[OH^-]^2}{\{1 + (K_a/K_\omega([OH^-]\}(1 + b[OH^-])} \quad (v)$$

We evaluated the constants a and b from a least-square correlation of $([OH^-]^2/(k_{obs.}\{1 + (K_a/K_\omega)[OH^-]\}$ and $[OH^-]$. Weights were assigned, assuming a constant percentage error in $k_{obs.}$ and negligible error in $[OH^-]$, as $\{1 + (K_a/K_\omega)\text{-}[OH^-]\}^3/[OH^-]^4$. This led to a 1.85 (±0.04) l^2 mol^{-2} s^{-1} and b 7.6 (±2.5) l mol^{-1}, corresponding in the terminology of ref. 7 to k_3k_1/k_{-1} and k_3/k_{-1}, respectively. The discrepencies between these and previous results [7] are due to the different ionic strength at which the runs were conducted, and to the different weightings we attached to individual datum points. Rate constants calculated using our values of a and b in equation (v) are compared with observed values in Table 6.

We note that with 3-arylimidazoline-2,4-diones,[15] a first-order rather than a second-order dependence of rate constant for hydrolysis on hydroxide ion concentration is observed even at pH as low as 9. The paper includes a useful survey of the literature on alkaline hydrolysis of amides.

DISCUSSION

The Acid-catalysed Cyclisation Mechanism.—The key observation is that the rate constant for oxygen exchange of 3-methylimidazolidine-2,4-dione is only 15 times smaller than that for cyclisation of *N*-(methylaminocarbonyl)glycine in 1M-HCl. If step E (Scheme) were rate determining, the rate constant for oxygen exchange would be half that for ring opening, and the equilibrium constant for reaction (i) would be 30. Titration of an equilibrated system shows the equilibrium constant to be $>10^3$. Step E is not rate determing, which is surprising because in the reverse direction it would represent rate-determining attack of water on the *O*-protonated amide, the mechanism of acid-catalysed amide hydrolysis.[16] Even more closely analogous is lactam formation from 3-(2-aminophenyl)propionic acid, where E is held to be rate limiting.[17] We attribute the difference to the very low basicity of the terminal nitrogen of the reactant in the present case. The rate constant for acid-catalysed proton exchange in *N*-methylurea [18] leads [19] to an estimate of the pK_a of (1; R = Me) protonated on the terminal nitrogen, of −3, and thence [20] of the pK_a for $T_+ \rightleftharpoons T_o$ (Scheme) of −6.3. Hydronium ion assisted loss of OH^- from T_o (step E) could well be faster than its *N*-protonation, leaving step A rate determining, with a transition state (3). The Jencks' rule [21] for a concerted process is met, and the zwitterionic intermediate $T_\pm$ which in this case has an exceptionally good leaving group, is bypassed because it is too unstable to exist. The observed general acid catalysis is thus explained, as is the fact that the terminal methyl substituent in the reactant provides a 50-fold rate enhancement (our results compared with those in ref. 2) because in (3) there is a partial positive change on nitrogen.

The other two experimental observations on the acid catalysed reaction, the linear dependence of the logarithm of the rate constant upon $-H_o$ (slope 0.87) and the solvent isotope effect (k_H/k_D 0.87) are consistent with step A [transition state (3)] being rate determining. The fractionation factors for protons in reactants and transition state can be estimated [22] to be ϕ_a 0.69, ϕ_b 1.0, ϕ_c 0.92, ϕ_d 0.83, ϕ_e 0.4, ϕ_f 1.2, ϕ_g 0.97. These lead to the prediction $k_H/k_D = \phi_a{}^3\phi_b\phi_c/\phi_d{}^2\phi_e\phi_f\phi_g = 0.94$, satisfactorily close to the observed value. The isotope effect is inverse even though a proton is in flight in the transition state. (The proton on the central nitrogen of the reac-

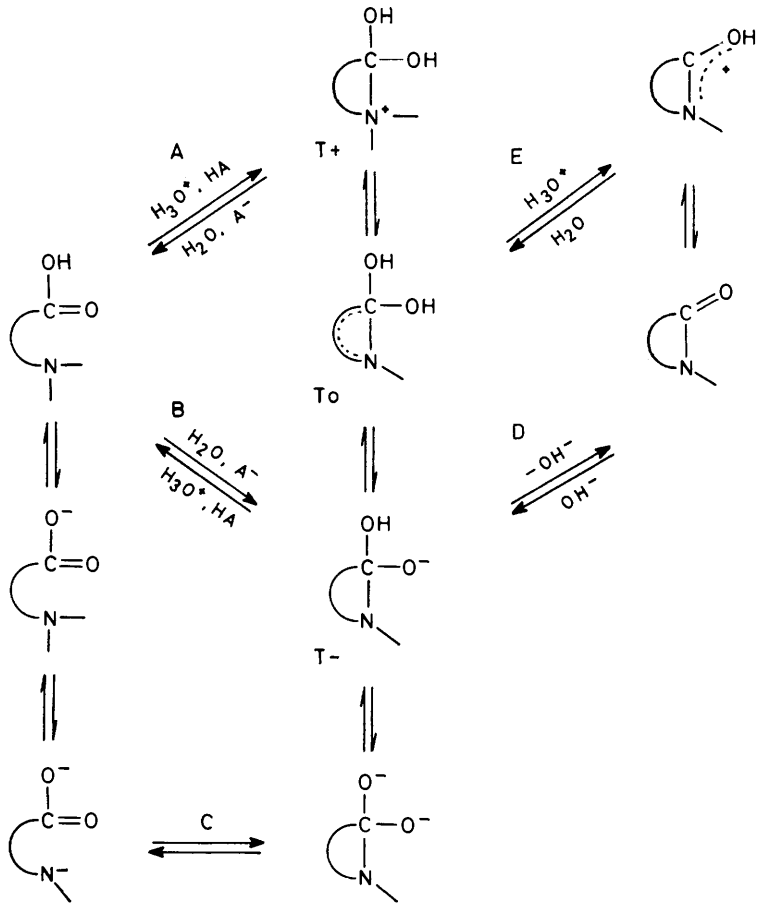
tant is ignored because its fractionation factor is unlikely to change significantly.)

The fact that acid-catalysed oxygen exchange of (2) occurs without ring opening is not in conflict with the theory of stereoelectronic control [23] because the nitrogen lone pair will be antiperiplanar to an equal extent with the bands to the two hydroxy groups of T_o (Scheme).

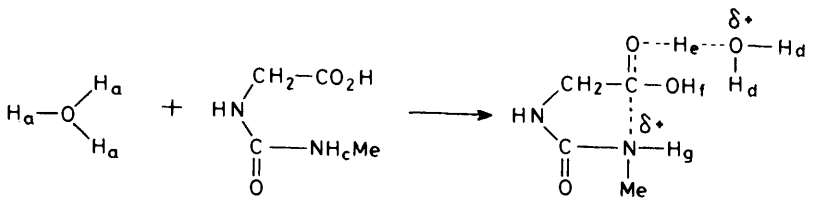
The Uncatalysed Cyclisation Reaction.—This reaction was too slow for detailed study but we speculate that it could be rate limited by step B (Scheme). In the reverse direction this corresponds to general acid catalysed breakdown of T_-, a pathway recognised [24] in amide hydrolysis.

The Alkaline Hydrolysis Reaction.—The mechanism is already well established,[3,8] with rate limitation by step C (pH < 13) or step D (pH > 13).

The Equilibrium Constant for Reaction (i).—The kinetics of alkaline hydrolysis indicate that reaction proceeds to completion at values of pH down to 11.3. We estimate that >10% of 3-methylimidazolidine-2,4-dione remaining at equilibrium would have detectably perturbed the kinetics, leading to the limit of $<10^6$ for the equilibrium constant for reaction (i) when account is taken of the ionisation of (1). The equilibrium constant is therefore in the range 10^3—10^6 at 298 K. [A closer estimate could be made if reaction (i) were allowed to



SCHEME



(3)

come to equilibrium at pH *ca.* 7, but our kinetic results indicate that ten half-lives for the reaction would be at least 5 years, and could be 500 years.]

EXPERIMENTAL

N-(Methylaminocarbonyl)glycine.—To glycine (7.5 g) in 0.1M-sodium hydroxide solution (100 cm^3) at room temperature was added slowly with stirring a solution of methyl isocyanate (6.3 g) in dried acetonitrile (20 cm^3). The pH of the solution was kept between 8 and 9 by simultaneous addition of 2M-sodium hydroxide solution. Thirty minutes after completion of the addition some water was removed under reduced pressure. The residue has passed through acidified Zeokarb 225 resin (50 g). Evaporation of the eluent gave *N*-(methylaminocarbonyl)glycine which was recrystallised from ethanol (yield based on glycine 80%), m.p. 153 °C (lit.,[25] 147—148 °C) (Found: C, 36.2; H, 6.0; N, 21.0. Calc. for $C_4H_8N_2O_3$: C, 36.4; H, 6.1; N, 21.2%).

3-Methylimidazolidine-2,4-dione.— *N*-(Methylaminocarbonyl(glycine (8 g) in trifluoroacetic acid (100 cm^3) was refluxed for 1 h. Removal of trifluoroacetic acid under vacuum and recrystallisation from ethanol–water (50 : 1) gave 3-methylimidazolidine-2,4-dione, m.p. 180° (Found: C, 41.9; H, 5.3; N, 24.3. Calc. for $C_4H_6N_2O_2$: C, 42.1; H, 5.3; N, 24.6%).

Protonation Equilibria.—An aqueous solution of *N*-(methylaminocarbonyl)glycine or of 3-methylimidazolidine-2,4-dione was added by syringe (50 μl) to a 10 mm cuvette containing aqueous sulphuric acid (2.5 cm^3). Absorbances at several wavelengths in the ranges 200—215 nm or 210—230 nm for the two compounds, respectively, were measured. The pK_a values of *N*-(methylaminocarbonyl)glycine and of methoxyacetic acid were determined from several measurements of pH of solution between one-quarter and three-quarters neutralised; the ionic strength was maintained at 0.2M with potassium chloride.

Kinetics.—The increase in absorbance at 220 nm of a solution of *N*-(methylaminocarbonyl)glycine initially 2.6×10^{-4}M or 7.7×10^{-3}M in aqueous acid was monitored. The lower concentration was used for the faster reactions, which were followed for 3—4 half-lives (infinity readings after 7—8 half-lives); reactions were first order and rate constants were obtained by computer. For the slower reactions, the higher concentration was used which gave an initial absorbance of 0.8; the increase with time to *ca.* 1.0 was monitored and rate constants estimated using a calculated infinity absorbance, derived by proportion from the runs using lower concentrations. This method was used for the runs in Table 4 and for those indicated in Table 2.

The alkaline hydrolysis of 3-methylimidazolidine-2,4-dione was monitored from the decrease in absorbance at 220 nm of a solution containing initially 4×10^{-4}M-substrate. The initial rate method was used only for the slowest run.

The Kinetics of ^{18}O Exchange of 3-Methylimidazolidine-2,4-dione in Acid.—Solutions were prepared by weight from $H_2{}^{18}O$ (20.1 atom %) and either 98% H_2SO_4 or 36.7% HCl, to give solutions containing 19.8 and 18.8 atom %, respectively. The sulphuric acid remained unenriched under the conditions of the experiment.[26] 3-Methylimidazolidine-2,4-dione was added (1M). Each of several tubes were filled with the solution, sealed, and immersed in a thermostat for the appropriate time. The substrate was recovered either by neutralisation, evaporation, and vacuum sublimation, or by extraction with dichloromethane and evaporation. Mass spectra were recorded (Micromass model MM 16F).

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