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Kinetics and mechanism of the cyclization of ω-(*p*-nitrophenyl)-hydantoic acid amides: steric hindrance to proton transfer causes a 10^4-fold change in rate †

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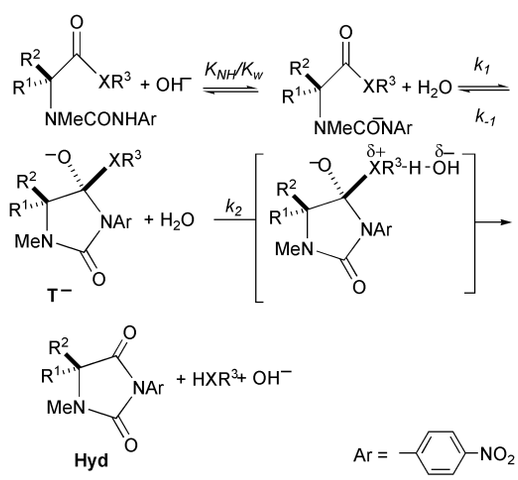
The pH-rate profiles for the cyclization of primary 2,3-dimethyl and 2,2,3-trimethyl-hydantoinamides (**2-UAm** and **3-UAm** respectively) differ strikingly from those for the cyclizations of the corresponding *N*-methylated amides **2-MUAm** and **3-MUAm**; which are dominated by the water reaction, spanning some 6 pH units. For the cyclization of **UAm** the plateau extends over no more than two pH units. The difference is due to the slower base-catalyzed cyclization of the *N*-methylamides. The solvent kinetic isotope effect for this hydroxide-catalyzed reaction is close to 1.2, consistent with a slow protonation by water of the amino-group of the negatively charged tetrahedral intermediate. General base catalysis was observed with bases of pK_{BH^+} up to 8. The Brønsted β are compatible with a hydrogen bonding mechanism for the GBC. In the gem-dimethyl compounds **3** the leaving group is flanked by substituents on both sides. The *N*-methyl group in **3-MUAm** hinders frontal access of the proton, causing a 14000 fold decrease in rate. This is only 3800 fold in the compound with one methyl group at position 2.

One of the main problems in studying chemical reactions to mimic *in vivo* processes is that they are very slow under biologically relevant conditions. Attaching the reactants to the same molecule converts bond forming reactions into cyclizations; the consequent entropic gain, reinforced by thermodynamically favourable ring formation, can bring about accelerations of up to 10^8-fold.[1] Reaction can be made faster still by introducing steric strain in the substrate, and a convenient way to do this is by introducing substituents into the interconnecting chain: the resulting increase in rate defines the gem-dimethyl effect (GDME).[2]

In a series of papers[3–5] on the cyclization of hydantoate‡ esters, **UE**, however, unexpected behaviour was observed in the OH- catalyzed reaction.§ When all hydrogens in the chain were replaced by methyl groups, structure **3**, the GDME either disappeared or was reversed, as a result of a change of mechanism. These observations were explained by steric hindrance slowing down proton transfer to the leaving ethoxy group, and thus making k_2 in Scheme 1 the rate determining step (rds) as opposed to k_1 in esters **1-UE** and **2-UE**. This does not happen upon acid catalysis going through $\mathbf{T}^+$¶ because only $\mathbf{T}^-$ is so unstable that protonation competes with heavy atom reorganization. When the ester OEt group was replaced by OH, in the permethylated acid **3-UAc**, a normal GDME and no change of mechanism (*i.e.* rate determining formation of $\mathbf{T}^-$) was observed.[6] Evidently the replacement opened sufficient access to the leaving group that protonation did not become the slow step.

In the case of hydantoic amides the amino group is a poorer leaving group and its protonation in $\mathbf{T}^-$ is usually rate determining under base catalysis.[7,8] Because of the similarities in steric requirements of esters and methylamides on the one hand and acids and unsubstituted amides on the other, the presence of an *N*-methyl group in structure **3** should similarly hinder the approach of the proton. In this case the expected result is simply a decrease in the reaction rate since proton donation to the leaving group already is rate limiting. The present paper identifies this effect and shows it to be remarkably strong: the ratio of the corresponding rate constants for **3-UAm** and for **3-MUAm** amounts to four powers of ten.



Structure	R^1	R^2	Compound	X	R^3
1	H	H	**UAm**	NH	H
2	Me	H	**MUAm**	NH	Me
3	Me	Me	**UAc**	O	H
			UE	O	Et

Scheme 1

Experimental

Uncorrected melting points were measured in capillaries, IR spectra on a Specord IR 75 or Bruker IFS 113v instrument, UV spectra on a Specord UV Vis or a UNICAM SP 800 spectrophotometer, and NMR spectra on a Bruker DRX 250 instru-

† Electronic supplementary information (ESI) available: Observed first-order rate coefficients, constants for solvent and buffer catalysis for the cyclization reactions. See http://www.rsc.org/suppdata/ob/b2/b211040g/

‡ The IUPAC name for hydantoic acid is ureidoacetic acid or *N*-carbamoylglycine.

§ The study encompassed also 5-methyl and 5-phenyl hydantoic esters, refs. 3 and 4

¶ According to ref. 6 most likely the amino group is positively charged.

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ment. Chemical shifts are quoted in ppm as δ values against TMS and couplings in Hz.

Materials

Inorganic reagents and buffer components were of analytical grade and used without further purification. Potassium hydroxide and buffer solutions were prepared with CO_2-free distilled water. D2O, 99 atom%, was from Aldrich.The preparations of 1,5-dimethyl-3-(4-nitrophenyl)hydantoin‖ and 1,5,5-trimethyl-3-(4-nitrophenyl)hydantoin have been described previously.[7]

3-Methyl-5-(4-nitrophenyl)hydantoinamides

The parent amides of 2-methylaminopropionic acid and 2-methylaminoisobutyric acid were prepared from the respective esters as described in ref. 7 and papers quoted therein. Several days in a saturated ammonia solution in methanol at room temperature were needed to complete conversion conveniently followed by IR of the dry residues. Literature melting points were obtained after crystallization from $CHCl_3$. The methylamino amides were treated with *p*-nitrophenylisocyanate in dry benzene as described in ref. 7 and used without further recrystallization because of their ready cyclization.

2-(1′-Methyl -3′-(4-nitrophenyl)ureido)propionamide. Yield 25%, mp 90 °C, $\lambda_{max}(H_2O)$/nm 330 nm, ν_{max}/cm^{-1} 3315 and 3175 (NH), 1690 (CO_{urea}), 1640 (CO_{amide}); δ_H (DMSO-d_6) 1.273 (3H, d, J 7.1, 2-Me), 2.903 (3H, s, 1′-Me), 4.710 (1H, q, *J* 7.2, 2-H), 7.763 (2H, d, *J* 9.2, *o*-H), 8.1458 (2H, d, *J* 9.2, *m*-H), 7.356 and 7.0557 (1H, s, NH_{amide}, hindered rotation, exchangeable with D_2O), 9.0260 (1H, s, NH_{urea}); MS electrospray M^+ + Na 289.0921

2-Methyl-2-(1′-methyl -3′-(4-nitrophenyl)ureido)propionamide. Yield 20%, mp 146–148 °C, $\lambda_{max}(H_2O)$/nm 330 nm, ν_{max}/cm^{-1} 3440 and 3270 (NH), 1680 (CO_{urea}), 1660 (CO_{amide}); δ_H (DMSO-d_6)** 1.347 (3H, s, 2-Me), 2.991 (3H, s, 1′-Me), 7.717 (2H, d, *J* 9.5, *o*-H), 8.130 (2H, d, *J* 9.5, *m*-H), 6.9 br s (1H) 6.6 br s (1H); MS CI M^+ + 1, 281.3.

Kinetic measurements

These were carried out as described previously.[7] Due to the ready conversion of **3-UAm** into hydantoin in DMSO, stock solutions were freshly prepared before each experiment. Multiple scan spectra taken during the course of the cyclization showed good isosbestic points and the infinity spectra ($10\tau_{1/2}$) were found to be identical with the spectra of the respective 3-(4-nitrophenyl)hydantoins at the same concentration. A "clean" reaction was also supported by well-behaved first order kinetics. In the case of **2-UAm** the kinetics at pH > 7 were complicated by partial hydrolysis of the product hydantoin: this process reached an equilibrium with the respective hydantoic acid (see Results). Solvent kinetic isotope effects were determined as described previously.[6]

Results

The data described in the Experimental Section show that the hydantoinamides are coverted quantitatively into hydantoins. This could occur directly (Scheme 1) or in two consecutive steps: hydrolysis of the hydantoinamides to hydantoic acids followed by cyclization of the latter. Our recent results with acids **2-UAc** and **3-UAc** show that they cyclize faster than the amides in most of the pH-range studied. Thus the kinetic data can not exclude participation of this second pathway, which has been observed by Machácek *et al.*[9] with some simple hydantoin amides when cyclization is slow. However, such participation can be confidently eliminated upon consideration of the rates involved. The second order rate constant for alkaline hydrolysis of hydantoinamide itself can be estimated as 2×10^{-4} dm^3 mol^{-1} s^{-1} from the data of ref. 9 while the second order rate constant for OH--catalyzed cyclization of **2-UAm** is about 1×10^4 dm^3 mol^{-1} s^{-1}. The sterically hindered amides studied in this paper should be hydrolyzed much more slowly than unsubstituted hydantoinamide as is well documented with carboxylic acid derivatives. Furthermore, the reaction of **3-UAm** compared to **2-UAm** (*vide infra*) is faster due to the GDME specific to cyclization reactions.

At pH-values above 7 the change of absorbance of **2-UAm** with time takes the form depicted in Fig. 1. This is due to the consecutive reactions:[7]

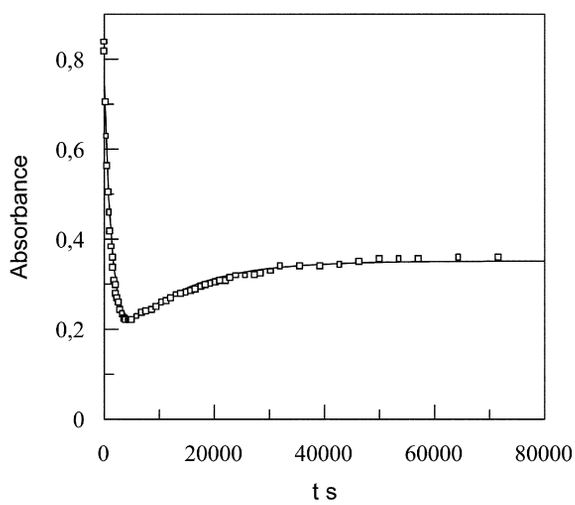


Fig. 1 The change of absorbance of **2-UAm** with time in a 0.008 M Tris buffer at 0.5 fraction base pH 8.30 (I = 1 M KCl) at 25.0 °C. The line is calculated using eqn. (2) and the rate constants reported in Table 1 and ref. 6.

$$\text{2-UAm} \xrightarrow[(-NH_3)]{k_{12}} \text{2-Hyd} \underset{k_{32}(-OH^-)}{\overset{k_{23}(+OH^-)}{\rightleftharpoons}} \text{2-UAc}^- \qquad (1)$$

Since the extinction coefficients of amide and acid are practically the same, the rate constants of the integrated kinetic equation of the system can be readily determined from curves as that of Fig. 1, using the following eqn. (2):

$$A_t = A_{eq} + \frac{\Delta A(a-c)e^{-at}}{b-a} + \frac{\Delta A a(b-c)e^{-bt}}{b(b-a)} \qquad (2)$$

Here A_t and A_{eq} are the absorbances at times t and infinity, $\Delta A = (\varepsilon_H - \varepsilon_A)C_0$ where ε_H and ε_A are the extinction coefficients of **Hyd** and **UAm** or **UAc** (3600 dm^3 mol^{-1} cm^{-1} and 13600 dm^3 mol^{-1} cm^{-1} respectively at 330 nm), C_0 the initial amide concentration, $a = k_{12}$, $b = k_{23} + k_{32}$ and $c = k_{32}$, the pseudo-first-order rates at the specific pH. In order to reduce the number of parameters fitted k_{23} and k_{32} were calculated from the rate constants and equations given in ref. 6 using K_e = **[Hyd]**[a_{OH}]/**[UAc]** = 4.44×10^{-6}. Thus k_{12} and A_{eq} were treated as adjustable parameters in nonlinear curve fitting by means of the GRAFIT program. For 0.9 fraction base (FB) phosphate and 0.1, 0.2 and 0.3 FB Tris only the first part of the curve shown on Fig. 1 was monitored, and the data treated by means of eqn. (2), to correct for deviations caused by participation of the second reaction.

The pH-rate profiles

The rate profiles for the cyclization of the hydantoic acid amide

‖ The IUPAC name for hydantoin is imidazolidine-2,4-dione.
** Due to the relatively rapid cyclization in DMSO the spectra show also the signals of product hydantoin.

Table 1 Rate constants for H^+, OH^- and H_2O catalyzed ring closure of amides of 5-(4-nitrophenyl)hydantoic acids at 25.0 °C and ionic strength 1.0 M

Compound	k_H/dm^3 mol^{-1}s^{-1}	k_w/s^{-1}	k_{OH}/dm^3 mol^{-1}s^{-1}
2-UAm[a]	$(2.24 \pm 0.25) \times 10^{-4}$	$(6.33 \pm 0.46) \times 10^{-6}$	$(1.17 \pm 0.08) \times 10^{4}$
3-UAm	$(1.60 \pm 0.12) \times 10^{-2}$	$(6.47 \pm 0.73) \times 10^{-5}$	$(1.12 \pm 0.08) \times 10^{6}$

[a] Parameters calculated by means of eqn. (3) omitting data in phosphate at FB 0.8 and 0.9 and Tris buffers.

Table 2 Buffer catalysis data for the cyclization of the amide 2,3-dimethyl-5-(4-nitrophenyl)hydantoic acid, **2-UAm**, at 25.0 °C and ionic strength 1.0 M

Buffer acid	pK_a[a]	Conc. range[b]/mol dm^{-3}	FB[c]	k_B/dm^{3}mol^{-1}s^{-1}[b]
$H_3N^+CH_2CO_2H$	2.45	0.01–1	0.3	[d]
		0.01–1	0.5	
		0.01–1	0.7	
		0.01–1	0.9	
HCO_2H	3.57	0.01–1	0.3	$(6.67 \pm 0.82) \times 10^{-5}$
		0.01–1	0.7	
CH_3CO_2H	4.62	0.01–1	0.3	$(3.47 \pm 0.50) \times 10^{-4}$
		0.01–1	0.7	
		0.01–1	0.9	
$(CH_3)AsO_2H$	6.19	0.01–0.15	0.3	$(7.02 \pm 0.45) \times 10^{-3}$
		0.01–0.15	0.5	
		0.01–0.15	0.7	
$H_2PO_4^-$	6.48	0.016–0.2	0.1	0.0196 ± 0.010[f]
		0.032–0.6	0.3	$k_{BOH} = (2.22 \pm 0.32) \times 10^5$
		0.032–0.5	0.5	
		0.0032–0.4	0.7	
		0.0016–0.008	0.8	
		0.0016–0.008	0.84[e]	
		0.0016–0.008	0.9	
Tris	8.42	0.0016–0.008	0.1	0.121 ± 0.012[g]
		0.0016–0.008	0.2	
		0.0016–0.008	0.3	
		0.0016–0.008	0.5	
		0.0016–0.008	0.7	
HPO_4^{-2}	12.32			508[h]

[a] pK_a-values at ionic strength 1 M from ref. 13. [b] Four or more runs carried out within each concentration range. [c] The fractions base of glycine and formate buffers were corrected for the change in pH with dilution. The initial FB values are quoted in the Table. [d] See text. [e] Determined from pH. [f] Calculated by means of eqn. (6), $k_{2OH} = (7{,}49 \pm 0.82) \times 10^6$. [g] Calculated from a linear fit of k_{buff} against FB. [h] Calculated from k_{BOH}.

Table 3 Buffer catalysis data for the cyclization of the amide of 2,2,3-trimethyl-5-(4-nitrophenyl)hydantoic acid, **3-UAm**, at 25.0 °C and ionic strength 1.0 M (KCl)

Buffer acid	pK_a[a]	Conc. range[b] mol dm^3	f.b.[c]	k_B/dm^{3}mol^{-1}s^{-1}
$H_3N+CH_2CO_2H$	2.45	0.01–1	0.3	$(5.53 \pm 0.65) \times 10^{-4}$[d]
		0.01–1	0.5	
		0.01–1	0.7	
		0.01–1	0.9	
HCO_2H	3.57	0.01–1	0.3	$(2.24 \pm 0.14) \times 10^{-3}$
		0.01–1	0.5	
		0.01–1	0.7	
		0.01–1	0.9	
CH_3CO_2H	4.62	0.01–1	0.3	0.0203 ± 0.0011
		0.01–1	0.5	
		0.01–1	0.7	
		0.01–1	0.9	
$H_2PO_4^-$	6.48	0.016-0.2	0.1	0.927 ± 0.035
		0.016-0.2	0.3	

[a] pK_a-values from ref. 13. [b] Four or more runs carried out within each concentration range. [c] The fractions base of glycine and formate buffers were corrected for the change in pH with dilution. The initial FB values are quoted in the Table. [d] See text.

2-UAm and **3-UAm** are k_0-values extrapolated to zero buffer concentration from the buffer experiments listed in Tables 2 and 3††, above. In the case of **2-UAm** above pH 7 these are the k_{12}-values discussed above. For the HCl solutions, activities, instead of the usual convention of concentrations, were used to bring these in line with the buffer data. An activity coefficient of 0.851 at $I = 1$ M KCl was used[7].

In the pH range studied the two hydantoinamides **2-UAm** and **3-UAm** gave rise to simple rate profiles (Fig. 2) with slopes of −1, 0 and 1 for H_3O^+, water and OH^--catalyzed reactions respectively:

†† All observed pseudo-first-order rate constants are available as electronic supplementary information (ESI)†.

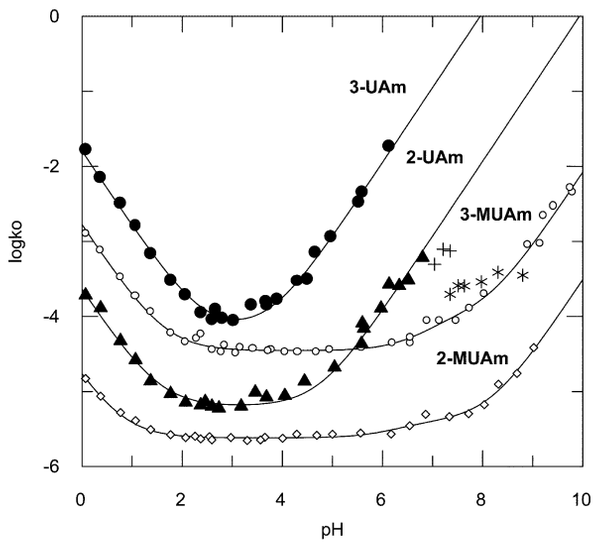


Fig. 2 pH-rate profiles for: **2-UAm** (triangles: also +: data in 0.8–0.9M phosphate and *: in Tris buffers) **3-UAm** (closed circles) **2-MUAm** (diamonds) and **3-MUAm** (open circles).

$$k_{obs} = k_H a_H + k_w + k_{OH} a_{OH} \quad (3)$$

In the case of **2-UAm**, however, the data obtained in phosphate buffers with >80% free base suggested a leveling of the rate increase with a_{OH}. Attempts to expand the pH-rate profile by studying the reaction in Tris buffers proved unsuccessful because the k_0-values in the latter were found to be about three times smaller than those obtained at the same pH in phosphate buffers (Fig. 2). This can be attributed to inhibition by the amine component of the buffer as has been observed in similar reactions.[10] In some cases[11] inhibition affects only k_0. This seems to be the present case as judged from the altogether "normal" behaviour of the k_{buff} versus fraction free base plot shown on Fig. 3.

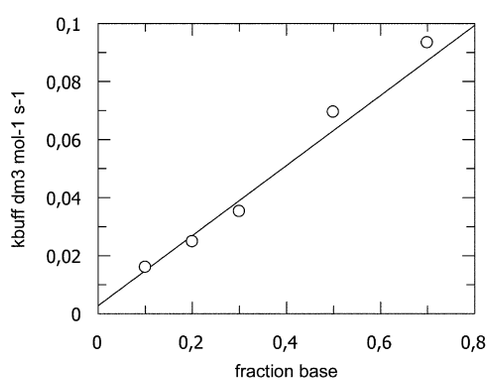


Fig. 3 Plot of k_{buff} in Tris buffers against fraction base.

The complication in Tris buffers compromised attempts for kinetic analysis of the deviation from linearity of the data for k_0 in phosphate buffers at FB greater than 0.8. For this reason the rate constants for **2-UAm** were derived by means of the simple eqn. (3) from the data collected in buffers more acidic than 0.8 FB phosphate. These, together with the results for **3-UAm**, are listed in Table 1.

Solvent kinetic isotope effects, k^H/k^D, SKIE, were measured for the alkaline reaction in 0.002 M phosphate buffers at 0.3 FB for **2-UAm** and 0.2 FB for **3-UAm** are shown in Table 4. Under these conditions buffer catalysis is less than 10% of the total reaction.

General base catalysis

Buffer catalysis was clearly apparent in all cases studied. The cyclization of amide **3-UAm** was studied in glycine, formate, acetate and phosphate buffers. For **2-UAm** the buffer range was extended to cacodylate and Tris. With the more acidic glycine and formate buffers pH increased upon dilution and the changes in pH and % free base were calculated as described previously.[3] The kinetic behaviour of the substrates in buffers was examined as follows. The rates determined at a certain buffer ratio were plotted against total buffer concentration. These plots were linear allowing the intercept k_0 and the slope k_{buff} to be obtained from a least squares fit. The k_{buff} *vs.* FB plots were also reasonably linear as demonstrated by the example of Fig. 3. The intercepts at fraction base 0 and 1 equal the rate constants for general acid and general base catalysis (GBC) respectively. No general acid catalysis, GAC, was observed and in this case the slope of a linear plot k_{buff} against FB equals k_B. The kinetics are thus described by eqn. (4):

$$k_{obs} = k_H a_H + k_w + k_{OH} a_{OH} + k_B[B] \quad (4)$$

Two exceptions to this straightforward behaviour were observed. In the case of **2-UAm** in phosphate buffer catalysis increased much more rapidly than the linear dependence on percentage of free base expected for simple GBC (Fig. 4a).

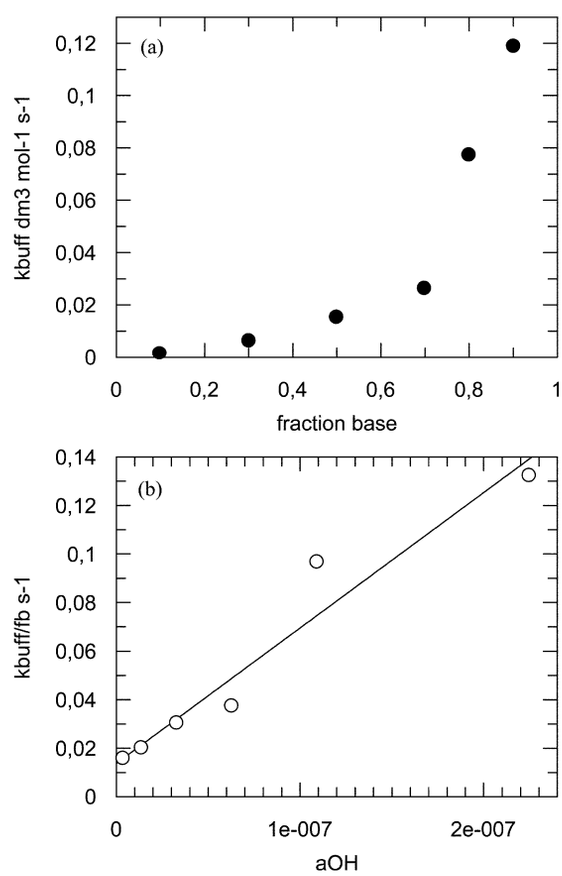


Fig. 4 (a) Plot of k_{buff} determined in phosphate buffers against fraction free base (FB). (b) Plot of k_{buff}/(fraction base) against hydroxide ion activity, a_{OH}.

The rising curve in Fig. 4a can be accommodated by adding a cross term $k_{BOH}[B]a_{OH}$.

As [B] = [buffer]FB

$$k_{buff}[buffer] = k_B[buff]FB + k_{BOH} a_{OH}[buffer]FB$$

then

$$k_{buff}/FB = k_B + k_{BOH} a_{OH} \quad (5)$$

The validity of eqn. (5) is illustrated by Fig. 4b. The most likely cause for the form of this equation is catalysis[3] by the phosphate trianion, PO_4^{-3} its concentration being proportional to $[HPO_4^{-2}]$ and $[OH^-]$ because of the equilibrium:

$$HPO_4^{2-} + OH^- \overset{K_{HPO_4^{2-}}/K_w}{\rightleftharpoons} PO_4^{2-} + H_2O$$

Therefore:

$$k_{BOH} = k_{phos}\frac{K_{HPO_4^{2-}}}{K_w}$$

where k_{phos} is the rate constant for catalysis by PO_4^{3-}.

A similar upward deviation from linearity was found for **2-UAm** in glycine buffers. The data, however, could not be accommodated by any simple equation derived for similar situations observed with hydantoic esters[5,12] and acids.[5] The pH of glycine buffers coincides with a region where the pH-rate profile changes its slope from 0 to 1 indicating a change in mechanism as the likely cause for non-linearity of the plot. With **3-UAm** the extent of the plateau is much smaller and eqn. (4) describes the data in glycine satisfactorily.

The rate constants for GBC listed in Tables 2 and 3, were obtained by a multivariable fit to eqn. (4) of the entire data set for a given buffer. In this way any variation of pH at constant FB was accounted for. The constants for specific catalysis, determined from the rate profile, were inserted as known parameters. For phosphate catalysis in the case of **2-UAm** eqn. (6) was used which includes the above cross term and the apparent leveling off in catalysis by the solvent species is accounted for by a denominator term:

$$k_{obs} = \frac{k_w + k_{OH}a_{OH}}{1 + k_{2OH}a_{OH}} + k_B[B] + k_{BOH}a_{OH}[B] \qquad (6)$$

Values of k_w and k_{OH} were taken from the rate profile and the remaining three constants determined as adjustable parameters. The rate constant for catalysis by Tris is the slope of the linear dependence k_{buff}/FB shown in Fig. 3.

Brønsted plots of the statistically corrected rate constants for GBC are presented in Fig. 5. In order to avoid the strong influence of the widely spaced points for water (k_w/55.5) and hydroxide anion the slopes of the linear fits, the Brønsted

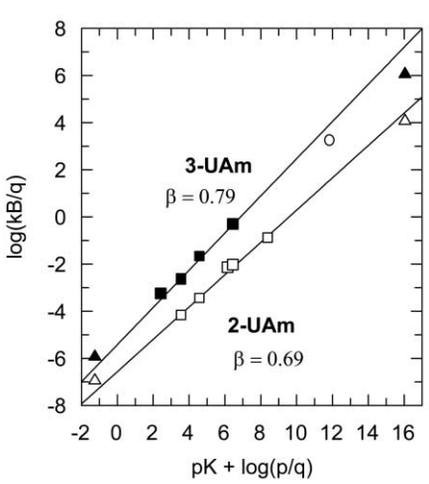


Fig. 5 Brønsted plots for GBC of the cyclization of hydantoinamides: open symbols **2-UAm**, closed symbols **3-UAm**. Squares represent catalytic constants listed in Table 2 and Table 3, circle the deviant point for PO_4^{3-}, triangles the data for water and OH^- catalysis. Least squares lines are drawn to fit the squares (see Table 4).

Table 4 Brønsted β-values for GBC of hydantoinamides and solvent kinetic isotope effects in phosphate buffers

Compound	β-values	pH[a]	k_{OH}/k_{OD}[b]
2-UAm	0.69[c]	5.95	1.28
3-UAm	0.79[d]	5.88	1.21

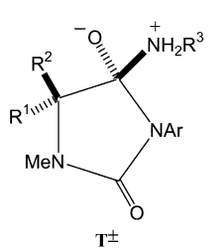
[a] Average value in H_2O of the SKIE experiments. [b] See Experimental. [c] From linear regression of data for catalysis by formate, acetate, cacodylate, monohydrogenphosphate and Tris ($r = 0.996$). [d] From linear regression of data for catalysis by formate, acetate and monohydrogenphosphate ($r = 0.998$). Inclusion of the point for glycine yields $\beta = 0.75$.

β-values were calculated using only the rate data for the "general" bases listed in Tables 2 and 3. The results of these excellent linear correlations are summarized in Table 4.

Discussion

Mechanism

In our previous report[7] on the cyclization of hydantoinmethylamides detailed evidence indicated that the hump in the **MUAm** rate profiles between pH 6 and 8 (Fig. 2) is due to a change in the rate determining step from k_1K_{NH}/K_w to k_2 (Scheme 1), resulting in two parallel reactions catalyzed by water and two reactions catalyzed by OH^-. In the present case of **UAm** only a single OH^- reaction is observed in the pH-region studied.‡‡ The similarity in Brønsted plots for GBC and SKIE represented in Table 4 leaves little doubt that the mechanism of cyclization of the two compounds is the same. For the reaction catalyzed by bases in general and that catalyzed by OH^- the mechanistic criteria: β-values and SKIE are best met by a hydrogen bonding mechanism for the former and trapping of an unstable intermediate for the second.[14] When diffusion controlled proton transfer is rate limiting in the so-called trapping of unstable intermediates, their further instability enforces preassociation[15] of the substrate and the catalyzing acid or base because proton transfer within the complex can proceed faster than diffusion. This rapid donation or abstraction of a proton can prevent the intermediate from returning to reactants and direct its transformation to products. Hydrogen bonding can stabilize the preassociation complex and so further lower the energy of the transition state. The dipolar tetrahedral intermediate $\mathbf{T}^{\pm}$ is such a highly unstable intermediate:



$\mathbf{T}^{\pm}$

The α- or β-values for hydrogen bonding equilibria are around 0.2 and similar values are expected for GBC by hydrogen bonding. Catalysis by the general base of the overall reaction can be formulated in the following manner (charges of base species are omitted):

$$\begin{aligned} UAm + OH^- &\overset{K_{T^-}}{\rightleftharpoons} T^- \\ T^- + BH &\xrightarrow{k_{BH}} P \end{aligned} \qquad (7)$$

‡‡ The apparent leveling in the pH-rate profile upon increasing pH cannot be interpreted unambiguously.

When $V = k_{BH}[T^-][BH]$ it can be readily shown from eqn. (7) that for the experimentally observed GBC, eqn. (8):

$$UAm + B \xrightarrow{k_B} P \qquad (8)$$

$$V = k_B[\mathbf{UAm}][B]$$

$$k_B = \frac{k_{BH}}{K_{BH}} K_w K_{T^-}$$

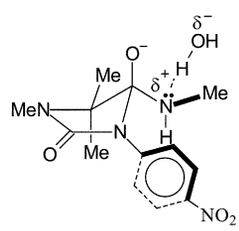
$\beta = 1 - \alpha$ because β for an ionization equilibrium, K_{BH}, is unity.Thus with $\alpha = 0.2$ a β-value of 0.8 is expected for the overall GBC eqn (8). The β-values listed in Table 4 are a little smaller than 0.8, but still compatible with hydrogen bonding.

The values of the solvent kinetic isotope effect in Table 4 apply for the OH^--catalyzed reaction where BH is a water molecule. The amino group in $\mathbf{T}^-$ should have a pK of about 8.4§§ so the proton donation by H_2O is an endothermic reaction for which a preassociation or hydrogen bonding mechanism is no longer possible. Simple proton transfer to $\mathbf{T}^-$ is the most likely mechanism. Such transfers are characterized by a SKIE of *ca.*1.2¶¶ when the participating acid and bases differ considerably in pK and this is consistent with the values found for **UAm**.||||

The chosen mechanism for the observed OH^- catalyzed cyclization of **UAm** coincides with the mechanism assigned to the OH^- catalyzed reaction of the *N*-methyl derivatives **MUAm** at higher pH. The remaining two reactions, acid and water catalyzed cyclization of **UAm** were not our main focus of attention. Our previous study on **MUAm** left the question of the rds of the acid reaction without a definite answer. Two mechanisms involving slow proton transfers were assigned to the two water-catalyzed reactions: deprotonation of the *p*-nitrophenylureido group concerted with formation of $\mathbf{T}^-$ and secondly, a rate determining water-mediated switch converting $\mathbf{T}^0$ into $\mathbf{T}^{\pm}$.

Steric hindrance to proton transfer

The major difference in the rate profiles of **UAm** and the *N*-methyl derivatives **MUAm** demonstrated in Fig. 2 is due formally to the much larger decrease in k_{OH} for alkaline cyclization for the latter, compared with the remaining constants. A decrease in the rate upon *N*-methylation is often observed in similar cyclizations and is due to an increase of steric strain in the tetrahedral intermediates. The effect on the rate is typically 5–100-fold: examples involving simple hydantoinamides are provided by the work of Šterba and coworkers.[9] Methylation of the amide group slows down alkaline cyclization five-fold for 3-methylhydantoinamide and 15-fold for 3,5-dimethylhydantoinamide. These are very similar to the ratios k_{UAm}/k_{MUAm} listed in Table 5 for the acid and water catalyzed cyclizations. Bearing in mind the well-established assumption in physical organic chemistry[17] that steric effects are closely similar in the acid and base catalyzed hydrolysis of carboxylic acid derivatives, the drastically greater effect for k_{OH} cannot be explained in terms of additional steric strain within $\mathbf{T}^-$. We consider, as suggested previously for the corresponding reactions of hydantoic acid esters, that steric hindrance to proton transfer to the leaving group is the basis of the unusual behaviour of the *gem*-dimethyl derivatives **3**. Structure **TS-3-MUAm** shows how the amino group is flanked on one side by the geminal methyl groups and on the other by the aryl group, **** with the *N*-methyl group barring the water molecule from the most accessible route from the front side of the nitrogen atom.



TS-3-MUAm

When the *N*-methyl group is removed in *gem*-dimethyl derivative **3-MUAm** the acceleration is 14000-fold, a rate increase that is spectacular even though it contains a contribution from steric strain in $\mathbf{T}^-$ (a factor of 10–15-fold is suggested by the results from k_H). Interestingly the effect, 3600-fold, of removing the *N*-methyl group in the derivative with the monomethylated side chain **2-MUAm** is still very large. This indicates that even a single methyl group at the α-carbon atoms can exert considerable hindrance to proton transfer to the methylamino group.

The lower k_{UAm}/k_{MUAm} ratios observed for the catalytic constants for GBC are not surprising because in a hydrogen-bonding mechanism the rate determining step does not involve the proton transfer itself, which is very fast, but formation and breakdown of $\mathbf{T}^-$ within the hydrogen bonded complex.

Table 5 Ratio of the rate constants of the primary (**UAm**) and secondary (**MUAm**) 5-(p-nitrophenyl)hydantoinamides[a]

Reaction	$k_{2\text{-UAm}}/k_{2\text{-MUAm}}$	$k_{3\text{-UAm}}/k_{3\text{-MUAm}}$
k_H	15	10
k_w[b]	3	2
k_{OH}[c]	3800	14000
$k_{H2N^+CH2CO2^-}$		15
k_{HCO2^-}	34	37
k_{CH3CO2^-}	58	164
k_{HPO4^-}	127	260
k_{Tris}	49	

[a] Data for **MUAm** from ref. 7. [b] Comparison with k_w of ref. 7. [c] Comparison with k_{OH}^b of ref. 7.

§§ For the *N*-methyl analogues we estimated previously[7] a pK of 8.7, using the procedure of Fox and Jencks.[16a] The reduction of 0.3 is based on Taylor's[16b] compilation of pK-values of amines with *geminal* substituents. The difference between NH_2 and NHMe averages to 0.31.

¶¶ Due to the change of viscosity with temperature.

|||| Depending on the life-time of the intermediate another possibility is a concerted mechanism but this particular proton transfer step goes however against Jencks's libido rule.

**** According to the crystal structure of a hydantoin derivative[18] the aryl group is twisted about 70° out of plane. Molecular mechanics on the tetrahedral intermediate in a related system yield a much smaller value of *ca.* 25° (unpublished results).

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