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

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Received 11th November 2002, Accepted 27th January 2003

First published as an Advance Article on the web 12th February 2003

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 \(pK_a\) up to 8. The Brønsted \(\beta\) 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\(^4\)-fold. 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). In a series of papers 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 T\(^+\) because only 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 T\(^-\)) was observed. 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 T\(^-\) is usually rate determining under base catalysis. 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.

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-
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 CO2-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-methylaminosobutyric 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 recrystallization from CHCl3. 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, δmax(H2O)/nm 330 nm, νmax/cm−1 3315 and 3175 (NH), 1690 (COmax), 1640 (COmin); δ (DMSO-d6) 1.273 (3H, d, d J 7.1, 2-Me), 2.903 (3H, s, 1-Me), 4.710 (1H, q, δ 9.5, 2-Me), 7.763 (2H, d, d J 9.2, 2-Me), 8.1458 (2H, d, d J 9.2, 2-Me), 9.9156 (2H, d, d J 9.3, 2-Me), 10.250 (1H, br s). MS electrospray M+ + Na 289.0921

2-Methyl-2-(1’-methyl -3’-(4-nitrophenyl)ureido)propionamide. Yield 20%, mp 146–148 °C, δmax(H2O)/nm 330 nm, νmax/cm−1 3440 and 3270 (NH), 1680 (COmax), 1660 (COmin); δ (DMSO-d6) 1.347 (3H, d, d J 7.1, 2-Me), 2.991 (3H, s, 1-Me), 6.717 (2H, d, d J 9.5, 2-Me), 8.130 (2H, d, d J 9.5, 2-Me), 6.9 br s (1H) 6.6 br s (1H); MS CI M+ + Na 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 (105εmax) 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 converted 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

|| 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.

[Image 326x340 to 521x365]

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.

2-UAm \( \frac{k_{\text{obs}}}{2} \xrightarrow{\text{2-Hyd}} 2\text{-UAc} \)

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):

\[
A_\tau = A_0 + \frac{\Delta A (a-c) e^{-\alpha t}}{b-a} + \frac{\Delta A (b-c) e^{-\beta t}}{b-a}
\]

Here \( A_\tau \) and \( A_0 \) are the absorbances at times \( t \) and infinity, \( \Delta A = (\epsilon_{\text{Ac}} - \epsilon_{\text{Am}})C_0 \) where \( \epsilon_{\text{Am}} \) and \( \epsilon_{\text{Ac}} \) are the extinction coefficients of Hyd and UAm or UAc (3600 dm3 mol−1 cm−1 and 13600 dm3 mol−1 cm−1 respectively at 330 nm), \( C_0 \) the initial amide concentration, \( a = k_{12} \) \( b = k_{23} \) and \( c = k_{12} \), the pseudo-first-order rates at the specific pH. In order to determine the number of parameters fitted \( k_{12} \) and \( k_{13} \) were calculated from the rate constants and equations given in ref. 6 using \( K_c = [\text{Hyd}][\text{Iont}]/[\text{UAc}] = 4.44 \times 10^{-4} \). Thus \( k_{12} \) and \( A_{\text{kin}} \) 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...
Table 1  Rate constants for H⁺, OH⁻ and H₂O catalyzed ring closure of amides of 5-(4-nitrophenyl)hydantoic acids at 25.0 °C and ionic strength 1.0 M.

<table>
<thead>
<tr>
<th>Compound</th>
<th>kᵢ/µmol⁻¹s⁻¹</th>
<th>kᵢ/s⁻¹</th>
<th>kᵢ/kᵢ⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-UAm</td>
<td>(2.24 ± 0.25) × 10⁻¹</td>
<td>(6.33 ± 0.46) × 10⁻⁴</td>
<td>(1.17 ± 0.08) × 10⁶</td>
</tr>
<tr>
<td>3-UAm</td>
<td>(1.60 ± 0.12) × 10⁻¹</td>
<td>(6.47 ± 0.73) × 10⁻⁴</td>
<td>(1.12 ± 0.08) × 10⁶</td>
</tr>
</tbody>
</table>

"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.

<table>
<thead>
<tr>
<th>Buffer acid</th>
<th>pKᵢ⁺</th>
<th>Conc. range/M ω mol dm⁻³</th>
<th>FB⁻</th>
<th>kᵢ/µmol⁻¹s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂N′CH₂CO₂H</td>
<td>2.45</td>
<td>0.01-1</td>
<td>0.3</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01-1</td>
<td>0.3</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01-1</td>
<td>0.7</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01-1</td>
<td>0.9</td>
<td>d</td>
</tr>
<tr>
<td>HCO₂H</td>
<td>3.57</td>
<td>0.01-1</td>
<td>0.3</td>
<td>(6.67 ± 0.82) × 10⁻⁵</td>
</tr>
<tr>
<td>CH₂CO₂H</td>
<td>4.62</td>
<td>0.01-1</td>
<td>0.3</td>
<td>(3.47 ± 0.50) × 10⁻⁴</td>
</tr>
<tr>
<td>CH₃AsO₂H</td>
<td>6.19</td>
<td>0.01-0.15</td>
<td>0.3</td>
<td>(7.02 ± 0.45) × 10⁻³</td>
</tr>
<tr>
<td>H₂PO₄⁻</td>
<td>6.48</td>
<td>0.016-0.2</td>
<td>0.1</td>
<td>0.0196 ± 0.0100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.032-0.6</td>
<td>0.3</td>
<td>0.0196 ± 0.0100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.032-0.5</td>
<td>0.5</td>
<td>0.0196 ± 0.0100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0016-0.008</td>
<td>0.7</td>
<td>0.0196 ± 0.0100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0016-0.008</td>
<td>0.8</td>
<td>0.0196 ± 0.0100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0016-0.008</td>
<td>0.84</td>
<td>0.0196 ± 0.0100</td>
</tr>
<tr>
<td>Tris</td>
<td>8.42</td>
<td>0.0016-0.008</td>
<td>0.1</td>
<td>0.121 ± 0.0124</td>
</tr>
<tr>
<td>HPO₄²⁻</td>
<td>12.32</td>
<td>0.0016-0.008</td>
<td>0.2</td>
<td>0.121 ± 0.0124</td>
</tr>
</tbody>
</table>

"pKᵢ⁺ values at ionic strength 1 M from ref. 13. 4 Four or more runs carried out within each concentration range. 5 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. 6 See text. 7 Calculated from pH. 8 Determined from pKᵢ⁺. 9 Calculated from pH.

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

<table>
<thead>
<tr>
<th>Buffer acid</th>
<th>pKᵢ⁺</th>
<th>Conc. range/M ω mol dm⁻³</th>
<th>FB⁻</th>
<th>kᵢ/µmol⁻¹s⁻¹</th>
</tr>
</thead>
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<tr>
<td>H₂N′CH₂CO₂H</td>
<td>2.45</td>
<td>0.01-1</td>
<td>0.3</td>
<td>(5.53 ± 0.65) × 10⁻⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01-1</td>
<td>0.5</td>
<td>(5.53 ± 0.65) × 10⁻⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01-1</td>
<td>0.7</td>
<td>(5.53 ± 0.65) × 10⁻⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01-1</td>
<td>0.9</td>
<td>(5.53 ± 0.65) × 10⁻⁴</td>
</tr>
<tr>
<td>HCO₂H</td>
<td>3.57</td>
<td>0.01-1</td>
<td>0.6</td>
<td>(2.24 ± 0.14) × 10⁻³</td>
</tr>
<tr>
<td>CH₂CO₂H</td>
<td>4.62</td>
<td>0.01-1</td>
<td>0.3</td>
<td>0.0203 ± 0.0011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01-1</td>
<td>0.5</td>
<td>0.0203 ± 0.0011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01-1</td>
<td>0.7</td>
<td>0.0203 ± 0.0011</td>
</tr>
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<td></td>
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<td>0.01-1</td>
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<td>0.0203 ± 0.0011</td>
</tr>
<tr>
<td>H₂PO₄⁻</td>
<td>6.48</td>
<td>0.016-0.2</td>
<td>0.1</td>
<td>0.927 ± 0.035</td>
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"pKᵢ⁺ values from ref. 13. 4 Four or more runs carried out within each concentration range. 5 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. 6 See text.

2-UAm and 3-UAm are kᵢ-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 kᵢ-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 hydantoimides 2-UAm and 3-UAm gave rise to simple rate profiles (Fig. 2) with slopes of −1, 0 and 1 for H₂O⁻, water and OH⁻ catalyzed reactions respectively:
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. 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 \( k_{\text{buff}} \) to be obtained from a least squares fit. The \( k_{\text{buff}} \) 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 \( k_{\text{buff}} \) against FB equals \( k_0 \). The kinetics are thus described by eqn. (4):

\[
k_{\text{obs}} = k_{\text{obs}} + k_w + k_{\text{OH}^+}\text{OH}^-
\]

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).

The rising curve in Fig. 4a can be accommodated by adding a cross term \( k_{\text{BOH}[B]}[\text{OH}^-] \). As \([B] = [\text{buffer}][FB]\)

\[
k_{\text{obs}}\text{[buffer]} = k_{\text{obs}} + k_{\text{OH}^+}[\text{OH}^-][\text{buffer}][FB]
\]

then

\[
k_{\text{obs}}/\text{FB} = k_0 + k_{\text{OH}^+}[\text{OH}^-]
\]

General base catalysis

Buffer catalysis was clearly apparent in all cases studied. The
The validity of eqn. (5) is illustrated by Fig. 4b. The most likely cause for this form of the equation is catalysis by the phosphate trianion, $\text{PO}_4^{3-}$, its concentration being proportional to $[\text{HPO}_4^{2-}]$ and $[\text{OH}^-]$ because of the equilibrium:

$$\text{HPO}_4^{2-} + \text{OH}^- \rightleftharpoons k_{\text{FF}} \frac{K_{\text{HPO}_4^{2-}}}{K_w} \text{PO}_4^{3-} + \text{H}_2\text{O}$$

Therefore:

$$k_{\beta} = k_{\text{FF}} = \frac{k_{\text{HPO}_4^{2-}}}{k_w}$$

where $k_{\text{HPO}_4^{2-}}$ is the rate constant for catalysis by $\text{PO}_4^{3-}$.

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 and acids. 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 regression analysis. 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:

$$k_{\beta} = \frac{k_u \left(1 + K_{\text{OH}^-} \alpha_{\text{OH}}[\text{OH}^-]ight)}{1 + K_{\text{OH}^-} \alpha_{\text{OH}}[\text{OH}^-]} = k_u + k_{\text{OH}^-} \alpha_{\text{OH}}[\text{OH}^-]$$

Values of $k_u$ and $k_{\text{OH}^-}$ 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 line.

$\beta$-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):

$$\text{UAm} + \text{OH}^- \rightleftharpoons T^+ \text{NH}_3^+$$

$\beta$-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 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 $k_1K_{\text{OH}^-}/k_2$ to $k_3$ (Scheme 1), resulting in two parallel reactions catalyzed by water and two reactions catalyzed by $\text{OH}^-$. In the present case of UAm only a single $\text{OH}^-$ 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 $\text{OH}^-$ the mechanistic criteria: $\beta$-values and SKIE are best met by a hydrogen bonding mechanism for the former and trapping of an unstable intermediate for the second. When diffusion controlled proton transfer is rate limiting in the so-called trapping of unstable intermediates, their further instability enforces preassociation, 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 $T^+$ is such a highly unstable intermediate:

$$\text{T}^+ + \text{BH} \rightarrow \text{P}$$

Table 4: Brønsted $\beta$-values for GBC of hydantoinamides and solvent isotope effects in phosphate buffers

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\beta$-values</th>
<th>pH$^*$</th>
<th>$k_{\text{OD}}/k_{\text{H}_2\text{O}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-UAm</td>
<td>0.69$^*$</td>
<td>5.95</td>
<td>1.28</td>
</tr>
<tr>
<td>3-UAm</td>
<td>0.79$^*$</td>
<td>5.88</td>
<td>1.21</td>
</tr>
</tbody>
</table>

$^*$ Average value in H$_2$O of the SKIE experiments. See Experimental.

From linear regression of data for catalysis by formate, acetate, cacoxydate, mono-hydrogenophosphate and Tris ($r = 0.996$). From linear regression of data for catalysis by formate, acetate and monohydrogenophosphate ($r = 0.998$). Inclusion of the point for glycine yields $\beta = 0.75$.

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 $\text{PO}_4^{3-}$, triangles the data for water and $\text{OH}^-$ catalysis. Least squares lines are drawn to fit the squares (see Table 4).
When \( V = k_{\text{obs}}T^2[B] \) it can be readily shown from eqn. (7) that for the experimentally observed GBC, eqn. (8):

\[
U_{\text{Am}} + B \xrightarrow{h^+} P
\]

\[
V = k_1[U_{\text{Am}}][B]
\]

\[
\beta = 1 - a \text{ because } \beta \text{ for an ionization equilibrium, } K_{\text{eq}} \text{, is unit-}
\]

\[
\text{y. Thus with } a = 0.2 \text{ a } \beta \text{-value of 0.8 is expected for the overall GBC eqn (8). The } \beta \text{-values listed in Table 4 are a little smaller than 0.8, but still compatible with hydrogen bonding.}
\]

The values of the soluble kinetic isotope effect in Table 4 apply for the OH \(-\) catalyzed reaction where BH is a water molecule. The amino group in \( T^- \) should have a pK of about 8.4\( \dagger\dagger \) 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 \( T^- \) is the most likely mechanism. Transfers are characterized by a SKIE of ca 1.2\( \dagger\dagger \) when the participating acid and bases differ considerably in pK and this is consistent with the values found for \( U_{\text{Am}} \).\[\dagger\dagger\]

The chosen mechanism for the observed OH \(-\) catalyzed cyclization of \( U_{\text{Am}} \) coincides with the mechanism assigned to the \( OH^- \) catalyzed reaction of the N-methyl derivatives 2-MUAm at higher pH. The remaining two reactions, acid and water catalyzed cyclization of \( U_{\text{Am}} \) were not our main focus of attention. Our previous study on \( U_{\text{Am}} \) 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 \( T^- \) and secondly, a rate determining water-mediated switch converting \( T^\circ \) into \( T^- \).

Steric hindrance to proton transfer

The major difference in the rate profiles of \( U_{\text{Am}} \) and the N-methyl derivatives 2-MUAm demonstrated in Fig. 2 is due formally to the much larger decrease in \( k_{\text{obs}} \) 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 hydantoimiamides are provided by the work of Sterba and coworkers.\( \dagger\dagger \) Methylation of the amide group slows down alkaline cyclization five-fold for 3-methylhydantoimiamide and 15-fold for 3,5-dimethylhydantoimiamide. These are very similar to the ratios \( k_{\text{M}}/k_{\text{HM}} \) listed in Table 5 for the acid and water catalyzed cyclizations. Bearing in mind the well-established assumption in physical organic chemistry\( \dagger\dagger \) that steric effects are closely similar in the acid and base catalyzed hydrolysis of carboxylic acid derivatives, the drastically greater effect for \( k_{\text{obs}} \) cannot be explained in terms of additional steric strain within \( T^- \). 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

\[\dagger\dagger\] For the N-methyl analogues we estimated previously\( \dagger \) a pK of 8.7, using the procedure of Fox and Jencks.\( \dagger \dagger \) The reduction of 0.3 is based on Taylor’s\( \dagger \dagger \) compilation of pK-values of amines with geminal substituents. The difference between NH and NHMe averages to 0.31.

\[\dagger\dagger\] Due to the change of viscosity with temperature.\[\dagger\dagger\] 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.

\[\dagger\dagger\] According to the crystal structure of a hydantoin derivative\( \dagger \) 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).

Acknowledgements

We thank the Bulgarian Academy of Sciences for support and the Royal Society for travel funds and Dr I. B. Blagoeva for helpful discussions.

References


Table 5 Ratio of the rate constants of the primary (UAm) and secondary (MUAm) 5-(p-nitrophenyl)hydantoimiamides

<table>
<thead>
<tr>
<th>Reaction</th>
<th>( k_{2-MUAm}/k_{3-MUAm} )</th>
<th>( k_{3-MUAm}/k_{5-MUAm} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_{\text{obs}} )</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>( k_{\text{obs}} )</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>( k_{\text{H}2O} )</td>
<td>3800</td>
<td>14000</td>
</tr>
<tr>
<td>( k_{\text{2-MUAm} - CHCO}_2 )</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>( k_{\text{CHCO}}_2 )</td>
<td>58</td>
<td>164</td>
</tr>
<tr>
<td>( k_{\text{HPO}}_4 )</td>
<td>127</td>
<td>260</td>
</tr>
<tr>
<td>( k_{\text{H}_{2}N} )</td>
<td>49</td>
<td>22</td>
</tr>
</tbody>
</table>

\( ^a \) Data for \( U_{\text{Am}} \) from ref. 7. \( ^b \) Comparison with \( k_{\text{obs}} \) of ref. 7. \( ^c \) Comparison with \( k_{\text{H}2O} \) of ref. 7.


