A large gem-dimethyl effect in the cyclization of \(\omega\)-phenylhydantoic acids: computational modeling of the gem-dimethyl effect on the acid- or base-catalyzed cyclization of hydantoic acids and esters

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ABSTRACT: The rates of the cyclization of methyl-substituted 5-phenylhydantoic acids were measured in acid solutions. A particularly strong gem-dimethyl effect (GDME) was observed with the \(N\)-methyl compounds amounting to an acceleration of six powers of ten for the 2,2,3-trimethyl derivative. The variations in the free energies of activation for the cyclization of hydantoic acids and esters were modeled by the strain energies of the tetrahedral intermediates and of the reactants calculated by the MM3 force field. The neutral tetrahedral intermediate \(T^0\) was used for reaction series involving acid catalysis and the negatively charged intermediate \(T^-\) for base catalysis. Very good agreement with the experimental GDME was obtained for the acid-catalyzed cyclizations of the complete series of the \(N\)-methyl-substituted substrates, showing that the accelerations result from a greater strain increase in the reactants. The results with \(T^-\) are closely parallel, indicating that the loss of GDME observed under base catalysis with 2,2,3-trimethylhydantoic esters is not due to intramolecular strain in \(T^-\). A linear correlation (slope 1.22, \(r = 0.934\)) is obtained for a plot of the free energy variations against strain energies for the reaction series of 5-phenylhydantoic acids when the data for the strongly deviating parent acid is excluded. Excellent LFERs are obtained between the reaction series of esters and acids. The observed large rate enhancements induced by \(N\)-substituents explain the switches to cyclization routes in synthetic reactions. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: gem-dimethyl effect; cyclization; hydantoic acids and esters; molecular mechanics; MM3

INTRODUCTION

We report that in acid solutions 2,2,3-trimethyl-5-phenylhydantoic acid cyclizes \(10^6\) times faster than the acid devoid of the three methyl groups. Ingold and co-workers were the first to observe that cyclizations are facilitated by substitution into the chain interconnecting the reacting groups although accelerations are seldom so large. The increase in rate or in ring stability was defined as the Thorpe–Ingold or gem-dimethyl effect (GDME) (the latter term was used by Hammond whereas some authors prefer the term gem-dialkyl effect). The idea of the Thorpe–Ingold that substituents decrease the adjacent bond angle (as far as internal strain in more complex molecules results from various non-bonded interactions, replacing two geminal hydrogens by two methyl groups can sometimes give rise to an increase in the adjacent angle at the quaternary carbon according to x-ray structures of some open-chain compounds), thus favouring the formation of small rings, has received ample experimental confirmation. In ‘normal’ (5–7-membered) rings, the internal bond angles are nearly tetrahedral and their reduction should be of no benefit towards ring formation. However, in normal rings a GDME is also observed. Several reviews have considered the GDME as a part of the general discussion of the origin of intramolecular accelerations in relation to enzyme catalysis. The controversy has not abated for several decades. Concepts such as ‘proximity effect’ or ‘near attack conformations’ attribute the GDME to increase in population of the latter and their similarity to the transition state. In this context, authors have looked for a Thorpe–Ingold compression to bring closer the reacting atoms to form normal rings and found it unimportant. Allinger and Zalkow were the first to expound an alternative view—that substituents in the chain change favourably both the enthalpy and entropy upon cyclization. They predicted the free energies of the formal closure of methylhexanes to methyl-cyclohexanes by counting the unavoidable gauche conformations in the open chain. In the ring, gauche repulsions are lost, becoming part of the ring itself.
Substituents hinder rotation around the bonds so that less entropy is frozen in the ring; this could also be accounted for by an additive scheme. Such a method is quantitatively untenable outside the scope of simple hydrocarbons. We could overcome this by estimating the strain energies from thermochemical data for homomorphic hydrocarbons which correlated with the GDME for a large number of reaction series. Molecular mechanics is, of course, the best method for estimating strain energies, as was demonstrated by the good agreement with the GDME on succinic acid—anhydride equilibria. In the much cited case of the ‘trimethyl lock’ (see formula I) on which Cohen and co-workers based their ‘stereopopulation control’ explanation for the 10^5-fold acceleration, strain has also been shown to be the main driving force. More recent studies have reiterated this conclusion. In similar cases the entropy contribution is not significant and in any case has been shown to be small.

Increasing the stability of cyclic transition states or products by substitution in the chain has found various applications. An early one is increasing the selectivity in acetalization of diketosteroids by use of 2,2-dialkyl-1,3-propanediols. Recently, attention has been drawn to the synthetic implications of the GDME. Agami et al. observed that N-methylation of N-Boc-β-amino alcohols strongly enhances the formation of oxazolidinones. Further examples of preferred heterocyclizations in similar systems have been reviewed. A ‘trimethyl lock’ facilitated lactonization has been used for releasing peptides from cyclic prodrug derivatives.

The high efficiency in cyclization reactions of sterically strained substrates makes them particularly suitable in the study of bioorganic mechanisms under physiologically relevant conditions. In a series of papers, we have widely exploited the effect of alkyl substituents in hydantoic acids and their derivatives in order to obtain reactive compounds for mechanistic studies. The base-catalyzed cyclization of the anion of tetramethylhydantoic acid used as a mimic of the carboxylation of biotin by hydrogencarbonate is an unusual reaction because with less heavy substitution the reverse process, hydrolysis of the hydantoin ring in base, proceeds fully in the opposite direction. The mechanisms of acylation of ureas by carboxy, ester and amide function was studied in detail using strained hydantoic acids and esters and amides. In these studies a remarkable phenomenon was encountered. In the case of ester cyclization under acid catalysis, introduction of methyl groups up to the permethylated ethyl 2,2,3-trimethylhydantoates smoothly increased the rate. Under base catalysis, however, the GDME was lost with the permethylated esters accompanied by a change in mechanism. A similar strong reduction of the rates of cyclization in base for N-methylamides compared with primary amides was observed. Two interpretations were put forward. One assumed that specific repulsions arose in the tetrahedral intermediate for base catalysis. The other attributed the phenomenon to steric hindrance in the permethylated ester causing proton transfer to the leaving ethoxy group to become rate determining. This step is an intermolecular process and no longer subject to the GDME. The second interpretation is supported by the ‘normal’ GDME and preservation of mechanism observed in the base-catalyzed cyclization of a permethylated hydantoic acid because of readier access of the proton donor to the hydroxy group.

An obvious way to check the two hypothesis was to estimate the steric effects arising during acid- and base-catalyzed cyclization of ethyl hydantoates by means of molecular mechanics. An advantage of the MM3 force field in comparison with all other additive molecular mechanics force fields is that MM3 permits strain energies to be determined with an accuracy sufficient to make estimates of steric effects versatile. Molecular mechanics has been used successfully in conformational studies of hydantoins. Previously we have shown that the MM3 force field reproduces successfully the rates of cyclization of 2,3-disubstituted hydantoinic esters by modeling the transition state as the tetrahedral intermediate.

For the purpose of this study, we calculated the strain energies of the ground-state hydantoinic acids or esters and the respective neutral and negatively charged tetrahedral intermediates using the MM3 force field and compared them with the free energies of activation of the cyclization reactions. The structures studied are shown in Scheme 1.

**EXPERIMENTAL**

Uncorrected melting-points were measured in capillaries, UV spectra on a Specord UV-visible or a Unicam SP 800 spectrophotometer and NMR spectra on a Bruker DRX 250 instrument. Chemical shifts are quoted in p.p.m. as δ values against TMS and couplings in hertz.
SYNTHESES

5-Phenylhydantoic acid (2a) and its 2-methyl (2b) and 2,2-dimethyl (2c) derivatives. These compounds are known and were synthesized from the amino acids and phenyl isocyanate by the usual procedure as follows. The amino acid was dissolved in a slight excess of 3M KOH and treated under stirring and ice cooling with an equivalent amount of phenyl isocyanate until a clear solution was obtained. The mixture was left overnight, any diphenylurea filtered off and the solution acidified with HCl (Congo Red) to give colorless crystals. Yields were around 90%. Recrystallization from ethanol–water (1:1) gave literature melting-points. The only exception was 2c, which in our hands melted at 165–166°C in a capillary with decomposition against the reported 117–118°C. 1H NMR: 2a, δ 3.788 (2H, d, 5.8, H2), 6.348 (1H, t, 5.8, H3), 6.894 (1H, tt, 7.3, 1.2, p-H), 7.219 (2H, t, 7.9, m-H), 7.383 (2H, dd, 8.6, 1.2, o-H), 8.75 (1H, s, H5), 12.56 (1H, s broad, CO2H); 2b, δ 4.169 (1H, quintet, 7.2, H2), 6.461 (1H, d, 7.4, H3), 6.892 (1H, tt, 7.3, 1.2, p-H), 7.217 (2H, t, 7.9, m-H), 7.369 (2H, dd, 8.7, 1.1, o-H), 8.87 (1H, s, H5), 11.42 (1H, s broad, CO2H); 2c, δ 1.413 (6H, s, CH3), 6.455 (1H, s, H2), 6.881 (1H, tt, 7.3, 1.2, p-H), 7.189 (2H, t, 7.9, m-H), 7.347 (2H, d, 8.0, o-H), 8.458 (1H, s, H5), 12.35 (1H, s broad, CO2H).

3-Methyl-5-phenylhydantoic acid (2d) and 2,2,3-trimethyl-5-phenylhydantoic acid (2f). A 10−2 M stock solution of 2d as the anion was prepared only in situ by hydrolysis of 1-methyl-3-phenylhydantoin in 0.005 M KOH. A stock solution of 2,2,3-trimethyl-5-phenylhydantoic acid (2f) was also prepared in situ in 1 M KOH by instantaneous cyclization of ethyl 2,2,3-trimethyl-5-phenylhydantoate to 1,5,5-trimethyl-3-phenylhydantoin and subsequent partial hydrolysis of the hydantoin was monitored by UV spectrophotometry.

Kinetic measurements

These were carried out at 25.0°C essentially as described by Blagoeva. The reaction proceeds quantitatively according to UV spectral data. With the more slowly cyclizing 2a, the sealed ampoule technique was used. First-order rate constants, \( k_{\text{obs}} \), were obtained by nonlinear regression curve fitting to the equation \( A_t = A_0 e^{-k_{\text{obs}} t} + A_1 \) by means of the GRAFIT program, where \( A_t, A_0 \) and \( A_1 \) are the absorbances at times \( t \), zero, and infinity, respectively. The results are averages from at least two determinations.

With 2a, 2b and 2c, rates were measured in 1 M HCl. With the faster reacting 2d, rates were obtained in the range 0.2–1 M HCl at ionic strength \( I = 1 \) M (KCl) and the second-order rate constant was calculated from linear plot of \( k_{\text{obs}} \) against [HCl]. In the case of the much faster cyclizing 2f, the rates were measured by mixing in the spectrophotometer cell 1 ml of the stock solution in 1 M KOH with 1.8 ml of an HCl solution of such concentration and KCl content as to obtain 0.001–0.002 M final concentrations of HCl \( [I = 1 \) M (KCl)]). The pH values of the reaction solutions were measured as described previously and the exact concentration of HCl was calculated from a calibration curve pH vs log[HCl].

Molecular mechanics modeling of the steric strain

The computational approach used in previous work was followed. The molecular mechanics modeling was carried out utilizing the MM3 force field and the CONFLEX searcher was used for finding the lowest energy conformations. Partial atomic charges of −0.7 and −0.6 were placed on the O atoms of the tetrahedral intermediates T as determined from AM1 computations of the reference compounds 1a and 3a for the acids and esters, respectively. An effective dielectric constant of 2.0 was used for the estimation of the electrostatic interactions. MOPAC 93.00 was used for the semiempirical molecular orbital calculations.
RESULTS AND DISCUSSION

Table 1 lists the rate constants determined for the cyclization of 5-phenylhydantoic acids. Adding methyl groups at position 2 repeats largely the GDME observed before with the parent hydantoic acids (Table 2); two methyl groups bring about a 50–60-fold acceleration. The effect of 740-fold of a single methyl at the 3-N atom (2d) is impressive, being 37 times more effective than a single methyl at 2-C. With an N-methyl group already present adding more methyl groups, acids 2e and 2f increases the rate 50- and a further 80-fold, respectively. Literature data for the base-catalyzed cyclization of esters (Table 3) show that the effect of a single methyl at 3-N atom upon N-methylation in N-Boc-2-amino alcohols (122.6 → 120.6°). We looked at the bond angles in the product hydantoins according to x-ray structural data. The average value of the bond angle at the 1-N atom was found to be 112° against 122° in the six-membered dihydrouracil.46 There is little doubt that in the transition state some reduction from the open-chain amide angle towards the product angle should take place, making the Thorpe–Ingold effect important. The second contribution is indicated by a significant acceleration of 46-fold observed upon 1'-N-methylation of β-ureidopropionic acid41 in spite of generally 'normal' angles in the product dihydrouracil. We believe this to be due to release of strain of the type discussed by Allinger and Zalkow.10 In Scheme 2, 2a is shown in the favored ZZ-conformation. The favored conformation of 2d should be as shown because Me is smaller than CH2CO2H. When 2d forms T′ the Me group changes its opposition to NHPhi in the open chain to the more favorable one against the carbonyl in the ring and this augments cyclization. The smaller effect with the ω-methyl ester referred to above becomes

Table 1. Rate constants, $k_{\text{H}}$ or $k_{\text{OH}}$ (dm$^3$ mol$^{-1}$ s$^{-1}$), for the cyclization of 5-phenylhydantoic acids in HCl or buffer solutions at 25.0 °C and $I = 1$ M (KCl)

<table>
<thead>
<tr>
<th></th>
<th>2a</th>
<th>2b</th>
<th>2c</th>
<th>2d</th>
<th>2e$^a$</th>
<th>2f</th>
<th>2g$^b$</th>
<th>2h$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{\text{H}}$</td>
<td>3.49 × 10$^{-6}$</td>
<td>7.03 × 10$^{-5}$</td>
<td>1.85 × 10$^{-4}$</td>
<td>2.60 × 10$^{-3}$</td>
<td>0.137</td>
<td>11</td>
<td>4.07 × 10$^{-3}$</td>
<td>0.19</td>
</tr>
<tr>
<td>$k_{\text{OH}}$</td>
<td>1.33 × 10$^{-6}$</td>
<td>1.45 × 10$^{-6}$</td>
<td>2.19 × 10$^{-7}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ From Ref. 22.
$^b$ From Ref. 23.

Table 2. Variation of strain energies (kcal mol$^{-1}$) and free energies of activation (kcal mol$^{-1}$, 298 K), in the acid-catalyzed cyclization of hydantoic acids in aqueous HCl at and ionic strength of 1 M (KCl), with strain energies for T$^-$ in parentheses

<table>
<thead>
<tr>
<th>Compound</th>
<th>$k_{\text{H}}$</th>
<th>$\Delta \Delta G^\ddagger$</th>
<th>$\Delta \Delta E_{\text{strain}}(T^\ddagger)$</th>
<th>$E^\ddagger (E_{T^-})$</th>
<th>$E_{R^\ddagger}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>1$^{a,b}$</td>
<td>0</td>
<td>0</td>
<td>−3.8 (−3.2)</td>
<td>4.8</td>
</tr>
<tr>
<td>1b</td>
<td>11$^b$</td>
<td>−1.4</td>
<td>0.6 (0.5)</td>
<td>−1.2 (−0.7)</td>
<td>6.8</td>
</tr>
<tr>
<td>1c</td>
<td>63$^b$</td>
<td>−2.4</td>
<td>−1.5 (−1.6)</td>
<td>0.1 (0.6)</td>
<td>10.2</td>
</tr>
<tr>
<td>2a</td>
<td>1$^c$</td>
<td>0</td>
<td>0</td>
<td>0.7 (2.1)</td>
<td>16.3</td>
</tr>
<tr>
<td>2b</td>
<td>20</td>
<td>−1.8</td>
<td>1.5 (1.4)</td>
<td>3.4 (4.7)</td>
<td>17.5</td>
</tr>
<tr>
<td>2c</td>
<td>53</td>
<td>−2.4</td>
<td>−0.7 (−0.6)</td>
<td>4.6 (6.1)</td>
<td>20.9</td>
</tr>
<tr>
<td>2d</td>
<td>740</td>
<td>−4.0</td>
<td>−1.5 (−1.6)</td>
<td>−0.7 (0.6)</td>
<td>16.4</td>
</tr>
<tr>
<td>2e</td>
<td>3.9 × 10$^4$</td>
<td>−6.3</td>
<td>−1.8 (−1.7)</td>
<td>2.2 (3.7)</td>
<td>19.6</td>
</tr>
<tr>
<td>2f</td>
<td>3.2 × 10$^6$</td>
<td>−9.0</td>
<td>−4.9 (−4.8)</td>
<td>4.0 (5.5)</td>
<td>24.5</td>
</tr>
</tbody>
</table>

$^a$ $k_{\text{H}}$ 1.5 × 10$^{-7}$ dm$^3$ mol$^{-1}$ s$^{-1}$.
$^b$ Ref. 43.
$^c$ $k_{\text{H}}$ 3.49 × 10$^{-6}$ dm$^3$ mol$^{-1}$ s$^{-1}$.
understandable with NHPh being larger than NHMe and will be more strongly buttressed by the carbonyl.

Further insight into the nature of the GDME in the series studied is gained from the linear free energy relationships (LFER) shown in Fig. 1, between the rates for base catalysis with the esters and for acid catalysis with the free acids. Linearity holds for all but the permethylated compounds, the deviation referred to above as the loss of GDME.

These excellent correlations hold between series with a huge difference in reactivity—the parent ester 4a cyclizes eight powers of ten faster than the parent acid 2a (see second-order constants in footnotes of Tables 2 and 3), indicating very substantial differences in the stabilities and electronic structures of the respective transition states. The two transition states are oppositely charged: positive for acid and negative for base catalysis. If the correlations reflected polar effects, the slope of the

**Table 3.** Variation of strain energies (kcal mol\(^{-1}\)) and free energies of activation (kcal mol\(^{-1}\), 298 K) in the base- and acid-catalyzed cyclization of ethyl hydantoates

<table>
<thead>
<tr>
<th>Compound</th>
<th>(k_{\text{OH}}) or (k_{\text{H}})</th>
<th>(\Delta G_{T}^\ddagger) or (\Delta G_{\text{M}}^\ddagger)</th>
<th>(\Delta E_{\text{strain}}(T^-)) or (\Delta E_{\text{strain}}(T^0))</th>
<th>(E_T^-) or (E_T^0)</th>
<th>(E_{\text{reactant}})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base catalysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>1.0(^{a,b})</td>
<td>0.0</td>
<td>0</td>
<td>-0.7</td>
<td>6.3</td>
</tr>
<tr>
<td>3b</td>
<td>8.0(^{b})</td>
<td>-1.2</td>
<td>2.6</td>
<td>2.0</td>
<td>6.4</td>
</tr>
<tr>
<td>3c</td>
<td>24(^{a}) (1)</td>
<td>-1.9 (0)</td>
<td>-0.9</td>
<td>-2.0</td>
<td>5.9</td>
</tr>
<tr>
<td>3d</td>
<td>2.5 \times 10(^{2}) (10)</td>
<td>-3.3 (-1.4)</td>
<td>-1.7</td>
<td>1.1</td>
<td>9.8</td>
</tr>
<tr>
<td>3e</td>
<td>5.8 \times 10(^{2}) (24)</td>
<td>-3.8 (-1.9)</td>
<td>-6.1</td>
<td>2.9</td>
<td>16.0</td>
</tr>
<tr>
<td><strong>Acid catalysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>1.0(^{a,e})</td>
<td>0.0(^{f})</td>
<td>-0.9(^{g})</td>
<td>-3.4</td>
<td>5.9</td>
</tr>
<tr>
<td>3d</td>
<td>37.0(^{e})</td>
<td>-2.2</td>
<td>-2.1</td>
<td>-0.7</td>
<td>9.8</td>
</tr>
<tr>
<td>3e</td>
<td>2.7 \times 10(^{3})</td>
<td>-4.7</td>
<td>-6.0</td>
<td>1.6</td>
<td>16.0</td>
</tr>
<tr>
<td><strong>Base catalysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>1.0(^{h,b})</td>
<td>0.0</td>
<td>0</td>
<td>5.9</td>
<td>16.6</td>
</tr>
<tr>
<td>4b</td>
<td>18.0(^{b})</td>
<td>-1.7</td>
<td>1.5</td>
<td>8.6</td>
<td>17.8</td>
</tr>
<tr>
<td>4c</td>
<td>3.5 \times 10(^{2}) (1)</td>
<td>-3.5 (0)</td>
<td>-0.1</td>
<td>4.5</td>
<td>15.3</td>
</tr>
<tr>
<td>4d</td>
<td>4.0 \times 10(^{3}) (11)</td>
<td>-5.0 (-1.5)</td>
<td>-1.4</td>
<td>7.3</td>
<td>19.4</td>
</tr>
<tr>
<td>4e</td>
<td>9.0 \times 10(^{2}) (2.6)</td>
<td>-4.0 (-0.5)</td>
<td>-5.0</td>
<td>9.5</td>
<td>25.2</td>
</tr>
<tr>
<td><strong>Acid catalysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4c</td>
<td>1.0(^{e,i})</td>
<td>0.0(^{j})</td>
<td>-0.2(^{k})</td>
<td>0.4</td>
<td>15.3</td>
</tr>
<tr>
<td>4d</td>
<td>32.0(^{e})</td>
<td>-2.1</td>
<td>-1.4</td>
<td>3.3</td>
<td>19.4</td>
</tr>
<tr>
<td>4e</td>
<td>1.2 \times 10(^{3})</td>
<td>-4.3</td>
<td>-4.0</td>
<td>6.5</td>
<td>25.2</td>
</tr>
</tbody>
</table>

\(^a\) \(k_{\text{OH}}\) 1.80 dm\(^3\) mol\(^{-1}\) s\(^{-1}\).
\(^b\) Ref. 50.
\(^c\) Ref. 23a.
\(^d\) \(k_{\text{H}}\) 7.41 \times 10\(^{-4}\) dm\(^3\) mol\(^{-1}\) s\(^{-1}\).
\(^e\) Ref. 24b.
\(^f\) 3c as the reference.
\(^g\) 3a as the reference.
\(^h\) \(k_{\text{OH}}\) 240 dm\(^3\) mol\(^{-1}\) s\(^{-1}\).
\(^i\) \(k_{\text{H}}\) 1.03 \times 10\(^{-4}\) dm\(^3\) mol\(^{-1}\) s\(^{-1}\).
\(^j\) 4c as the reference.
\(^k\) 4a as the reference.
correlation should be negative, contrary to the observed positive slopes. This implies that a significant polar effect of the methyl groups does not tally with the correlation for the same reasons that ortho substituents do not obey the Hammett equation correlating polar effects.

The conversion of hydantoic acid derivatives to hydantoins in aqueous solutions proceeds through tetrahedral intermediates, **T**, as indicated on Scheme 1 both under acid or base catalysis. Depending on the structure and conditions, a wide range of mechanisms have been documented differing according to whether formation or breakdown is rate determining and the fashion in which the concurrent proton transfers are involved. As far as steric effects are concerned, these are usually dominated by the requirements of **T** because of the structural changes accompanying the transformation of the carbonyl sp² C-atom into an sp³ carbon. In this respect, the assumption has been widely accepted that the loss of GDME under hydroxide catalysis does not result from specific repulsions arising in the negatively charged tetrahedral intermediates derived from ethyl 2,2,3-trimethyl-R′-hydantoates 3e and 4e. The phenomenon is due to the crucial role of protonation for the leaving of ethoxy group. The proton donor is a water molecule. In 3e and 4e the ethoxy group is flanked on both sides by the substituents at 5-C and 1-N and access from the front side is hindered by the ethyl group. This suffices for the proton transfer to become rate determining and a change of mechanism takes place. The new rate-determining step is controlled by intermolecular steric hindrance and thus not subject to the GDME.

The agreement between observed rate ratios and calculated strain energies is less good with the compounds not carrying a methyl group on 3-N. The discrepancy between the calculated ∆∆E strain and ∆∆G‡ values is strongly exaggerated by the deviating high value for ∆E strain of 1a, 2a, 3a and 4a used as references in the double differences as demonstrated for 2a in Fig. 2, showing a plot of ∆∆G‡ values for the acid-catalyzed

The variation of the strain energies of 19 compounds for which experimental rate constants at 25 °C are available for either acid- or base-catalyzed cyclization are compared in Tables 2 and 3 with the variation of the free energies of activation.

The results in Table 3 give a definite answer to the question of whether the differences under base and acid catalysis observed in the cyclization of esters are due to different intramolecular steric effects in **T**⁻ and **T**⁺. The GDME in the acid-catalyzed cyclization of esters 3e-e and 4e-e encompasses about three powers of 10 and both are very well predicted by the molecular mechanics calculations. In accord with Allinger’s treatment, the decrease in ∆∆G‡ is due to a larger increase in ground state strain. The GDME calculated for **T**⁻ for the same esters is very similar to that calculated for **T**⁺ and is drastically different from the experimental variation of ∆∆G‡. This strongly supports the conclusion reached before that the loss of GDME under hydroxide catalysis does not result from specific repulsions arising in the negatively charged tetrahedral intermediates derived from ethyl 2,2,3-trimethyl-R'-hydantoates 3e and 4e. The phenomenon is due to the crucial role of protonation for the leaving of ethoxy group. The proton donor is a water molecule. In 3e and 4e the ethoxy group is flanked on both sides by the substituents at 5-C and 1-N and access from the front side is hindered by the ethyl group. This suffices for the proton transfer to become rate determining and a change of mechanism takes place. The new rate-determining step is controlled by intermolecular steric hindrance and thus not subject to the GDME.

The conversion of hydantoic acid derivatives to hydantoins in aqueous solutions proceeds through tetrahedral intermediates, **T**, as indicated on Scheme 1 both under acid or base catalysis. Depending on the structure and conditions, a wide range of mechanisms have been documented differing according to whether formation or breakdown is rate determining and the fashion in which the concurrent proton transfers are involved. As far as steric effects are concerned, these are usually dominated by the requirements of **T** because of the structural changes accompanying the transformation of the carbonyl sp² C-atom into an sp³ carbon. In this respect, the assumption has been widely accepted that the loss of GDME under hydroxide catalysis does not result from specific repulsions arising in the negatively charged tetrahedral intermediates derived from ethyl 2,2,3-trimethyl-R′-hydantoates 3e and 4e. The phenomenon is due to the crucial role of protonation for the leaving of ethoxy group. The proton donor is a water molecule. In 3e and 4e the ethoxy group is flanked on both sides by the substituents at 5-C and 1-N and access from the front side is hindered by the ethyl group. This suffices for the proton transfer to become rate determining and a change of mechanism takes place. The new rate-determining step is controlled by intermolecular steric hindrance and thus not subject to the GDME.
cyclization of hydantoic acids 2 against $\Delta \Delta E_T^0$. When the point for 2a is excluded, a satisfactory linear correlation is obtained: $r = 0.934$, slope = 1.22, implying that with this reaction series the steric interactions are reasonably well modeled by MM3 strain energies of the tetrahedral intermediate. According to Marcus theory, the slope in Fig. 2 should be unity when the intrinsic reaction coordinate is unity and less than unity for an earlier transition state. In the present case, however, if the transition state involves breakdown of T, the slope should be greater than unity because the GDME continues to act until the final ring formation. Finally, it should be noted that kinetic evidence shows the observed rates of cyclizations of hydantoic derivatives to present a balance between ‘specific’ substituent effects and a ‘general’ effect which can be defined in principle by the GDME on the equilibria of the reaction.\(^{49}\) The work of Stella and Higuchi\(^{43}\) on cyclizations in acid of a large set of 2-substituted hydantoic acids showed that the GDME more or less disappeared with substituents larger than methyl. They attributed this to strains arising in the tetrahedral intermediate with the larger substituents overcoming the GDME. With 1a-c (Table 2) they considered the GDME ‘normal’. We observed a similar loss of the GDME in the base-catalyzed cyclization of 2-methyl-3-substituted hydantoic acid esters when $R^3$ was larger than methyl. The rate variations agreed well with MM3 strain energies for reactants and tetrahedral intermediates.\(^{35}\)

**CONCLUSIONS**

The strong accelerations in cyclization rate give a quantitative indication of the synthetic consequences of introducing $N$-substituents by enhancing heterocyclizations. Strain energies of the tetrahedral intermediates and the reactants obtained by means of MM3 agree well with variations of the free energies of activation in cyclization of substituted hydantoic acids and esters. The results obtained strongly support the assumed role of steric hindrance to proton transfer in the mechanism of base-catalyzed cyclization of sterically crowded hydantoic esters.

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