Linear Free Energy–Steric Strain Energy Relationships for the *gem*-Dimethyl Effect. Acid-catalysed Ring Closure of Methyl-substituted 3-Ureidopropionic Acids [1]

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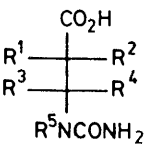
The rate data for the acid-catalysed ring closure of eight methyl-substituted 3-ureidopropionic acids constitute an isokinetic series according to Exner's statistical criteria. Linear relationships were obtained for the free energies in the reaction series for rates and equilibria exhibiting the *gem*-dimethyl effect with steric strain energies estimated from enthalpies of formation of homomorphic hydrocarbons. These estimates were obtained by means of Istomin and Palm's procedure and are of two kinds, the *P* values measuring the total strain energy and $\triangle P$ values measuring the strain between two fragments in the model hydrocarbon. Some reaction series correlated with $\triangle P$ values when one of the functional groups was taken as an invariable fragment and the rest of the molecule as a variable substituent. Other reaction series correlated with *P* values. The approach has the advantage that it takes into account directly the non-additivity of *gauche*-interactions and permits evaluation of the data for substituents at various positions of the chain in a single correlation. For cyclization to five- and six-membered rings, the data form a single reaction series when the rates for the parent compounds are close in value. Only certain hydrocarbon models and manners of fragmentation lead to satisfactory correlations. These, and the correlation with *P* or with $\triangle P$ values, or whether a correlation can be obtained at all, indicate the steric requirements of the reaction and thus its mechanism. Linear relationships with strain energies were obtained for reaction series where the rate accelerations have been attributed to entropy effects.

THE quantitative study of the *gem*-dimethyl effect dates from the pioneering work [2] of Thorpe and Ingold and recently the problem has been extensively studied in relation to intramolecular participation as a model for enzyme catalysis.[3,4] In model compounds, rate enhancements of intramolecular *versus* intermolecular reactions of the order of 10^8—10^{15} have been observed. The initial interpretations in terms of 'stereopopulation control' [5] and 'orbital steering' [6] have been corrected and the order of magnitude of the various contributions, bringing about rate accelerations comparable to those of enzymic reactions, appears to be established.[4,7] Such large accelerations usually involve highly strained ground states.[8] The success of quantitative treatments of the *gem*-dimethyl effect in reaction series of varying substituents has been rather limited. Although the size of substituents generally parallels acceleration of ring closure, the rate data for the various reaction series as a rule do not correlate with each other. To our knowledge, two reaction series have been correlated with Taft's E_s values involving, however, substituents at only one position of the chain.[9,10] A general treatment of the *gem*-dimethyl effect based on thermodynamic considerations has been outlined by Allinger and Zalkow.[11] They have demonstrated that the effect can be satisfactorily predicted in the hypothetical gas phase reaction, hexane $\rightleftharpoons$ cyclohexane + H_2, by estimating the $\Delta\Delta H$ contributions from the *gauche*-interactions arising upon branching and the $\Delta\Delta S$ contributions from empirical additive increments. In the common case of cyclization to a heterocyclic compound it is difficult to obtain reliable estimates of the *gauche*-interactions. Eberson and Welinder [12] could obtain a fair agreement between calculated $\Delta\Delta H$ values and experimental $\Delta\Delta G$ values only after making the additional assumption of 'hard' and 'soft' methyl–methyl interactions.

The acid-catalysed cyclization of β-ureido acids was found previously [13,14] to be a reversible reaction for three examples, 3-ureidopropionic acid (1), *erythro*- and *threo*-3-ureido-2-methylbutyric acids (4) and (5), and the rates of ring closure, ring opening, and equilibria could be



	R^1	R^2	R^3	R^4	R^5	
(1)	H	H	H	H	H	
(2)	Me	H	H	H	H	
(3)	H	H	Me	H	H	
(4)	Me	H	Me	H	H	*erythro*
(5)	Me	H	H	Me	H	*threo*
(6)	Me	Me	H	H	H	
(7)	H	H	Me	Me	H	
(8)	H	H	H	H	Me	

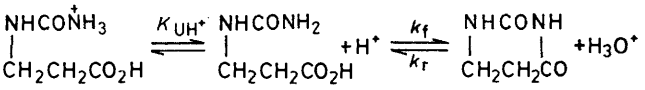
readily determined. The reaction seemed suitable for a study of the *gem*-dimethyl effect, using the approach of Allinger in particular, as a lot of information has been collected on the conformations [15-17] and the steric effects on alkaline hydrolysis of these compounds.[1] To this purpose the acid-catalysed cyclization of a further five methyl-substituted 3-ureidopropionic acids was studied.

We now report linear relationships of the free energies of this and other reaction series described in the literature with steric strain energies estimated from enthalpies of formation of homomorphic hydrocarbons.

RESULTS

The acid-catalysed cyclization of 3-ureidopropionic acid was found [13] from a rate profile in 0.5—7.8M-HCl to proceed

according to the Scheme. At infinity times the concentration of the initial ureido acid was appreciable so that the observed equilibrium constant K_E', the ratio of dihydrouracil to total ureido acid concentration, and from it, k_f and k_r, the observed first-order rate constants of ring closure



SCHEME

and ring opening, respectively, could be determined. The former reaction followed Hammett's H_0 function with a K_{UH^+} value of 1.8 [equation (1)]. The observed equilibrium

$$k_f = k_2 K_{UH^+} h_0/(h_0 + K_{UH^+}) \quad (1)$$

shifted towards the ureido acid with increased acidity because the rate of ring closure levels off. A plot of $\log K_E'$ against $\log(h_0 + K_{UH^+})$ is linear with a slope of *ca.* −0.5.

The rates of ring closure of the methyl-substituted ureido acids (2), (3), and (6)—(8) were measured in 0.94M-HCl. In this solution only the 2-methyl derivative (2) exhibited a measurable equilibrium, the latter being strongly shifted to dihydrouracil for the remaining compounds. The rates were then measured in 6.50M-HCl in order to obtain data on k_r and K_E'. With the methods used, these could only be obtained for compounds (2) and (3) in addition to the data obtained previously [13,14] for ureido acids (1), (4), and (5).

The rates of ring closure of all ureido acids increased only 1.9—3.4 times on going from 0.94 to 6.50M-HCl indicating that with the latter acid concentration, the observed rates have reached the limiting value of $k_2 K_{UH^+}$ [see equation (1), h_0 changes from 1.48 to 214]. This was confirmed as no further increase in rate was observed in 7.78M-HCl. The acidity constants for protonation of the ureido-group, K_{UH^+}, were assessed from the data obtained in 0.94 and 6.50M-HCl using equation (1). The enthalpies and entropies of activation for the cyclization reaction were determined from the k_f values obtained in 0.94M-HCl. The use of k_2 values was avoided as the dependence of K_{UH^+} on the temperature was unknown; moreover the differences in K_{UH^+} is rather small, and fortuitously the k_2 values calculated with $h_0 = 1$ as the standard state are practically equal to k_f; for the *N*-methyl derivative (8) only k_2 is 0.18 log units larger than k_f.

TABLE 1

Pseudo-first-order rate constants (s^{-1}) for ring closure of methyl-substituted 3-ureidopropionic acids in 0.94M-HCl

(2)		(3)		(6)	
t/°C	$10^5 k_f$	t/°C	$10^5 k_f$	t/°C	$10^5 k_f$
55.0	5.01	55.0	12.9	65.62	3.40
60.0	7.79	60.0	18.8	71.10	5.90
65.0	11.8	65.0	27.8	76.95	9.74
70.0	18.5	70.0	45.9	84.25	18.9

(7)		(8)	
t/°C	$10^5 k_f$	t/°C	$10^5 k_f$
30.50	8.30	45.11	77.9
38.34	18.7	50.01	121
47.06	39.8	54.71	194
55.02	67.8	60.17	305
59.96	119		

TABLE 2

Data for ring closure of methyl-substituted 3-ureidopropionic acids in 6.50M-HCl

Compound	t/°C	$10^4 k_f$/s^{-1}	$10^4 k_r$/s^{-1}	K_E'	K_{UH^+}
(2)	70.0	4.51	1.76	2.56	2.1
(3)	70.0	10.5	1.68	6.25	2.0
(6)	71.35	1.74			2.8
(7)	59.95	40.1			3.4
(8)	45.25	14.4			1.2

Inspection of the activation parameters of Table 3

TABLE 3

Enthalpies and entropies of activation for the ring closure of methyl-substituted 3-ureidopropionic acids in 0.94M-HCl *

Compound	$\Delta H^\ddagger$/kJ mol^{-1}	$-\Delta S^\ddagger$/J K^{-1} mol^{-1}
(1) [a]	74.6 ± 2.9	102 ± 8.7
(2)	78.3 ± 0.9	89.2 ± 2.7
(3)	75.7 ± 3.2	89.5 ± 9.7
(4) [b]	83.1 ± 2.1	77.6 ± 6.1
(5) [b]	69.2 ± 0.6	109 ± 1.9
(6)	89.1 ± 1.0	68.2 ± 2.9
(7)	70.8 ± 2.1	89.6 ± 6.7
(8)	77.9 ± 1.2	59.9 ± 3.8

* Data calculated according to equation (5). [a] From ref. 13. [b] From ref. 14.

reveals a tendency for a compensation effect, suggesting that the series could be an isokinetic one. This was examined by means of Exner's criteria.[18] A preliminary test is the linearity of a plot of the log*k* values at two different temperatures against each other. Such a plot is shown on Figure 1; extrapolated values for compounds (6)—(8) were used. In view of the good linearity obtained (r 0.999) a full statistical treatment of the data was undertaken. This involves testing the hypothesis that the Arrhenius regression lines have a common point of intersection. For this purpose the minimum of the standard deviation, s_0, was sought iteratively for intersection at variable inverse temperatures by means of a computer program based on the

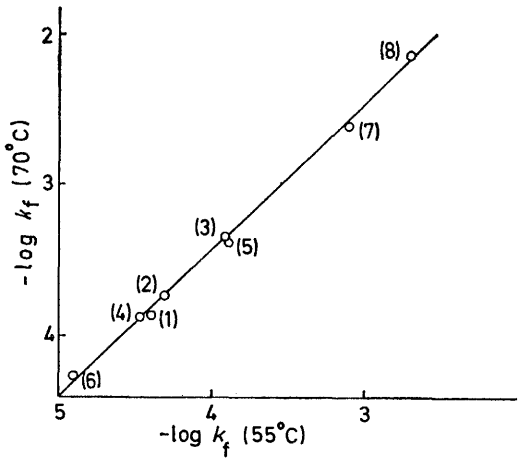


FIGURE 1 Plot of log k_f for cyclization of β-ureido acids (1)—(8) at two temperatures

algorithm given by Exner for the case of kinetic measurements at arbitrary temperatures. The minimum value of s_0 is then compared with the standard deviation, s_{00}, calculated for the free set of Arrhenius lines. For compounds (1)—(7), a minimum was obtained at an inverse

temperature of 1.7×10^{-4} K^{-1}, s_0 0.020 7, which is less than the value of 0.0219 obtained for s_{00}. This, according to Exner, proves that the isokinetic relationship holds for the series. For all eight compounds, s_0 is greater than s_{00} but the hypothesis is still valid according to the F test at a confidence level of 0.05. It should be noted that the minimum obtained in both cases is very flat and the confidence limits of β, the isokinetic temperature, are very broad as judged from the estimated experimental error. This is, however, a general drawback of Exner's method.[19]

DISCUSSION

Our attempts to interpret quantitatively the rate data for the ring-closure reaction by means of Allinger's approach were unsuccessful. This involved assessment of the $\Delta\Delta H^{\ddagger}$ contributions from conformational analysis of the ureido acids and the presumed tetrahedral intermediate and the assumption of constant $\Delta\Delta S^{\ddagger}$ increments upon branching. The compensation effect observed in the series explains this failure because in such cases enthalpy and entropy cannot be treated independently; furthermore Allinger's approach predicts in most cases that both the $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ contributions should be favourable upon branching, the former due to a decrease in new *gauche*-interactions in the cyclic transition state and the latter because of hindered rotation in the open-chain compound.

As an isokinetic relationship is considered a prerequisite of linear free energy relationships our attention turned to such correlations. The use of steric constants for ring-closure reactions is by no means straightforward. There are two reaction centres and difficulties arise in defining the substituent. Thus the correlation found by Bruice and Bradbury [9] of the rates of the intramolecularly assisted hydrolysis of *p*-bromophenyl 3-substituted glutarates with Taft's E_s values has been criticized by Palm [20] because these authors use an E_s scale based on a value of 1.24 for E_s of hydrogen. This is incorrect for a substituent removed from the reaction centre by two carbon atoms as the value of 1.24 includes a 'hyperconjugation' effect. A more appropriate procedure would be to define the substituent by including the chain or a pertinent part of it. Further, if one follows Bruice and Bradbury in considering the substituent separately from the chain, different reaction constants are to be expected for the various positions of the chain. Inclusion of the chain, however, increases the complexity of the 'substituent' and the need for a wider range of steric constants arises. Such a large set of steric constants has recently been suggested by Istomin and Palm; [21] the F and F^{H} values are based on the standard enthalpies of formation, ΔH_f^0, of alkanes. The procedure by which the F^{H} values were obtained permits the evaluation of steric strain in various model hydrocarbons. We briefly outline how we shall use it. Istomin and Palm showed that ΔH_f^0 of normal chain alkanes can be described by a simple additive equation (2), where a_1 is ΔH_f^0 of methane, n_1 the number of carbon atoms, a_2, a_3, *etc.* the formal interactions between carbon atoms in positions 1 and 2, 1 and 3, *etc.*, and n_k their number. Only a_5 is a destabilizing non-bonded interaction. The total destabilizing non-bonded interactions of a branched alkane P are given by equation (3).

$$\Delta H_f^0 = \sum_{k=1}^{5} n_k a_k \qquad (2)$$

$$P = \Delta H_f^0 - \sum_{k=1}^{4} n_k a_k \qquad (3)$$

The strain between two fragments, R_i and R_j, of the alkane R_iR_j, $\Delta P_{R_iR_j}$, is assumed to be equal to the right hand term in equation (4) where P_{R_iH} and P_{R_jH} are the total strains in the alkanes corresponding to the fragments R_i and R_j. A scale of steric constants F^{H} is

$$\Delta P = P_{R_iR_j} - P_{R_iH} - P_{R_jH} \qquad (4)$$

based on $\Delta P_{R_iR_j}$ values obtained with R_i as Bu^t and R_j as a variable fragment. This scale is practically equivalent to Palm's E_s^0 values.[22]

The problem remained to be solved as to how to define the 'reaction centre' and the 'substituent'. Taking as a guide line the assumption that the rate accelerations are due to release of steric strain in the cyclic transition state, this was done by considering the reactivities observed. Inspection of the rate data for cyclization of the β-ureido acids reveals that the rate accelerations are greatest for substituents most removed from the carboxy-group (Table 4). A methyl group in the γ-position accelerates the reaction 46 times, in the β-position 2.8 times, and only 1.2 times in the α-position. Two methyl groups in the α-position even retard the reaction. It thus appeared that release of strain between the nucleophile, $CONH_2$, and the rest of the molecule is the major contribution. For this reason a correlation was attempted with Istomin and Palm's F^{H} values by taking as substituent the fragment $NHCH_2$-CH_2CO_2H in the form of $CH_2CH_2CH_2CH_3$. The carboxy-group was modelled as a methyl function from practical considerations as F^{H} values only up to C_6 are available.

TABLE 4

Relative rates and equilibria for ring closure of β-ureido acids and ring opening of dihydrouracils

Compound	k_f [a]	k_r [b]	K_E' [b]	$k_{obs.}$ [c] for alkaline hydrolysis
(1)	1	1	1	1
(2)	1.17	0.40	3.5	0.44
(3)	2.83	0.39	8.6	0.29
(4)	0.84	0.11	8.6	0.061
(5)	2.98	0.28	12.8	0.039
(6)	0.35			0.046
(7)	17.9			0.001 26
(8)	45.9			

[a] In 0.94M-HCl at 60 °C. [b] In 6.50M-HCl at 70 °C for (2) and (3) and at 60 °C for (4) and (5). [c] From ref. 1 for hydrolysis at pH 13 at 25 °C.

Stella and Higuchi have reported [23] rate data on the

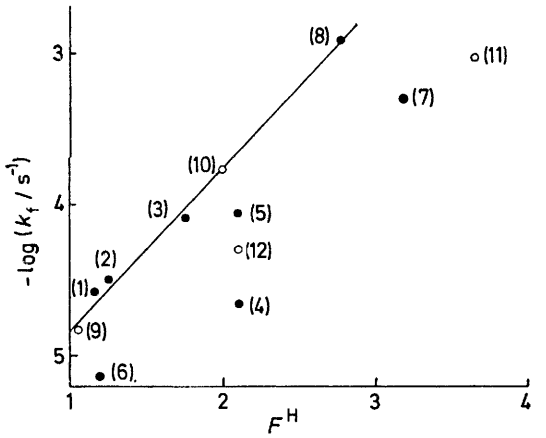


FIGURE 2 Plot of log k_f for ring closure at 50 °C *versus* Istomin and Palm's F^H constants; ●, β-ureido acids (extrapolated values), ○, hydantoic acids [data from ref. 23, (9), hydantoic acid; (10), 2-methyl-; (11), 2,2-dimethyl-; (12), 2-isopropyl-hydantoic acid]. The line drawn is the least-squares fit for the unsubstituted and monomethylsubstituted compounds

closely related ring closure of hydrantoic acids to the five-membered hydantoins. It was of interest whether these data would conform to the same relationship. Presenting $NHCH_2CO_2H$ as $CH_2CH_2CH_3$, four examples could be included for which F^H values were available.* The plot in Figure 2 shows that the unsubstituted and monomethyl-substituted ureido acids fall on one line but the compounds with *gem*-dimethyl substituents and isopropylhydantoic acid deviate strongly. The β-ureido acids belong to an isokinetic series and are thus expected to form a single reaction series. The deviations correspond to exaggeration of strain release. This could be due to exaggeration of the total strain $P_{R_iR_j}$ in equation (4), since R_i, the $CONH_2$ fragment, is taken as Bu^t, or to underestimation of P_{R_j} due to the replacement of CO_2H with CH_3, or both. In fact a satisfactory correlation (Figure 3) was obtained with $\Delta P_{R_iR_j}$ values calculated with R_i = Et for the group $CONH_2$ and taking CO_2H as Pr^i in the variable fragment R_j. DeTar and Tenpas have recently obtained a good correlation of rates of ester hydrolysis with the steric components of ΔH_f^0 of isoalkanes and neoalkanes calculated by means of Schleyer's molecular force field. The alkoxycarbonyl group was modeled as Pr^i and the tetrahedral intermediate as Bu^t.[24] The ΔP values were calculated with the parameters given by Istomin and Palm [21] from equations (2)—(4) using the ΔH_f^0 values of ref. 25.† Those for C_9 and C_{10} are mostly calculated values; recent experimental work has shown them to be reliable.[26]

A correlation embracing 10 compounds with rates spread over more than two powers of ten can hardly be fortuitous. In this case the *N*-methyl derivative (8) was omitted as it deviated strongly; this compound also deviates from the isokinetic relationship and is probably least well presented by the hydrocarbon model. Of the two stereoisomers of the 2,3-dimethyl derivatives, *erythro* (4) and *threo* (5), only the *threo* compound was included as it fell on the regression line. The ΔP value was obtained for a hydrocarbon of

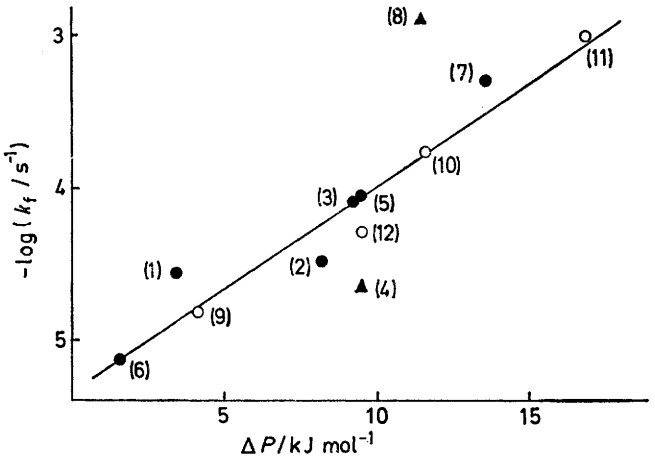


FIGURE 3 Correlation of log k_f for ring closure at 50 °C *versus* ΔP values (see text). ●, β-Ureido acids; ○, hydantoic acids, ▲, points not included in the correlation (numeration as in Figure 2)

TABLE 5

Parameters of the linear free energy-steric strain energy regressions [a]

Reaction series	Variable used in correlation	Number of points	Slope	Intercept	r	$S_{y(est)}$
1 Rates of ureido acids	ΔP	10	0.135	−5.342	0.965	0.19
2 Rates of succinanilic acids	ΔP	6	0.049	−6.382	0.993	0.16
3 Equilibria succinic acids ⇌ anhydrides	ΔP	5	0.065	−5.452	0.992	0.24
4 Rates of hydrolysis of *p*-bromophenyl glutarates	P	6	0.045	−3.340	0.964	0.17
5 Equilibria γ-hydroxybutyric acids ⇌ lactones	P	5	0.057	0.253	0.928	0.20
6 Equilibria δ-hydroxyvaleric acids ⇌ lactones	P	5	0.060	−1.451	0.932	0.34
7 Rates of epoxidation of 2-chloroethanols [b]	F^H	8	0.774 [c]	−0.794	0.988	0.23

[a] Calculated with ΔP or P values in kJ mol^{-1}. [b] Correlation with $k_{rel.}$. [c] Value obtained with the F^H constants (see text).

* The two sets of data were brought onto the same scale by extrapolating k_f for the β-ureido acids to 50 °C. The rate constants for the hydantoic acids are calculated with $a_H = 1$ as the standard state.

† The $P_{R_iR_j}$ and $\Delta P_{R_iR_j}$ values calculated for the purposes of this paper are deposited in Supplementary Publication No. SUP 22524 (4 pp.). For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1978, Index issue.

unspecified configuration and the inclusion is arbitrary, a justification being that in two other series (*vide infra*) it is again the *threo* or DL isomer which fits the linear relationship. Another choice, also arbitrary, is to use the average of the rates for the two isomers. In such a case the regression does not deteriorate considerably, the correlation coefficient r changing from 0.965 in the former case (Table 5) to 0.954.

A remarkable feature of the above correlation is that it includes in a common series the rate data for cyclization to five- and six-membered rings. This shows that in the reaction no strong specific ring-size effects are involved. An indication is the similarity in the rate constants of the parent compounds, 3-ureidopropionic acid reacting 1.8 times faster than hydantoic acid.

The correlation brings into line observations which could not be consistently explained. Thus in an attempt to correlate the rate data for hydantoic acid ring closure with that for the *p*-bromophenyl glutarate series,[9] Stella and Higuchi [23] were forced to assume an inhibition factor based on ester hydrolysis data which purported to take into account steric strains in the tetrahedral intermediate arising with bulkier substituents. If this is assumed to be the cause of the slower rate for 3-ureido-2,2-dimethylpropionic acid (6) it is not clear why dimethylhydantoic acid cyclizes 63 times faster than hydantoic acid. Upon alkaline hydrolysis 6,6-dimethyldihydrouracil opens its ring *ca.* 200 times more slowly than dihydrouracil which is readily explained by a diaxial 4-OH–6-Me interaction in the transition state. Yet the rate acceleration observed with the respective 3,3-dimethyl-substituted ureido acid (7) is similar to that observed with *p*-bromophenyl 3,3-dimethylglutarate where rate accelerations have been attributed to favourable rotamer distribution.[9] In terms of the hydrocarbon model on which the above correlation is based, the slower rate of the 2,2-dimethyl derivative (6) means that the increase of total strain, $P_{R_iR_j}$, upon introduction of the two methyl groups in position 2 is less than the increase of strain in the variable fragment R_j, P_{R_j}.

That the rates of ring closure correlate with the strain between one of the functional groups and the remaining part of the molecule is not entirely an expected result. For the cyclization of ureido acids in particular, the release of strain between the $CONH_2$ group and the substituents can be understood by taking into account the planarity of the hydantoin and dihydrouracil rings. The $CONH_2$ group becomes eclipsed with the ring bonds in the transition state and so moves away from the substituents. The steric requirements of the carboxy-group in the ground state could remain similar to those of the incipient tetrahedral intermediate in the case of an early transition state.

Some support to the latter suggestion of an early transition state is lent by the rate data for the ring-opening reaction which in Table 4 are compared with the rates of alkaline hydrolysis of dihydrouracils under conditions where the rate is to a large extent determined by addition of OH^- to the carbonyl group. The rate retardations observed for the more heavily substituted *cis*- and *trans*-5,6-dimethyldihydrouracil are much less for acid hydrolysis suggesting a less strained transition state. This could be a late breakdown of the tetrahedral intermediate. Unfortunately, the data are too few to allow definite conclusions to be drawn.

The available equilibrium constants appear to be roughly parallel to the rate constants for the cyclization reaction in the sense that larger k_f values correspond to more stable dihydrouracils, the equilibrium being more sensitive to the effect of the substituents. This is, however, not true of the whole series. Apart from the exception of the 2,3-dimethyl derivative (4), an example is 3-ureido-2,2-dimethylpropionic acid which reacts more slowly than 3-ureidopropionic acid but has $K_E' > 20$ as it is >95% converted into dihydrouracil in 6.50M-HCl. An analysis of the equilibrium results is deferred until data on the remaining compounds are obtained.

Linear Free Energy–Steric Strain Energy Relationships of Other Reaction Series.—The successful correlation of the free energies of the ring closure of ureido acids with the ΔP values of Istomin and Palm turned our attention to other reaction series. One series for which a linear relationship was obtained is the intramolecularly assisted hydrolysis of succinanilic acids studied by Higuchi *et al.*[27] The logarithms of the rate constants depended linearly on the $\Delta P_{R_iR_j}$ values when these were calculated by taking the anilide group in the form of isopropyl as R_i, the invariable fragment, and the carboxy-group in the variable fragment, R_j, as methyl (see Table 5). This correlation differs substantially from the previous one of the ureido acids since here the ΔP values refer to strains between the group giving rise to the tetrahedral intermediate and the remaining fragment of the molecule. The hydrolysis of anilides commonly takes place with rate-limiting breakdown of the tetrahedral intermediate. An attractive possibility is that the correlation is due to relief of strain in an anhydride-like transition state. This is supported by observation by Eberson and Welinder [12] that the logarithms of the rates of hydrolysis of succinanilic acids are linearly related to those of the equilibrium constants of the succinic acid $\rightleftharpoons$ anhydride equilibria. As would be expected the equilibrium data are linearly related to the same ΔP values (Table 5). In the case of the stereoisomeric 2,3-dimethyl derivatives, it is the DL-isomer which fits the relationship in both series.

Attempts to correlate the series of the intramolecularly assisted hydrolysis of *p*-bromophenyl glutarates with ΔP values obtained by means of various fragmentations and models including Istomin and Palm's F^H values failed in spite of the fact that this series has been shown by Bruice and Bradbury [9] to give a linear relationship for the substituents at position 3 with Taft's E_s values. When, however, the logarithms of the rate constants are plotted against the total steric strains P a satisfactory correlation is obtained (see Table 5) which includes the only available example for substitution at position 2, the 2,2-dimethylglutarate.[28] The P values

were obtained using $(CH_3)_2CHCH_2CH_2CH_2CH_3$ as the model in which the ester group is replaced by isopropyl, and the carboxy-group by methyl. Altogether six compounds could be included in the series due to the limitation that data for enthalpies of formation were available only up to C_{10}. The very large difference,[28] 230 times, in the rate of hydrolysis of the unsubstituted glutarate and malonate precluded their inclusion in a common series. The relief of total strain introduced by the substituent is compatible with a largely strain-free transition state. We consider this to be an anhydride-like transition state for a slow breakdown of the tetrahedral intermediate which would be in agreement with the high sensitivity of the reaction to polar substituents in the phenyl ring observed by Gaetjens and Moravetz [29] and the large difference in rate of ring closure to five- and six-membered rings.

The difference between the series of succinanilic acids and that of *p*-bromophenyl glutarates, the first correlating with ΔP values and the second one with P values, is probably due to different steric requirements of the five- and six-membered anhydride-like transition states. In the transition state of the glutarate series the substituents in position 3 will be staggered and for those in an equatorial conformation relief of strain in the sense discussed by Allinger and Zalkow [11] will occur. The strain associated with axial substituents should also be alleviated because of the two carbonyl groups in the β-position in the case of an anhydride-like transition state. In the five-membered anhydride-like transition state the substituents attain an essentially eclipsed conformation and strain in the variable fragment, R_j, is retained.

In general, the steric strain in the hydrocarbon model of the open-chain compound is expected to describe adequately the *gem*-dimethyl effect when no new important steric interactions arise in the transition state. Probably correlations of the above type will be observed with reactions of carboxy derivatives when the transition state has some sp^2 character. This suggestion is supported by the results of Wheeler and Rodriguez [30] for lactonization of γ-hydroxybutyric acids and δ-hydroxyvaleric acids. No correlation was found for the ring-closure rates; fair correlations (Table 5) were, however, obtained for the equilibrium constants with P values (CO_2H = Pr^i, OH = Me). In this case the two ring systems give rise to two separate relationships. There is a difference of 47 times in the equilibrium constants of the unsubstituted compounds.

In the cases hitherto described, linear relationships could be obtained when the carboxy-group or its derivative giving rise to the tetrahedral intermediate were modelled as an isopropyl group and the nucleophile as a methyl or ethyl group.

The above approach to the *gem*-dimethyl effect is not limited only to reaction of carboxy derivatives. A linear relationship of the log k values for the base-catalysed epoxidation of 2-chloroethanols [31] with the F^H values of Istomin and Palm was obtained when the fragment CR_2CR_2Cl was taken as the substituent in the form $CR_2CR_2CH_3$ (Table 5). A poorer correlation (r 0.962) was obtained with the alternative fragmentation taking CR_2CR_2OH as the substituent. Bearing in mind that the F^H values are derived with Bu^t as the reference group, the correlation indicates that considerable relief of steric strain occurs in the transition state.

The least squares parameters of the linear regressions obtained are summarized on Table 5. The equations used were of the form $\log k_x = aX_x + b$, where X_x is the respective ΔP, P, or F^H value. The F^H values are ΔP values normalized as steric constants. The slope of the regression line for reaction series 7 of Table 5 should be divided by 7.85 before comparing with the slopes of the remaining series obtained for ΔP or P values in kJ.

The foregoing discussion shows that the quantitative approach outlined in this paper, although not universal, has wide application. The correlations are based on estimates of steric strain energy which are adaptable to various reactions by adjusting the hydrocarbon model and kind of fragmentation and by correlating with ΔP, the strain between two fragments of the molecule, or with P, the total strain. All these, together with the fact that a correlation is obtainable at all, indicate the steric requirements of the reaction and thus its mechanism. A limitation is encountered in the availability of data on the enthalpies of formation of the homomorphic alkanes.

Two advantages of the linear relationships under discussion should be noted. Allinger and Zalkow [11] gave a sound basis for the understanding and quantitative treatment of the *gem*-dimethyl effect but this had few applications. The main obstacle to its application is that *gauche*-interactions, in open-chain compounds in particular, are usually unknown and more important are not additive and change from compound to compound. These interactions are directly accounted for, although approximately, in the homomorphic hydrocarbon model. Secondly, as the substituents and the chain are treated as a whole fragment, a single correlation is obtained for substituents at various positions of the chain and even for cyclization to five- and six-membered rings when ring-size effects are not important.

The linear relationships observed between estimates of steric strain energies from homomorphic hydrocarbons and the free energies of reaction series exhibiting the *gem*-dimethyl effect are a clear indication that the main contribution to the observed rate accelerations and equilibrium shifts is release of steric strain in the cyclic systems. This is contrary to the commonly held opinion, iterated recently by Bruice,[4] that the phenomenon is mainly due to entropy effects, one interpretation of which is that the substituents by their sheer bulk reduce the volume available to the two reacting groups. The major role of steric strain in the ground state is already well established [8] for cases of extremely large rate accelerations. The above linear relationships show this to be a more general case. Noteworthy in this respect is the linear relationship (Figure 4) obtained for $\Delta H^\ddagger$ for the ring closure of β-ureido acids with the ΔP values used before. Although the fit of the average of $\Delta H^\ddagger$ for

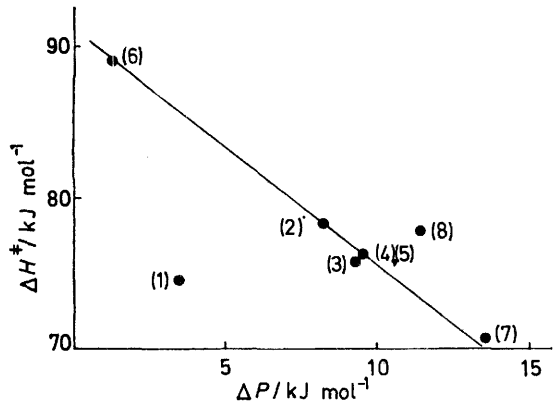


FIGURE 4 Plot of $\Delta H^{\ddagger}$ for the ring closure of β-ureido acids *versus* ΔP values (see text)

the two isomers could be fortuitous and 3-ureidopropionic acid falls off the line, the trend is demonstrated sufficiently well.

The above correlations bear upon another controversial point in the interpretation of ring-closure tendencies, namely, the effect of ring size or, as it has been interpreted, the contribution of freezing the rotation around a single bond. Page [7] claimed from statistical mechanics considerations that this contribution can bring about a five-fold increase in the ring-closure rates. The fact that the rate data for ring closure to five- and six-membered rings form a single series when the rates for the parent compounds are similar shows that the cases of widely differing rates are due to specific ring-size effects.

EXPERIMENTAL

Materials.—Methyl-substituted 3-ureidopropionic acids. Only 2-methyl-3-ureidopropionic acid has been described.[32] The free ureido acids were isolated by stirring the solutions with a 10—20% excess of Dowex-50 in the H^+ form and evaporation *in vacuo* of the filtrates. The dry residues were recrystallized twice to obtain analytically pure samples in *ca.* 50% yield.

3-(1-Methylureido)propionic acid (8) was obtained from 3-methylaminopropionic acid (0.1 mol) in water (25 ml) and potassium cyanate (0.25 mol) by heating for 150 min at 80 °C. The solution was diluted with water and Dowex-50 in the H^+ form was added to pH 3. The resin was filtered off and the filtrate evaporated *in vacuo* to dryness. The residue was crystallized first from acetone and then from ethanol.

Hydrochloric acid solutions were prepared by diluting analytical grade concentrated acid with distilled water.

Rate Measurements.—The rates of cyclization of ureido acids (2) and (3) was followed by the titration procedure described in ref. 13. The temperature was controlled to ±0.05°. Equilibrium and rate constants were determined as described.[13]

The cyclization of ureido acids (6)—(8) was followed by the increase of absorbance of the product dihydrouracil at 220 nm on a Carl Zeiss VSU-1 spectrophotometer. In the case of the faster reacting compounds (7) and (8) the reaction was carried out in the spectrophotometer cell. Temperature control was achieved by means of a metal block with water circulation. To improve temperature homogeneity, the cell was stirred with a glass stirrer driven by an electric motor. The temperature in the cell was measured with a thermistor frequently calibrated against a precise thermometer. The cyclization of the more slowly reacting compound (6) was carried out in sealed tubes in a ultrathermostat and the reaction quenched by cooling the tubes in ice and then measuring the absorbance rapidly. In all three cases the ureido acid concentration was 3—5 × 10^{-4}M. The reaction was practically irreversible even in 6.5M-HCl as judged from infinity absorbances and attempted hydrolysis so that the rates were obtained from least-squares fits of log $(A_\infty - A_t)$ against time.

The activation parameters were obtained by least-squares fit to equation (5).

$$\log k_t/T = 10.319 - \Delta H^{\ddagger}/4.574T + \Delta S^{\ddagger}/4.574 \quad (5)$$

TABLE 6

M.p.s and analytical data for β-ureido acids

Compound	M.p. (°C) [a]	Elemental analysis			Equivalent weight [b]	
		Formula	Requires (%)	Found (%)	Requires	Found
(2)	119—121 [c,d]	$C_5H_{10}O_3N_2$	N, 19.15	19.05	146.2	145.8
(3)	134—136 [c]	$C_5H_{10}O_3N_2$	N, 19.15	19.1	146.2	147.2
(6)	152—154 [e]	$C_6H_{12}O_3N_2$	H, 7.55	7.7	160.2	162.0
			C, 45.0	45.0		
(7)	148—149 [e]	$C_6H_{12}O_3N_2$	H, 7.55	7.5	160.2	161.5
			C, 45.0	45.25		
(8)	154—155 [f]	$C_5H_{10}O_3N_2$	N, 19.15	18.9	146.2	146.9

[a] In capillary at a rate of heating of 2—3° min^{-1}. The compounds melt with effervescence. [b] Determined by titration with 0.1M-NaOH under nitrogen with Cresol Red as indicator. [c] From water. [d] Lit.,[32] m.p. 120—121 °C. [e] From acetone. [f] From ethanol.

The paper chromatography R_F value of 3-ureidobutyric acid has been reported.[33]

2-Methyl-(2), 3-methyl-(3), 2,2-dimethyl-(6), and 3,3-dimethyl-3-ureidopropionic acid (7) were obtained by alkaline hydrolysis of the respective methyl-substituted dihydrouracils. The preparation and purity of the latter have already been described.[34] Hydrolysis was carried out in 1M-NaOH in 10-fold excess for 24 h at room temperature for compounds (2), (3), and (6) and for 7 h at 50 °C for compounds (7). In the latter case hydrolysis at higher temperatures or for longer times produced the amino acid.

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