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Linear free energy relationships of the *gem*-dimethyl (*gem*-dialkyl) effect

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Dedicated to Academician Ivan Juchnovski on the occasion of his 70th birthday

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The *gem*-dimethyl effect, GDME, or dialkyl effect, defined by the acceleration of cyclization reactions or the retardation of ring-opening by substituents in the chain, can not be satisfactory predicted by means of Hammett linear free energy relationships, LFER, e.g. using Taft's E_S-values. The reason for this can be traced to the nature of the GDME. Examination of a large series of the reversible cyclization of 3-(3-phenylureido) acids showed that good LFER of the Leffler type, i.e. rates against equilibria of the same reaction, are obtained encompassing substituents at various position of the ring. The LFER defines a general *gem*-dimethyl effect; a few outliers are due to specific interactions arising in the transition states and not in the reactant or product. Extension to other reactions of the ring system was carried out in two ways: correlation of rates with the equilibrium constants of the acid catalyzed cyclization of ureido acids assumed as reference or correlating two series of reaction rates with similar transition states which can eliminate outliers due to specific transition state effects. The rates of alkaline hydrolysis of a large number of dihydrouracils nicely illustrated the versatility of the two approaches.

The one pot Rodionov procedure readily provided several β-amino acids with β-alkyl substituents from the corresponding aldehydes and malonic acid. Most of the equilibrium and rate data for acid and base catalysed hydrolysis of 3-phenyldihydropyrimidine-2,4-diones are reported in this paper.

Key words: Linear free energy relationships, *gem*-dimethyl effect, rates and equilibrium constants, acid and base catalysed hydrolysis, dihydrouracils, β-ureido acids.

INTRODUCTION

The quantitative prediction of substituent effects is widely used in the form of Quantitative Structure Activity Relationships, QSAR, [1] for drug design and related biological applications and Quantitative Structure Property Relationships, QSPR, for chemical and physical goals. An integral part of these methods are the Hammett Linear Free Energy Relationships, LFER, [2] based on equations of the type

$$\log(\frac{k_x}{k_o}) = \rho\sigma \qquad (1)$$

where ρ describes the susceptibility of the reaction rate constant (or equilibrium constant or some other property) to polar effects of substituents while σ is the substituent constant based on substituent effects of a reference reaction. Soon LFER were extended to other types of effects.

The LFER are classified as "extrathermodynamic" because they are empirical and can be deduced from theoretical concepts such as the Marcus equation [3] which describes the variation of the potential with the reaction coordinate as a function of the energy of the reaction and the so called "intrinsic barrier", $\Delta G_o^{\ddagger}$, i.e. the energy of activation when the reaction energy ΔG, is zero (for the sake of simplicity we assume $\Delta G \approx \Delta H$). The equation predicts reduced kinetic barriers for exothermic reactions (low selectivity and early transition states) and increased kinetic barriers for endothermic reactions (high selectivity and late transition states). Under certain conditions the approximation for a LFER holds i.e. $\Delta\Delta G^{\ddagger} = \rho\Delta\Delta G$ where $\Delta\Delta G = \Delta G_x - \Delta G_o$. The free energies and those of activation apply for the same reaction series whereby the intrinsic barrier remains the same. Such relationships are usually referred to as the Leffler relationships [4]. The first linear free energy relationship was discovered by Pedersen and Brønsted [5]. It correlates rates and pK's in general acid or base catalysis and presents a Leffler type LFER. The slopes α or β in the Brönsted linear correlations play a great role in study of reactivity because their values $0 < \alpha$ or $\beta > 1$ have been shown by Leffler as well as by the Markus equation to measure directly the reaction coordinate in the transition state [6]. In

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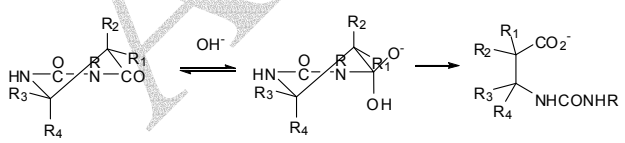
the Hammett equation the slopes ρ compare the selectivity to substituent effects of an arbitrary reaction to a reference one and their values are not confined in the limits from zero to unity. The means of calibrating ρ in terms of a Leffler equation have been discussed by A. Williams [7].

Seventy years after its conception as a quantitative description of polar effects, the Hammett equation and its applications have witness an immense proliferation and sophistication. One line of development is definition of substituent constants for all kind of effects. Those for steric effects, originally the E_S constants of Taft Jr. [8], have proved least useful because of deviations from linearity. This is not surprising bearing in mind that steric repulsion is dependent on twelve powers of r – the distance between the interacting atoms. In conformationally restricted transition states typical of cyclization and ring-opening reactions the situation becomes worse because the geometrical requirements become more specific and no longer correspond to those defining E_S – the steric hindrance arising in acid catalyzed hydrolysis of open-chain carboxylic esters. One of the few successful applications of E_S values in cyclizations or ring-opening was reported by Bruice and Bradbury [9a] who could correlate linearly the effect of 3-substituents in the hydrolysis of glutaric anhydrides with E_S. Palm [9b] has criticized their approach for using E_S for substituents removed from the reaction center and suggested inclusion of the interlinking chain to obtain more accurate description of the steric effects. Of course, another procedure would be to have separate series for the various positions with different ρ's. We however encountered the problem of specificity of the various ring positions in spite of assigning a unified set of E_S-values by treating part of the chain linked to the reaction center as the backbone of the substituent [10]. The steric effects in question were observed in the alkaline hydrolysis of dihydrouracils, Scheme 1.



Scheme 1

We had assigned E_S-values to the substituents in the following manner:

When all R = H, E_S for Et was assumed; R^1 = Me: E_S^{iPr}, $R^1 = R^2$ = Me: E_S^{tBu}; R^3 = Me: E_S^{nPr}; $R^3 = R^4$ =Me: E_S^{iBu}, $R^1 = R^4$ (or $R^1 = R^3$) = Me: E_S^{EtMeCH}. However, the available five points clearly defined two lines: one for 5-substituents (R^1 and R^2) and the other one for 6-substituents (R^3 and R^4). The data for the 5,6-dimethyl isomers appeared in between, Fig. 1.

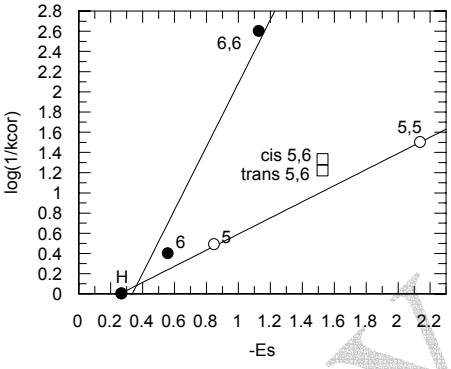


Fig. 1. Plot of $\log(1/k_{cor})$ where k_{cor} are the relative observed hydrolysis rate constants at pH 13 adjusted for ionization at 3-N against $-E_S$ (see text). Open circles: 5-methyl; closed circles: 6-methyl; squares 5,6-dimethyl. The point for R = H is common for both lines.

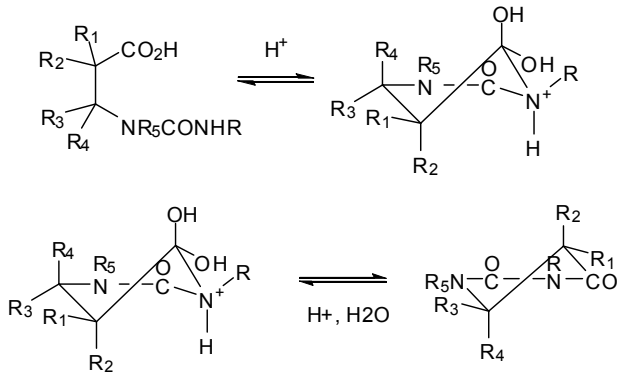
The deceleration by substituents in the 6th position is stronger (ρ = 3.14, r = 0.981) than in the 5th position(ρ = 0.80, r = 0.999). In the opposite reaction of cyclization of β-ureido acids [11] substituents accelerate the reaction, the effect of β-substituents being the stronger. Thus the greater retardation caused by 6-substituents is demonstration of the reverse *gem*-dimethyl effect.

The Thorpe-Ingold or *gem*-dimethyl (more generally dialkyl) effect is defined by the increase in both rate and equilibrium constants of cyclization reactions resulting from the introduction of substituents in the linking chain [12–14]. The nature of the effect has been the subject of a long controversy. It is best understood in terms of stain arising in the open-chain upon substitution which is released either by reduced ring bond angles in small rings or by diminishing the number of new gauche interactions because part of these are enforced upon the ring atoms [13].

Prediction of the GDME can be made by estimation of the strains involved [11], the best method for which is molecular mechanics [15].The strains released upon ring closure have to be overcome upon ring opening, an effect which is seldom recognized [16]. Further, in the case of reactions going through intermediates as the hydrolysis shown on Scheme 1, part of the strains due to the GDME arise in forming the intermediate because it is usually a looser structure than the parent ring [17].

The virtual inapplicability of steric constants to describe the GDME for varying positions in the ring prompted us to check whether Leffler type relations would provide a more coherent approach because a similar GDME is expected in the reaction equilibria and in the transitions states leading to these parti-

cular equilibria. We showed in an preliminary communication [18] that a log/log linear relationship does hold between the rates of acid catalyzed cyclization β-(3-phenylureido)propionic acids to 3-phenyldihydrouracils and the respective equilibrium constants♥.



K_E = [DHU]/[UA] =.(k_{cycl}/k_{open}); $k^{rel} = k_x/k_o$
subscript *x* or *o* referring to substituted and unsubstituted derivative, respectively.

Scheme 2.

Linear fit of seven points produced the following equation:

$$\log k_{cycl}^{rel} = (0.35 \pm 0.03) \log K_E^{rel} \quad (r = 0.938) \quad (2)$$

Two neglected points deviated negatively by 0.5 log units; the deviations could be traced specifically to an axial methyl in position 5 of the tetrahedral intermediate or the transition state respectively.

The present paper reports extension of this correlation in two aspects:

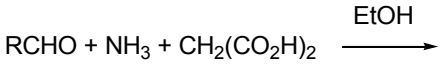
a) enlarging the list of substituents in order to outline the permitted variation of structure;

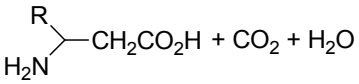
b) correlating reactions of similar transition states and ring structure whereby transition state effects as the two above mentioned deviations can be avoided.

RESULTS AND DISCUSSION

Synthesis of β-amino acids, β-(3-phenylureido) acids and 3-phenyldihydrouracils

The Rodionov reaction [19] provides a convenient one pot procedure for β-monosubstituted β-alanines:





In the case of aliphatic aldehydes, the yields are usually low 20–30% which we found to be true for propanal and pivalaldehyde. However, with isobutyraldehyde a reasonable yield of 52% of the amino acid was obtained. The α-substituted β-alanines studied could be obtained in high yields by hydrogenation over PtO_2 of the respective α-cyano esters and subsequent hydrolysis [20].

The 3-phenylureido acids were obtained by the standard Schotten-Baumann procedure with phenylisocyanate. Prolonged heating of the phenylureido acids upon recrystallization from water caused caused in some cases decomposition to amino acid and diphenylurea leading to lower m.p. Refluxing the ureido acids with dilute hydrochloric acids in water/ethanol produced the dihydrouracils. The cyclization can be complicated by several factors exemplified in the synthesis of the bicyclic dihydrouracils from the geometrical isomers of 2-(3-phenylureido)cyclohexane carboxylic acid. Adding more ethanol to augment solubility lead to a complex mixture from which the ethyl esters (according to elemental analysis and mass spectra) instead of dihydrouracils could be isolated. Prolonged reflux in 1:5 HCl solutions lead to some hydrolysis generating the parent amino acid. The appreciable reversibility of the cyclization reactions also complicated the isolation of the cyclic products. The reaction conditions were optimized by monitoring the reaction by means UV-spectrometry.

Kinetics of the reversible cyclization of 3-(3-phenylureido) acids and the Leffler linear free energy relationships between rate and equilibrium constants

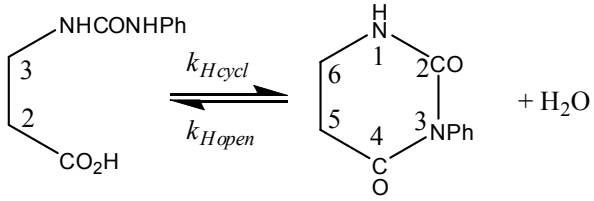
The studied reactant and product pairs in the reversible cyclization of β-phenylureido acids are designated by numbers in Table 1. The reaction kinetics were monitored by means of UV-spectrophotometry [20].

The phenylureido acids were chosen as substrates because the weak nucleofilicity of the ω-phenylureido group shifted the equilibria towards the open form and so a greater range of equilibrium constants could be determined by means of UV. Of the compounds listed on Table 1 the equilibrium could not be measured only with the β,β-dimethylalanine derivative (**11**) obviously showing the strongest GDME.

Fig. 2 shows the log/log plot of the relative rates of hydrolysis of 3-phenyldihydrouracils against the equilibrium constants.

♥ These N-phenyl derivatives allow a wide range of equilibrium constants to be determined by UV-spectrophotometry.

Table 1. Apparent equilibrium constants and rate constants, s^{-1}, for cyclization of 3-(3'-phenylureido)propanoic acids in 1 M H_2SO_4 at 70.0°C



K_E = [DHU]/[UA]

#	Substituent	K_E	K_E^{rel}	$10^5 k_{Hcycl}$	k_{Hcycl}^{rel}	$10^5 k_{Hopen}$	k_{Hopen}^{rel}
1	None	0.337	1	2.56	1	7.79	1
2	2-Me	0.968	2.87	2.92	1.41	3.01	0.386
3	2-Et	0.814	2.42	2.23	0.871	2.73	0.350
4	2,2-diMe	3.10	9.20	1.40	0.574	0.452	0.058
5	2,2-diEt	7.30	21.7	0.601	0.235	0.0824	0.0106
6	3-Me	3.09	9.17	5.50	2.15	1.78	0.228
7	3-Et	2.11	6.42	4.51	1.76	2.16	0.277
8	3-isoPr	3.64	10.8	4.97	1.94	1.37	0.240
9	3-tert-Bu	5.56	16.5	3.07	1.20	2.97	0.381
10	3-Ph	1.35	4.01	2.71	1.06	2.01	0.258
11	3,3-diMe [a]	[a]		32.0	12.5		
12	R*,R*-2,3-diMe	12.4	36.9	8.11	3.17	0.650	0.0834
13	R*,S*-2,3-diMe	6.96	20.6	2.11	0.824	0.304	0.039
14	N-Me	7.33	21.7	85.7	33.5	11.7	1.50
15	*trans* 2,3-TM [b]	5.26	15.6	13.1	5.12	2.49	0.320
16	*cis* 2,3-TM [b]	23.2	68.8	3.01	1.18	7.71	0.989

[a] Equilibrium strongly shifted to the ring form and could not be measured. [b] TM = tetramethylene.

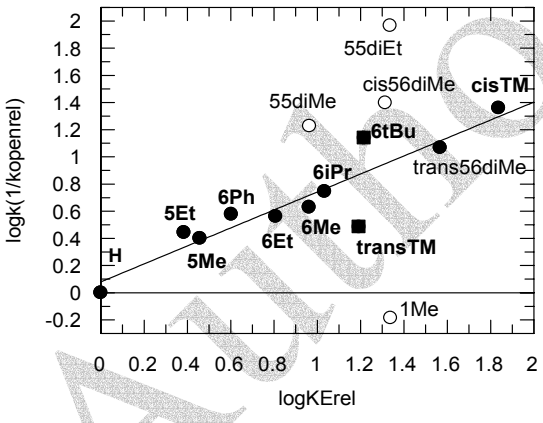


Fig. 2. Logarithmic plot of the relative rates of acid catalyzed hydrolysis of 3-phenyldihydrouracils against the relative equilibrium constants. Full circles and squares: data used in the linear fits, open circles: remaining data of Table 1.

This plot defines two types of substituent behaviour:

(a) The larger part (11 out of 15) exhibit the general GDME defined by its linear correlation with the GDME of the equilibrium between the open and ring forms:

$$\log(1/k_{Hopen}^{rel}) = \rho \log K_E^{rel} \qquad (3);$$

(b) the remaining substituents show deviations from linearity due to specific effects arising in the transition state.

The linear fit on Fig. 2 defines an equation** with following parameters:

$$\boldsymbol{\log(1/k_{Hopen}^{rel}) = (0.65 \pm 0.1) \log K_E^{rel}} \quad (r = 0.909) \text{ (4a)}$$

Actually if the points denoted as squares are omitted the remaining 9 points give a linear relationship of much improved statistics with practically the same slope:

$$\log(1/k_{Hopen}^{rel}) = (0.66 \pm 0.05) \log K_E^{rel} \quad (r = 0.981) \text{ (4b)}$$

The greater scatter of the two points depicted as squares is not surprising – the *t*-butyl group is one of the most bulky groups while *trans*-5,6-tetramethylenedihydrouracil is a rigid structure. For these reasons the capacity for accommodating strains in the various species involved in pairs **9** and **15** could differ in some extent from the "better-behaved" substituents.

Comparison of Fig. 1 and Fig. 2 clearly shows the advantage of a Leffler relationship with respect

** $(1/k_{open})$ was chosen in order to deal with a positive slope.

to correlations of the GDME with Taft's *E*s constants – the points for substituents on C-atoms at different positions of the ring fall on the same line.

The data designated with open circles deviate strongly and can not be included in the correlations. Compounds 5,5-dimethylDHU, 5,5-diethylDHU, *cis*-5,6-dimethylDHU react more slowly than demanded by the LFER. All these necessarily have an axial 5-methyl group (in the last compound the alternate conformation with equatorial 5-methyl will give rise to the strong repulsion between axial 6-methyl and axial OH at 4-C, see Scheme 2, $R^4 \leftrightarrow OH$). 3-N is positively charged because of rate determining ureido group attack [21] and solvated respectively causing strong steric repulsion with an axial 5-substituent (Me or Et) ($R^2 \leftrightarrow H$, Scheme 2). This interaction is specific for the transition states of these compounds being absent in the product DHU bringing about deviation from linearity. A very large deviation but in the opposite direction (faster hydrolysis) is observed with 1-methylDHU. For the pair **14** K_E^{rel} is 21.7 showing considerable relaxation of strain in the ring form but contrary to the remaining cases, the transition from ring to the transition state is accompanied by greated release of strain indicated by k_{open}^{rel} is 1.5. Accordingly, $k_{cycl}^{rel} > K_E^{rel}$. These observations can be understood in terms of the bond angles in six-membered rings with planar segments. In the fully planar case, all these tend to be 120° because of the requirement for a sum of 720°. The smaller the planar segment the smaller the pressure for enforcing these angles because of the accommodation due to puckering [14]. In the product DHU ring planarity encompasses four atoms, while only two in the tetrahedral intermediate of Scheme 2 thus the squeeze exercised by the N-methyl group (R^5) will meet less resistance.

Correlation of systems with similar steric requirements

There are two obvious ways of expanding the correlations of the GDME to other reactions in dihydrouracil systems. One is to use the equilibrium series as a reference series in the way σ-values are defined for use in the Hammett equation. The other is to correlate rates of cyclizations or rates of ring opening of various derivatives, the common feature being the tetrahedral intermediates. The second procedure bears the promise of incorporating the cases of specific interactions in the transition states.

To test those two approaches, correlations with the rates for alkaline hydrolysis of 3-phenyldihydrouracils were attempted. These could be were measured in 0.01 M KOH for a lot of the compounds of Table 1 and supplemented with previously obtained second order rate constants. The data are listed in Table 2 which preserves the numbering of Table 1.

Table 2. Rates of alkaline hydrolysis of 3-phenyldihydropymidine-2,4-diones at 25.0°C I = 1 M (KCl).

#	Substituent	k_{OH} $dm^3 \cdot mol^{-1} \cdot s^{-1}$	k_{OH}^{rel}	$1/k_{OH}^{rel}$
1	None [a]	2.26	1	1
2	5-Me [b]	1.55	0.69	1.46
4	5,5-diMe [b]	0.453	0.200	5.00
5	5,5-diEt [c]	0.0165	0.00730	137
6	6-Me [b]	1.24	0.549	1.82
7	6-Et [c]	1.04	0.460	2.17
8	6-isoPr [c]	0.802	0.355	2.82
10	6-Ph [c]	0.800	0.354	2.82
11	6,6-diMe [b]	0.0127	0.00562	178
12	R*,R*-5,6-diMe [b]	0.373	0.165	6.06
14	1-Me [b]	1.44	0.637	1.57

[a] From Ref. 22; [b] From Ref. 23; [c] Measured in 0.01 M KOH and converted into second order rate constants by multiplication by 100 because hydrolysis 3-phenyldihydrouracils is 1st order in [KOH] [22].

Fig. 3 shows a log/log plot of the inverse relative constants for alkaline hydrolysis against the ureido acid = dihydrouracil equilibrium constants.

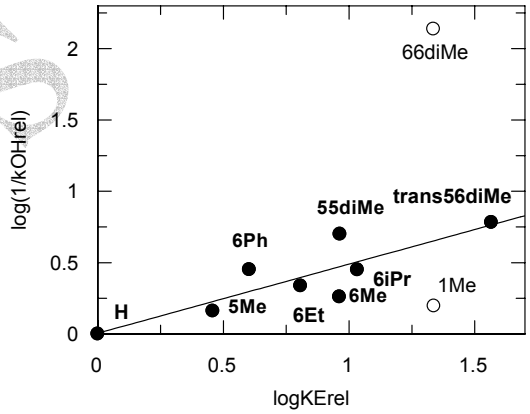


Fig. 3. Plot of $\log(1/k_{OH}^{rel})$ for the alkaline hydrolysis of 3-phenyldihydrouracils against $\log K_E^{rel}$

As readily seen the larger part of the points (8 out of ten) fit a linear relationship:

$$\log(1/k_{OH}^{rel}) = \rho \log K_E^{rel}, \quad \rho = 0.48 \pm 0.12, \; r = 0.853 \qquad (5)$$

The transition state is negatively charged, the 3-N atom is sp^2 hybridized and the planar segment consists of three atoms (Scheme 1). Compared to the positively charged transition state in acid the alkaline one has a ring geometry closer to that of the product dihydrouracil. This reduces the "specific" effects allowing the 5,5-dimethyl and the R*,R*-dimethyl derivative to be included in the common correlation. Exclusion of the former point, however, improves the linear fit (ρ = 0.46, r = 0.900).

The second approach to correlate two reaction series with sterically similar transition states is demonstrated on Fig. 4 depicting a log/log plot of relative rates of ring opening under alkaline conditions against acid catalysis:

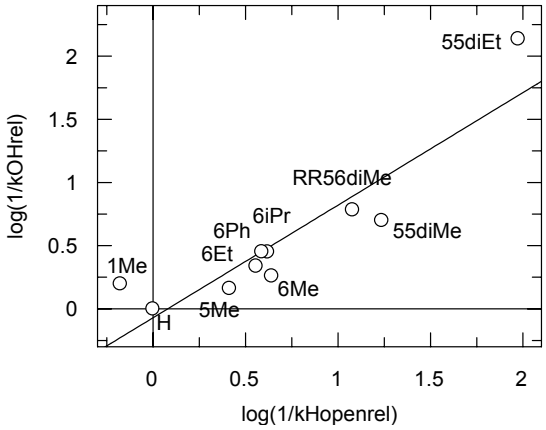


Fig. 4. Plot of $\log(1/k_{OH}^{rel})$ for the alkaline hydrolysis of 3-phenyldihydrouracils against $\log(1/k_{Hopen}^{rel})$.

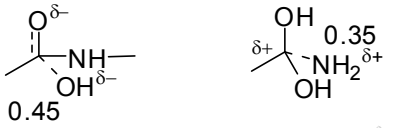
All points fitted the equation

$$\log(1/k_{OH}^{rel}) = \rho \log(1/k_{Hopen}^{rel}), \quad \rho = 0.89 \pm 0.15, \quad r = 0.906 \qquad (6)$$

which is a good achievement in itself taking into account the large variation in substitution.

An important application of Leffler type LFER is that the slopes, α, measure the value of the internal reaction coordinate, IRC. These for acid and alkaline hydrolysis of dihydrouracils are 0.65 (Eqn. 4a) and 0.48 (Eqn. 5), respectively, indicating a more advanced transition state under acid catalysis. This agrees with the smaller than unity slope of the k_{OH}/k_H correlation (Eqn. 4) but quantitatively the agreement is not close. Actually when the strongly deviating points for 1-Me and 5,5-diMe are excluded from the correlation on Fig. 4, a line of slope of 0.65 (r = 0.939) obtains which is in much better agreement with the ρ-values of Eqns. 2 and 3.

Because these hydrolysis reactions proceed through tetrahedral intermediates some elucidation is needed with regard to the meaning of the IRC. A convenient way is to assign 1 to the intermediate and zero to both reactants (the ring systems in our case) and products. With regard to steric effects to a large extent these are symmetrical on both sides of the intermediate♣. This allows conclusions to be drawn both in the cases of breakdown and of formation of tetrahedral intermediate. Rate determining in the alkaline hydrolysis of 3-phenyldihydrouracils is the attack of OH^- [22, 23], while in acid hydrolysis this is breaking of the C–N bond [21]. Thus α = 0.48 for alkaline hydrolysis means that the C–O bond is 48% formed, while in the acid hydrolysis IRC for the breakdown of the C–N bond will be (1 – 0.65) i.e. the breaking will be 35%.



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. Mass spectra EI on a JEOL JMS-D 300 spectrometer. The 1H NMR spectra on a Bruker DRX250 or a Avance II+ 600MHz instruments in DMSO-d_6 unless stated otherwise. ^{1}H-NMR signals were referenced TMS and coupling constants are given in Hz and without sign.

Materials

Inorganic reagents and buffer components were of analytical grade and were used without further purification. Potassium hydroxide solutions were prepared with CO_2-free distilled water. 3-(3-phenylureido)propanoic acid and its 2-methyl, 3-methyl, 2,2-dimethyl, 3,3-dimethyl, (R*,S*)-2,3-dimethyl derivatives as well as their cyclization products dihydropyrimidinediones have been described in Ref. 23. *cis*- and *trans*-2-Aminocyclohexane-carboxylic acid were obtained as described previously [24].

3-amino acids

β-Monosubstituted β-alanines were prepared essentially by the procedure developed by Rodionov and Zworykina [25] for 3-aminooctanoic acid.

3-Aminopentanoic acid. An ethanolic solution of ammonia (200 ml, 3.5% w/v) was added to propanal (16 g, 0276 mol) and malonic acid (28.7 g, 0.275 mol) in a round bottom flask under cooling with water. This was attached to a Liebig's condenser and the mixture slowly heated to 50–60°C and kept at this temperature for 2–3 h. The mixture was then brought to boiling and the oil remaining after ethanol was distilled off was heated further 3 h at 120°C on a glycerol bath. After cooling the oil (which hardens upon standing) was triturated with 200 ml diluted (1:3 v/v) hydrochloric acid. The mixture extracted three times with ether, the organic layer discarded. The water layer evaporated on a

♣ This applies to polar effects as well.

rotatory evaporator to dryness, adding twice some water and evaporating again to remove residual HCl. The residue dissolved in a minimal amount of water and passed through a column packed with the strong cation exchanger Wofatit KPS 200 I H^+-form. After washing the column with water to neutral reaction the amino acid was eluted with 1 L of diluted 1:10 v/v ammonia solution (ca. 1 M). The eluate evaporated to dryness gave an oil consisting of the amino acid according NMR, 6.8 g (yield 21%). Dissolved under reflux in 70 ml of dry ethanol and precipitated with 150 ml of dry ether to give 4.8 g (15%), m.p. 164–168°C decomp. ending at 185°C (lit. decomp. 160–165°C 185 clear [26]. ^{1}H NMR: (D_2O) 0.99 (t 3H 7.3), 1.69 (quintet 2H 7.3), 2.51 (2H AB octet of ABX Δν 31.8 Hz, J_{AB} 16.6, J_{AX} 8.1, J_{BX} 4.2), 3.44 (m 1H).

3-Amino-4-methylpentanoic acid. iso-Butyraldehyde (23 g, 0.319 gmol) and 6 g of ammonia dissolved in 50 ml of EtOH were mixed under ice-cooling followed by 33.2 (0.32 gmol) of malonic acid. The mixture was heated gradually to 80°C and kept at this temperarue for 3 h. over a period of two hours the temperature of the bath was raised to 120°C and kept at this temperature 4 h until evolution of CO_2 ceased. After work up as above and recrystallization of the free amino acid from ca. 250 ml of ethanol 22.0 g (52%) were obtained, m.p. 195.5–197°C (lit. m.p. 197–197.5°C [27]).

3-amino-4,4-dimethylpentanoic acid. Pivalaldehyde (6.9 g 0.08 mol), 8.3 g (0.08 mol) of malonic acid and 12 ml of 10–12% ethanolic ammonia under the above procedure gave 1.7 g (15%) of the free amino acid. m.p. 224–225°C (from ethanol, Kofler). Anal. Calcd for $C_7H_{15}NO_2$: N, 9.65. Found: N, 9.76.

2-(aminomethyl)butanoic acid. The amino acid was obtained from ethyl 2-cyanobutanoate [27] by hydrogenation [28] over PtO_2 under 40 atm of H_2 at room temperature for 1 h and subsequent hydrolysis of the amino ester. Ethyl 2-(aminomethyl)butanoate, (10.3 g 0.07 mol), was refuxed in 10 ml of 1/1 HCl for 11 h. Two layers were formed, the oil decreasing in the course of the reaction. After cooling, the oil was extracted with ether. The water layer evaporated to dryness. To remove residual HCl twice small amounts of water were added and evaporated again. The free amino acid was obtained by means of a strong cation exchanger as described above in a 66% yield. Recrystallized from ethanol/water. Could not be obtained in an entirely pure state according to t.l.c. (on silica with mobile phase MeOH/$CHCl_3$ (4/1) presaturated with ammonia placed in a separate vessel). This product was further transformed into N-phenylcarbamoyl derivative with phenylisocyanate.

2-(aminomethyl)-2-ethylbutanoic acid. The amino acid was obtained by hydrogenation from ethyl 2-cyano-2-ethylbutanoate [29] as described above. Ethyl 3-amino-2-ethylbutanoate (12.1 g 0.07 mol) was refluxed for 9 h in 60 ml of 1/1 (v/v) HCl. Some oil extracted with ether and the aqueous layer evaporated to dryness *in vacuo* to give 7.6 g of the hydrochloride (59%). The free amino acid was obtained by means of a strong cation exchanger as described above in a 43% yield. Recrystallized from ethanol/water. The crystal plates transform into needles at 180°C which melt at 225–230°C. Gives one spot on t.l.c. on silica with mobile phase MeOH/$CHCl_3$ (4/1) presaturated with ammonia placed in a separate vessel. This product was further transformed into N-phenylcarbamoyl derivative with phenylisocyanate.

3-(3-phenylureido) acids

3-(3'-Phenylureido)pentanoic acid. 3-Aminopentanoic acid (3.80 g, 32.5 mmol) was dissolved in 4.9 ml of 1 M KOH. Under stirring and cooling with ice 4.6 g, 38.7 mmol, of phenylisocyanate were added. After an hour, the cooling bath was removed and the mixture stirred at room temperature until the smell of PhNCO disappeared. Some diphenylurea was filtered off and the filtrate acidified with HCl (1:1 v/v) on Kongo Red. An oil was obtained which solidified with some crystalline phase upon standing in the fridge, 6.6 g (86%). Recrystallized twice from water/ethatnol 2.7 g m.p. 147–147.5°C with decomp. (lit. m.p. 141.5°C [30]). NMR: The precise assignments of the ^{1}H and ^{13}C NMR spectra could be achieved on a 600 MHz instrument and were accomplished by measurement of 2D homonuclear correlation (COSY), DEPT-135 and 2D inverse detected heteronuclear (C–H) correlations (HSQC and HMBC).

The spin system including protons from $CH_3CH_2CH(NH–)CH_2–$ fragment was simulated and the parameters were iterated by program DAISY (included in the program package TOPSPIN 2.1) in order to obtain precise values for chemical shifts and coupling constants. The fragment was treated as $ABMNP_2X_3$ system.

δ = 0.861 (t, J = 7.4 Hz, 3H, CH_3), 1.445 (qdd, J = 7.4, 8.1, 13.6 Hz, 1H, A-part), 1.523 (dqdd, J = 0.2, 5.3, 7.4, 13.6 Hz, 1H, B-part), 2.395 (d, J = 6.3 Hz, 2H, C<u>H</u>$_2$COOH), 3.866 (dtdd, J = 5.3, 5.3, 8.1, 8.6 Hz, 1H, CH), 6.094 (d, J = 8.6 Hz, 1H, N<u>H</u>CH), 6.871 (tt, J = 1.1, 7.4 Hz, 1H, *p*-Ph), 7.201 (dd, J = 7.4, 8.5 Hz, 2H, *m*-Ph), 7.365 (dd, J = 1.1, 8.6 Hz, 2H, *o*-Ph), 8.456 (bs, 1H, N<u>H</u>Ph), 12.2 (bs, 1H, COOH).

^{13}C NMR (150 MHz, DMSO-d6, 25°C): δ = 10.20

(CH_3), 27.06 (CH_2), 39.06 ($\underline{C}H_2COOH$), 47.48 (CH), 117.38 (*o*-Ph), 120.83 (*p*-Ph), 128.52 (*m*-Ph), 140.43 (*i*-Ph), 154.60 (NHCONH), 172.71 (COOH).

4-methyl-3-(3'-phenylureido)pentanoic acid. Obtained as above from the respective amino acid and phenylisocyanate in a 93% yield. Recystallized from water/ethanol m.p.143–145°C with decomp. Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25. Found: C, 62.74; H, 7.44.

4,4-Dimethyl-3-(3'-phenylureido)pentanoic acid. Obtained as above from the respective amino acid and phenylisocyanate in an 80% yield. M.p. 188–192°C decomp. (from ethanol/water). ^{1}H NMR (CD_3CN) 1.00 (s 9H), 2.33 (q 1H 9.8, 15.1), 2.695 (q 1H 3.7, 15.1), 4.099 (m 1H), 4.11 (t 1H ~ 1.5 Hz) 5.35 (d 1H) 7.04 (app. t 1H) 7.33 (app. t 2H) 4.45 (app. d 2H). Anal. Calcd for $C_{14}H_{20}N_2O_3$: N, 10.60. Found: N, 10.32.

3-((3'-phenylureido)methyl)butanoic acid. 2-(aminomethyl)butanoic acid (0.3 g 2.6 mmol) was treated with phenylisocyanate as described above to give 0.36 g (60%) phenylureido acid, m.p. 145–148°C decomp. (from ethanol/water). ^{1}H NMR: 0.89 (t 3H 7.0); 1.50 (m 2H); 2.38 (quintet 1H 6.5); 3.24 (m 2H); 6.19 (t 1H 5) 6.89 (app. t 1H 7); 7.21 (app. t 2H 7); 7.36 (app. d 2H 7); 8.52 (s). Anal. Calcd. for $C_{12}H_{16}N_2O_3$: N, 11.86. Found: N, 11.36.

2-ethyl-2-((3-phenylureido)methyl)butanoic acid. 2-(aminomethyl)-2-ethylbutanoic acid (0.70 g 4.8 mmol) was treated with phenylisocyanate as described above to give 1.01 g (78%) phenylureido acid, m.p. 182–184°C with decomp. (from ethanol/water). ^{1}H NMR: 0.80 (t 6H 7.3); 1.50 (quartet 4H 7.3); 3.30 (d 2H 5.9); 6.02 (t 1H 5.9); 6.89 (app. t 1H 7); 7.22 (app. t 2H 7); 7.37 (app. d 2H 7); 12.41 (broad s). Anal. Calcd. for $C_{14}H_{20}N_2O_3$: N, 10.60. Found: 10.42.

(R,S*)-2-methyl-3-(3-phenylureido)butanoic acid. (R*,S*)*-3-Amino-2-methylbutanoic acid (1.17 g 0.01 mol) was treated with phenylisocyanate as described above to give 2.27 g (96%) phenylureido acid. Recrystallized by dissolving at room temperature in 1:1 water/ethanol and cooling, m.p. 181–181.5°C with decomp. Anal. Calcd. For $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.84. Found: C, 60.82; H, 6.95; N, 11.31.

cis-2-(3-phenylureido)cyclohexane carboxylic acid. cis-2-Aminocyclohexane carboxylic acid (3.66 g 25.6 mmol) was treated with 3.62 ml of phenylisocyanate as described above to give 2.73 g (40%) phenylureido acid, m.p. 157–158°C from ethanol, one spot on t.l.c. on silica with petroleum ether/ethyl acetate/2-butanol 2/2/1, R_f 0.6. Anal. Calcd. for $C_{14}H_{18}N_2O_3$: N, 10.68. Found: 10.35.

trans-2-(3-phenylureido)cyclohexane carboxylic acid. trans-2-aminocyclohexane carboxylic acid (0.406 g 2.8 mmol) of was treated with 0.40 ml of phenylisocyanate as described above to give 0.609 g phenylureido acid, m.p. 196–199°C from ethanol/water, one spot on t.l.c. on silica with petroleum ether/ethyl acetate/2-butanol 2/2/1, R_f 0.3. Anal. Calcd. for $C_{14}H_{18}N_2O_3$: N, 10.68. Found: 10.80.

Dihydropyrimidine-2,4-diones

6-*Ethyl-3-phenyl-dihydropyrimidine-2,4-dione.* 3-Phenylureidopentanoic acid (0.60 g, 2.5 mmol) were refluxed for one hour in 5 ml of ethanol and 10 ml of 1:2 HCl. After concentrating the solution and cooling, the formed precipate was filtered and recrystallized from 10 ml of ethanol. Yield 0.28 g, 41%. M.p. 199–200°C (lit. [22] m.p. 192°C). ^{1}H NMR: 0.90 (t 3H 7), 1.53 (m 2H) 2.69 (2H AB octet of ABX Δν 54 Hz, J_{AB} 16, J_{AX} 9.5, J_{BX} 5.5,), 3.50 (m 1H) 7.14 (app. d 2H), 7.38 (m 3H) 8.06 (s).

6-I*sopropyl-3-phenyl-dihydropyrimidine-2,4-dione*. 4-Methyl-3-(3'-phenylureido)pentanoic acid (2.0 g 8 mmol) in 50 ml 1:5 (v/v) HCl and 30 ml of ethanol were refluxed for 3 h. Upon cooling and recrystallization from ethanol 0.67 g (36%). M.p. 183–185°C. Anal. Calcd for $C_{13}H_{16}N_2O_2$: N, 12.06. Found: N, 12.27.

6-*tert.-Butyl-3-phenyl-dihydropyrimidine-2,4-dione*. 4,4-Dimethyl-3-(3'-phenylureido)-pentanoic acid (0.264 g 1 mmol) was refluxed for 8 h 8 ml of 1:1 (v/v) HCl to which 10 ml of ethanol have been added. A solution was obtained from which upon cooling 70 mg (38%) of the dihydrouracil precipitated as needles. The mother liquor contained a mixture of dihydrouracil and the initial ureido acid (t.l.c. on silica $CDCl_3$ as the eluent). M.p. 228–230°C. ^{1}H NMR: ($CDCl_3$) 1.03 (s 9H), 2.82 (m 2H; AB octet of ABX; lines of lower field quartet additionally split into doublets (^{14}J = 1.3 Hz to 1NH), Δν 29 Hz, J_{AB} 16.4, J_{AX} 10.1, J_{BX} 4.9), 3.42 (octet 1H 10.1, 4.9. 1.7), 5.53 (m 1H unresolved) 7.17 (m 2H) 7.35–7.49 (m 3H). Anal. Calcd for $C_{14}H_{15}N_2O_2$: N, 11.37. Found: N, 11.12.

5-Ethyl-3-phenyl-dihydropyrimidine-2,4-dione. 2-Ethyl-2-((3-phenylureido)methyl)butanoic acid (0.472 g 2 mmol) were refluxed for 10 h in 15 ml of 1:1 (v/v) HCl. After cooling the homogenous solution was evaporated to dryness, adding water and repeating the process until HCl was removed. The residue was an oil consisting of a mixture of the reactant and product dihydropyrimidinedione. Attempts for separation by crystallization were unsuccessful. The oil was triturated with $CHCl_3$. The chloroform extract 160 mg was subjected to

preparative t.l.c. on 20×20 cm glass plates coated with silica. Eluted three times with diethyl ether. The slices containing the product were extracted with 500 ml of $CHCl_3$. The dry residue 120 mg subjected to analysis. M.p. 109–111°C Anal. Calcd for $C_{12}H_{14}N_2O_2$ N, 12.84. Found: N, 12.81.

5,5-Diethyl-3-phenyl-dihydropyrimidine-2,4-dione. 2-Ethyl-2-((3-phenylureido)methyl)butanoic acid (0.528 g 2 mmol) was refluxed for 10 h in a mixture of 15 ml 1:1 HCl and 5 ml ethanol. After cooling 0.4 g precipitated presenting a mixture of starting ureido acid and the cyclic product. The two show very similar R_f-values on t.l.c. and could be separated after multiple elution with ether. Pure dihydropyrimidine-2,4-dione was obtained by means of repeated recrystalliztion. UV monitoring of the cyclization showed that equilibrium is reached with a half-live of ca. 1 h at 90°C. M.p. 122–124°C Anal. Calcd for $C_{12}H_{14}N_2O_2$: N, 11.37. Found: N, 11.37.

cis-5,6-tetramethylene-3-phenyldihydropyrimidine-2,4-dione. *cis*-2-(3-phenylureido)cyclohexane carboxylic acid (0.203 g 0.78 mmol) in 360 ml of 1:6 HCl was stirred at 70°C for 14 h. The reaction course was followed by means of UV-spectral analysis in the following manner: Aliquots: 0.8 ml of the reaction solution were diluted to 25 ml with distilled water and the extinction measured at λ_{max} = 238.5 of the phenylureido acid (the absorbance of dihydrouracils is negligible at this wave-length. Aliquot of the diluted sample was mixed with an equal volume of 0.1 M NaOH whereby the dihydrouracil was rapidly hydrolysed. The extinction of the hydrolysate should equal that of 1/2 of the initial ureido acid and can serve also to assess to any degradation to amino acid. Under the above conditions over 90% yield of the pyriminedione was estimated and no significant amounts of amino acid. As no precitate was formed after cooling, the reaction solution was evaporated to dryness washed with water to remove HCl and recrystallised from ethanol/water to give 0.113 g (59%) m.p. 219–220°C after second recrystallization. One spot on t.l.c. on silica with petroleum ether/ether/2-butanol 2/2/1 as the eluent

trans-5,6-tetramethylene-3-phenyldihydropyrimidine-2,4-dione. trans-2-(3-Phenylureido)cyclohexane carboxylic acid, 0.150 g 0.57 mmol, in 360 ml of 1:5 HCl were heated for 9 h at 65°C. The reaction mixture evaporated to ca 20 ml and left to crystallize. The precipitate filtered, dissolved in hot EtOH, treated with carbon and left to crystallize. 120 mg (86%) m.p. after second recrystallization in sealed capillary 260–261°C. Sublimates around 250°C in a Koffler apparatus.

cis-5,6-dimethyl-3-phenyldihydropyrimidine-2,4-dione. (R*,S*)-2-Methyl-3-(3-phenylureido)butanoic acid (0.52 g 2.2 mmol) in 15 ml 1:5 (v/v) HCl and 10 ml of ethanol were refluxed for 3 h. The solution concentrated and left to crystallize. The precipitate was recrystallized from ethanol/water to give 0.12 g (25%) of *cis*-dihydropyrimidinedione, m.p. 181–181.5°C. Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.00, H, 6.83, N, 12.86. Found: C, 60.82, H, 6.95, N, 12.29.

trans-Ethyl 2-(3-phenylureido)cyclohexane carboxylate. *trans*-2-(3-Phenylureido)cyclohexane carboxylic acid (0.286 g 1.1 mmol) was refluxed in a mixture of 7 ml of 1:5 HCl and 8.5 ml of EtOH for 10 h. t.l.c. (ethyl acetate/petroleum ether/*n*-butanol 2/2/1) showed under UV a mixture of the initial ureido acid and a faster miving product. Upon cooling 96 mg of amino acid hydrochloride separated (ninhydrin reaction on t.l.c.). The mother liquor was evaporated to dryness and the residue dissolved in a mixture of water and ether and alkalized to pH 8 with aqueous ammonia. The ether layer yielded 80 mg product purified from admixture of the ureido acid by preparative t.l.c. with ether as the mobile phase. The extracted oil recrystallized from ethanol/water bright plates, m.p. 117–118°C. Anal. Calcd. for $C_{16}H_{22}N_2O_3$: N, 9.65. Found: 9.95. MS (chemical ionization) [M+1] 291 (fragments: 198, 172, 94).

cis-Ethyl 2-(3-phenylureido)cyclohexane carboxylate. *cis* 2-(3-phenylureido)cyclohexane carboxylic acid (0.450 g 1.7 mmol) was refluxed for 3 h in a mixture of 10 ml of 1:5 HCl and 6 ml of ethanol. Similar work up as with the *trans* isomer and preparative t.l.c. with ether/petroleum ether 1/1 gave 85 mg product which was recrystallized from methanol/water, m.p. 99–101°C. Anal. Calcd. for $C_{16}H_{22}N_2O_3$: N, 9.65. Found: 10.18. MS (chemical ionization) [M+1] 291 (fragments: 198, 172, 94).

Kinetic runs

The acid catalyzed reactions were carried out in 1 M H_2SO_4 at 70.0°C as described in Ref. 21 using two techniques: in the 10 mm stoppered quartz cells or in sealed ampoules for the slow reactions. The monitoring of both the cyclization and ring-opening reactions as well as the equilibrium concentrations was done at 238–240 nm which is λ_{max} due to the phenylureido chromophore. The extent of further hydrolysis to amino acid was checked by means of alkaline hydrolysis of the product which restored the expected ureido acid absorption within experimental error. To this purpose, after completion of the reaction 1, 2 ml of the solution of the substrate in

1 M H_2SO_4 were diluted with 3 ml of 3 M KOH and 5 ml of water. At this alkalinity of 0.22 M the hydrolysis to the ureido acid is complete within several minutes and the absorption of the ureido acid salt can be compared to that of the acid because the extinctions are equal. Equilibria were reached starting from ureido acid and from dihydrouracil.

The rates of alkaline hydrolysis of the dihydrouracils were measured in 0.01 M KOH, I = 1 (KCl) at 25.0°C in the temperature controlled cell holder of the UNICAN SP 800 instrument using motors for fast scanning essentially as described in Ref. 23.

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ЛИНЕЙНИ ЗАВИСИМОСТИ НА СВОБОДНИТЕ ЕНЕРГИИ НА *гем*-ДИМЕТИЛ ЕФЕКТА (*гем*-ДИАЛКИЛ ЕФЕКТА)

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Посветена на акад. Иван Юхновски по повод на 70-та му годишнина

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гем-Диметил ефектът или диалкил ефектът, ГДМЕ, изразяващ се в ускорение на реакции на циклизация или забавяне на отварянето на пръстени от заместители във веригата, не се описва задоволително от Хаметови линейни зависимости на свободните енергии, ЛЗСЕ, напр. използване на Тафтовите E_S-константи. Причина затова е природата на ГДМЕ. За голяма реакционна серия на обратимата циклизация на 3-(3-фенилуреидо) киселини бе намерена добра ЛЗСЕ от Лефлеров тип, т.е. корелация на скоростните константи с равновесните константи на същата реакция, която обхваща заместителите при различни положение в пръстена. Тази ЛЗСЕ дефинира общия ГДМЕ; малък брой отклоняващи се точки се дължат на специфични взаимодействия, възникващи в преходните състояния, но не и в реактантите или продуктите. Приложение към други реакции на същата пръстенна система може да се осъществи по два начина: корелация на скоростните константи с равновестните константи на киселинно катализираната циклизация на β-уреидо киселини приета за референтна реакция или като се корелират скоростните константи на две реакции с подобни преходни състояния. Вторият подход трябва да елиминира появата на „специфични” взаимодействия при стерично подобие на преходните състояния. Двата подхода се илюстрират много добре от корелации на голяма серия скоростни константи на алкална хидролиза на дихидроурацили.

Редица β-амино киселини с β-алкил заместители бяха успешно синтезирани с еднокюпната процедура на Родионов от съответните алдехиди и малонова киселина. Голяма част от скоростните константи и равновесни константи за киселинно и основно катализирана хидролиза на 3-фенилдихидропиримидин-2,4-диони се съобщават за първи път в настоящата работа.