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The Electronic and Steric Effects in Heterolytic Intramolecular Cyclisation Reactions

R.Valters

Data concerning the influence of the electronic and steric effects of substituents as well as the structure of the connecting units on the rate and equilibrium constants for cyclisation reactions, occurring as intramolecular nucleophilic addition to a trigonal carbon atom, are examined. The general characteristics permitting the prediction of the ease of ring closure and the stability of the heterocycles are specified.
The bibliography includes 166 references.

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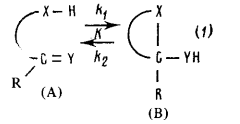
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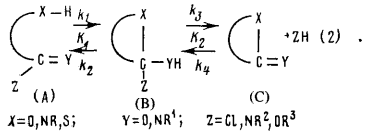
I. INTRODUCTION

The assessment of the influence of structural factors on intramolecular cyclisation reactions makes it possible to predict the ease of formation and the stability of heterocycles[1-3]. Factors promoting ring closure act similarly in the recyclisation reactions of heterocycles[4], in intramolecular catalysis[5-10], in the migration of acyl and other groups[8,10-12], and in other reactions which proceed with formation of cyclic transition states or cyclic intermediates. Studies of the mechanisms of enzymatic reactions[8,9,13-15], of the formation of chelates[16], and of the intramolecular hydrogen bond[17-19] are closely related to the problem of the influence of structural factors on intramolecular cyclisation.

The aim of the present review is to examine the influence of the electronic and steric effects of substituents at the reacting groups and the structure of the unit connecting them (the carrier system) on the relative stabilities of the heterocycles formed (represented by $\lg K$, where K is the ring–chain equilibrium constant) or on the ease of their formation (represented by $\lg k$, where k is the rate constant for the cyclisation reaction).

We shall confine ourselves to the consideration of the intramolecular nucleophilic reactions involving the addition of the O–H, N–H, and S–H groups to the multiple polar bonds C=Y [reactions (1)] occurring with subsequent elimination [reactions (2)] or without it, i.e. with retention or cleavage of the tetrahedral intermediate; there is yet another limitation, i.e. only the closure of the so-called[2] normal, i.e. five-membered, six-membered, and seven-membered, heterocycles will be considered†. The molecular fragment which constitutes the carrier system for the groups reacting with one another is designated by a half-circle in Eqns.(1) and (2).





This choice makes it possible to employ the accumulated data on the ring–chain isomerism of organic compounds[20-23]; it is dictated primarily by the availability of quantitative literature data precisely for such reactions.

In reaction (1) the thermodynamic stability of the ring will be characterised by the ring–chain equilibrium constant K or the free energy difference ΔG, which is proportional to the logarithm of K. It is most rational to examine the influence of the relevant structural factors precisely on the equilibrium constant K. However, one must then take into account the fact that small changes in structure very frequently displace the system from the state of tautomeric equilibrium[12,23] and the possibility of employing the equilibrium constant for comparative purposes is lost. The use of the enthalpy and entropy components (ΔH and ΔS) of the free energy difference is limited by the comparatively small amount of experimental data. The use of ΔH and ΔS involves a number of uncertainties which are difficult to overcome and which have been examined by Jencks[9] (p.246). Among these, the impossibility of applying corrections for solvation effects is most important for reactions in solutions.

The energetic aspect of intramolecular reactions with separate analysis of the enthalpy and entropy contributions and their comparison with intermolecular reactions have been described in a review[24]. It is easy to show that the estimation of the individual components of the difference between the potential energies of the open-chain and cyclic structures, which are due to changes in bond lengths, the deformation of valence angles, the non-bonding and electrostatic interactions, steric strain, solvation, and the formation of hydrogen bonds, is difficult to achieve experimentally.

†The influence of structural factors on cyclisation reactions with formation of large rings has been examined in a recently published review: G.Illuminati and L.Mandolini, Acc.Chem.Res., 1981, **14**, 95.

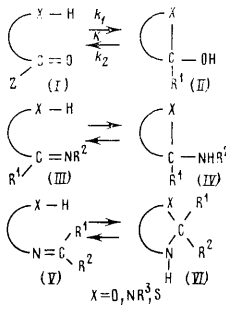
The use of the cyclisation rate constant k_1 for the estimation of the ease of formation of the ring is associated with another type of uncertainty. The transformation (A) → (B) [Scheme (1)] consists of three stages: the abstraction of a proton from the group X–H, the formation of the X–C bond, and the addition of a proton to Y. The sequence of these stages is determined by the acidity of the groups X–H and Y–H and also by the protolytic properties of the medium and is not the same for different systems[23]. The ease of formation of the ring is characterised by the constant k_1 (or the corresponding activation energy $\Delta G^{\neq}$) only when the ring closure stage, i.e. the formation of the X–C bond, is slowest and the transition state has a cyclic structure. However, this is not always the case, because it has been shown experimentally for certain ring–chain tautomeric systems that the rate is limited by the proton transfer stage[25–27].

The suitability of thermodynamic and kinetic characteristics of the second group of reactions [reactions (2)] for the estimation of the stability and ease of formation of heterocycles is limited by the presence of the stage involving the cleavage of the tetrahedral intermediate. The equilibrium (B) ⇌ (C) is usually displaced to the right, but it is necessary to take into account the fact that the equilibrium constant $K = [B]/[A] = k_1/k_2$ and k_2 can be determined experimentally only by an indirect method.

The employment of the kinetically determined rate constant for the transformation (A) → (B) for our purposes is also correct (when account is taken of the considerations presented above) only when $k_1 < k_3$.

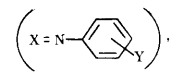
II. ELECTRONIC EFFECTS OF SUBSTITUENTS AT THE REACTING GROUPS

Inspection of a large number of ring–chain equilibrium systems of the type (I) ⇌ (II), (III) ⇌ (IV), and (V) ⇌ (VI) [23] permits the conclusion that the stability of the cyclic form, produced as a result of the intramolecular nucleophilic addition of the group X–H to a polar multiple bond, increases in the sequence of atoms X = O < N < S (naturally, other structural conditions being equal or similar).



This sequence agrees with the equilibrium constants for intermolecular reactions involving addition to the C=O bond[28] and can be accounted for both by the increase of the nucleophilicity of the atom X and by the smaller strain energy[24] in sulphur-containing heterocycles compared with the oxygen- and nitrogen-containing heterocycles.

The influence of the nucleophilicity of the atom X on the stability of the cyclic isomer can be traced in the series of amino-derivatives with different substituents at the nitrogen atom. Thus the introduction of electron-donating substituents Y into the phenyl group at the nitrogen atom

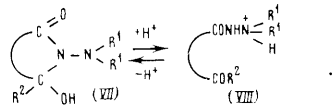


shifts the equilibrium towards the cyclic form, while electron-accepting substituents shift the equilibrium in the opposite direction[29,30]. The foregoing is confirmed by the negative value of the constant ρ,[30] obtained from the correlation between the ring–chain equilibrium constants for *N*-arylamides of 3,3-dimethyl-levulinic acid and the polar constants of the substituents Y (Table 1).

N-Methylated derivatives (X = NCH_3) almost always exhibit a greater tendency towards cyclisation than their analogues unsubstituted at the nitrogen atom (X = NH).[38–48] Several exceptions can be explained[44–46] by the steric influence of the methyl group, which destabilises the cyclic structure. As the length and degree of branching of the alkyl substituent at the nitrogen atom increase, its electronic influence cannot be estimated, because the steric effects are much stronger.

The cyclic structure is also destabilised by the decrease of the nucleophilicity of the nitrogen atom as a result of the introduction of aryl or acyl substituents at this atom[23].

The protonation of the dialkylamino-group in the cyclic isomer of the *N,N*-dialkylhydrazide of a 3-acylcarboxylic acid proceeds with ring opening [(VII) → (VIII)], while deprotonation is accompanied by the reverse process[47,48]. This phenomenon can be explained by the influence of the strong $-I$ effect of the substituent $N^+HR_2^1$, which reduces the nucleophilicity of the second nitrogen atom.



The higher ring–chain equilibrium constants in solutions for 2-acylmercaptoperimidines compared with 2-acylmercaptobenzimidazoles have been explained[49] by the greater basicity of the perimidine nitrogen atom compared with the benzimidazole nitrogen atom.

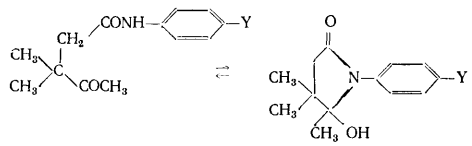
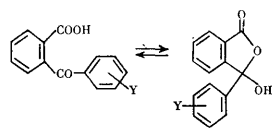
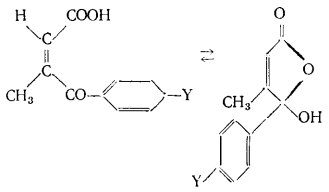
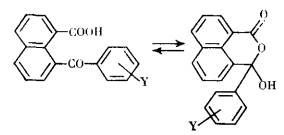
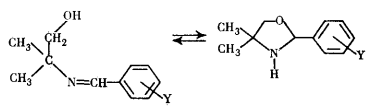
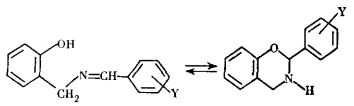
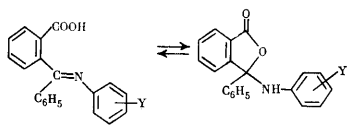
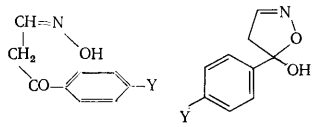
In the series of 3- and 4-acylcarboxylic acid [(I) ⇌ (II), X = COO] it is easy to trace the influence of the structure of the substituent on the ring–chain equilibrium constants. A pronounced shift of the equilibrium towards the cyclic form in the series of substituents aryl < alkyl < H is observed[21,23]. The enhanced stability of the open-chain isomers of aroylcarboxylic acids is caused not only by the reduced electrophilicity of the carbon atom of the group ArCO but also by the gain of the conjugation energy.

For tautomeric systems producing the cyclic form as a result of intramolecular addition to the C=N bond, the pattern of the influence of the electronic effect of substituents at this bond is more complex[50].

For hydroxyaldehyde imines [(III) ⇌ (IV), X = O, R^1 = H], the equilibrium is much more displaced towards the cyclic form than for hydroxyketone imines [(III) ⇌ (IV), X = O, $R^1 = CH_3$].[51] Similarly the *N*-(2-hydroxyalkyl)hydrazones of aldehydes show a greater tendency towards cyclisation compared with the *N*-hydroxyalkylhydrazones of ketones[50,52]. However, in this case the electronic effect of the alkyl group, which reduces the electrophilicity of the carbon atom in the C=N bond, is overlapped by the stronger steric effect of the alkyl substituent, which destabilises the cyclic structure[50–52].

The opposite effect has been observed[53] in the series of *N*-(2-mercaptoalkyl)hydrazones of aromatic aldehydes: on passing from a benzaldehyde derivative to an acetophenone derivative, the ring–chain equilibrium shifts towards the

Table 1. Examples of the linear correlation of the ring–chain tautomeric equilibrium constants $K = [B]/[A]$ and the polar constants of the substituents Y in the benzene ring at the reaction centre.

Ring-chain equilibrium (A) ⇄ (B)	Solvent	Method of determination of K	lg K/K_0	n	r	References
	50% aqueous pyridine	^{1}H NMR	$-1.38\,\sigma^+$ $-1.85\,\sigma$ $-1.45\,\sigma^-$	8	1.96 0.93 0.94	[30]
	$MeNO_2$ MeCN dioxan $CHCl_3$	i.r.* i.r. i.r. i.r.	$0.87\,\sigma$ $0.60\,\sigma$ $0.54\,\sigma$ $1.15\,\sigma$	9	— — — —	[31]
	dioxan	i.r.	$0.374\,\sigma_I + 1.885\,\sigma_R^0$	6	0.990	[32]
	dioxan	i.r.	$1.286\sigma_I + 2.918^0_R$	8	0.970	[33]
	CCl_4	^{1}H NMR	$0.856\,\sigma$ $0.543\,\sigma^+$	8	0.973 0.999	[34]
	$CDCl_3$	^{1}H NMR	$0.738\,\sigma$ $0.680\,\sigma^+$	5	0.993 0.999	[34,35]
	*dioxan*	u.v.**	$0.58\,\sigma$ $0.35\,\sigma^+$	7	0.94 0.97	[36]
	C_5D_5N	^{1}H NMR	$1.26\,\sigma^+$ $1.41\,\sigma_I + 1.26\,\sigma_R^+$	9	0.993	[37]

Note. K_0 is the ring–chain equilibrium constant for the unsubstituted derivative (Y = H), K the constants for substituted derivatives, n the number of compounds with different substituents Y, and r the correlation coefficient. The signs of the constants ρ are quoted in accordance with the condition $K = [B]/[A]$. Sheiman et al.[30] and Paukstelis and Lambing[34] calculated the equilibrium constants from the formula $K = [A]/[B]$.

*Infrared spectroscopy. ** Ultraviolet spectroscopy.

cyclic form, which has been explained by the influence of the breakdown of the conjugation $\diagdown N-N=\overset{|}{C}-Ar$ in the open-chain isomer after the introduction of the methyl group.

The *N*-(2-hydroxybenzyl)imines of aromatic aldehydes exhibit a smaller tendency towards cyclisation than the corresponding derivatives of acetone or cyclohexanone[35] owing to the gain in the conjugation energy in the open-chain isomer.

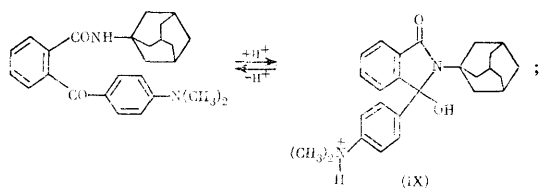
An increased stability of the cyclic form has been observed in the *N*-arylimines of 5-hydroxypentanal compared with the *N*-alkylimines[51,54,55]. The authors explain this remarkable effect by the energy gain in the $p-\pi$ conjugation of the unshared electron pair of the nitrogen atom with the arene ring in the cyclic isomer compared with the $\pi-\pi$ conjugation,

which is disrupted, according to the authors, by the non-coplanarity of the C=N–Ar system in the open-chain isomer.

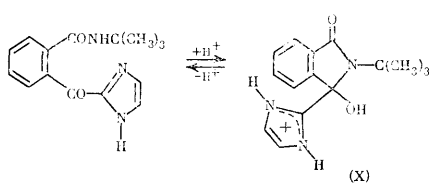
The introduction of an acyl group at the imine nitrogen atom in the imines of 2-benzoylbenzenesulphonamides stabilises the cyclic structure of 3-acylamino-3-phenylbenzoisothiazoline 1,1-dioxides[56]. The introduction of electron-accepting substituents Y in the phenyl groups of the C=O or C=N bonds [R^1 and R^2 in compounds (I)–(VI)] as a rule shifts the equilibrium towards the cyclic form, while electron-donating substituents act in the opposite direction. This conclusion confirms the examples of the linear correlation of the ring–chain tautomeric equilibrium constants for aroylcarboxylic acids and their *N*-arylimines, *N*-(2-hydroxybenzyl)- and *N*-(2-hydroxyalkyl)aldimines, and 3-aryl-1-hydroxyimino-3-propanones with the polar constants of the substituents Y ($\rho > 0$), which are presented in Table 1.

In addition, for certain systems, for example, for *N*-t-alkyl-2-aroylbenzamides, the introduction of electron-accepting substituents in the aroyl group made it possible to obtain cyclic isomers of compounds which did not undergo cyclisation in the absence of such substituents[57,58]. The rate constants for the interconversions of the isomers then increase and the equilibrium shifts towards the cyclic form[59].

An interesting example of the stabilisation of the cyclic form of *N*-t-alkyl-2-(4-dimethylaminobenzoyl)benzamides (IX) and 2-(2-imidazoylcarbonyl)benzamides (X) by the protonation of the dimethylamino-group or the imidazole ring has recently been observed[60–62].



(IX)

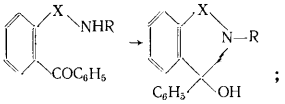


(X)

The protonation of the nitrogen-containing substituent increases its *–I effect*, which enhances the electrophilic properties of the carbon atom of the C=O group and displaces the equilibrium towards the cyclic form. Deprotonation is accompanied by the reverse process.

Numerous qualitative and quantitative data[20–23] confirm the following general rule: the influence of the electronic effects of substituents on the relative stabilities of cyclic isomers formed as a result of the intramolecular nucleophilic addition of the group X = H to the polar multiple bonds C=O, C=N, etc. can be predicted by estimating the influence of these substituents respectively on the nucleophilic and electrophilic properties of the atoms between which the bond is formed on ring closure. As the nucleophilic properties of the atom X are enhanced and (or) with increase of the electrophilicity of the carbon atom in the groups C=O, C=N, etc., the equilibrium shifts towards the cyclic form.

This rule applies not only to the substituents R^1, R^2, and R^3 in compounds (I)–(VI) but also to the electronic influence of the structure of the connecting unit and the substituents incorporated in this unit. Thus it has been shown that 2-benzoylbenzenesulphinamides are capable of intramolecular cyclisation [(XI) ⇌ (XII), X = SO],[63] whereas the analogous reaction for 2-benzoylbenzenesulphonamides (XI, X = SO_2) is not feasible[64]. This phenomenon can be explained by the reduction of the nucleophilicity of the nitrogen atom on passing from the sulphinamide to the sulphonamide group.



(XI) (XII)

X = SO, SO_2 .

However, the estimation of the electronic influence of the structure of the connecting unit on the reacting groups is associated with difficulties due to the overlap of the electronic effects with the steric effects, which alter the geometry of the mutual approach of the reacting groups.

The influence of the electronic effects of the substituents on the ring–chain equilibrium constants can be effectively predicted in conformity with the principle of the linearity of the variation of the free energies in those cases where the substituents are introduced into aryl groups at the reaction centres.

When the substituents R^1, R^2, or R^3 in compounds (I)–(VI) are varied in the sequence H, alkyl, aryl, their electronic influence is much more difficult to estimate, because it is then necessary to take into account also their steric effects, the gain in the stabilisation energy of the corresponding isomers as a result of the conjugation of the C=O and C=N bonds or the *p* electrons of the nitrogen atom with the aryl substituents, the stabilisation of the individual isomers as a result of the formation of intramolecular and intermolecular hydrogen bonds, or various solvation effects.

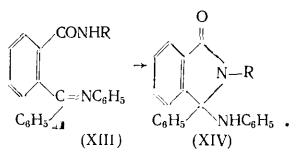
An estimate[23] of the thermodynamic stabilities of cyclic isomers from the changes in the nucleophilic and electrophilic properties of the reaction centres aroused objections[65], because a kinetic characteristic was used to estimate thermodynamic quantities. Although the stabilities of the corresponding cyclic isomers are usually satisfactorily correlated with the O < N < S nucleophilicity series in relation to the electrophilic carbon, one may agree that, in comparing different atoms X acting as nucleophilic centres, it is necessary to take into account also factors such as the different strains in the rings formed, the different capacities for the formation of hydrogen bonds, etc. However, under the influence of substituents, the difference between the free energies of the isomers varies in proportion to the difference between the free energies of activation, i.e. the polar constants of the substituents are correlated both with the equilibrium constants and with the reaction rate constants[66].

In other words, the changes in the structures of the carbonyl compounds are reflected similarly in the rates and equilibria of non-catalysed reactions involving addition to the carbonyl group, because both the transition state and the final product are destabilised by electron-accepting substituents to a smaller extent than the initial carbonyl compound[28].

III. STERIC EFFECTS OF SUBSTITUENTS AT THE REACTING GROUPS

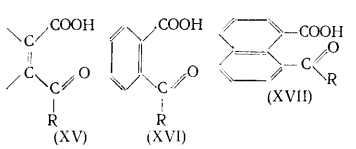
In order to estimate the steric influence of substituents at the reacting groups on the relative stabilities of cyclic isomers, the influence of the substituents on the possibility of the optimum intramolecular mutual approach of the reaction centres is usually considered. A more profound approach involves the calculation or empirical estimation of the difference between the energies of the non-bonding interactions between the substituent and the remainder of the molecule in the open-chain and cyclic isomers.

An increase in the length and branching of the alkyl substituent at the nitrogen atom in aminocarbonyl compounds [(I) ⇌ (II), X = NMe > NEt > NPr-iso > NBu-t] destabilises the cyclic structure. There exist examples of such influence on the ring–chain isomerism of *N*-monosubstituted amides of acylcarboxylic acids[21,23,56,67–69], *N*-alkyl-*N'*-(3-oxoalkyl)-thioureas[70], *S*-(2-oxoalkyl)dithiocarbamates[71], and other compounds[23]. Similar features have also been observed for reactions involving intramolecular addition to the C=N bond. Increasingly severe conditions are required for the isomerisation (XIII) → (XIV) in the presence of the series of substituents R = Pr, $PhCH_2$, iso-Pr, or t-Bu at the nitrogen atom[72]. The reverse reaction—the thermal isomerisation of the aminolactam [(XIV) → (XIII)]—has been achieved for the first time in the case of *N*-t-butylamide[73,74]:



Branching of the alkyl substituent at the keto-group [R^1 in formulae (I) and (II)] in different systems has the opposite influence on the stability of the cyclic form:

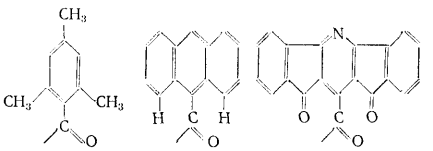
(1) If the connecting unit contains a double bond or an aromatic ring conjugated with the keto-group, as happens in *cis*-3-acylacrylic acids (XV),[75] 2-acylbenzoic acids (XVI),[76] and 8-acylnaphthoic acids (XVII),[33] then an increase in the bulk of the alkyl substituent R in the sequence Me < Et < iso-Pr < t-Bu shifts the equilibrium (I) ⇌ (II) (X = COO) towards the cyclic form:



With increase of the bulk of R, the keto-group "unscrews itself" from the plane of the double bond or the aromatic ring and assumes the conformation most suitable for intramolecular addition; furthermore, the electrophilicity of the carbonyl carbon atom increases owing to the decrease of the effect of conjugation as coplanarity breaks down. All these factors destabilise the open-chain structure. In the series of 8-acylnaphthoic acids (XVII) [33] the ring–chain equilibrium constants are satisfactorily correlated with the Taft steric substituent constants E_S [$\lg(K/K_0) = -0.60\,E_S$, $r = 0.977$].

(2) If the connecting unit forms a conformationally mobile chain, the opposite effect is observed: an increase in the bulk of the substituent R destabilises the cyclic structure. Thus, on branching of the substituent, the content of the cyclic form decreases in the series of *S*-(2-oxoalkyl)dithiocarbamates[71], 2-acylmethylmercaptobenzimidazoles[49,77], 2-acylmethylmercaptoperimidines[49], and 1-(2-oxoalkyl)-3-phenyltriazenes[29]. This effect is less clear-cut than the first effect and there are exceptions. For example, the influence of the branching of the alkyl substituent at the keto-group on the ring–chain equilibrium constants for 3-alkyl-1-hydroxyimino-3-propanones[37] is extremely complex and is not correlated with the steric substituent constants E_S.

The 2,6-dimethylphenyl and 9-anthryl residues as well as the analogous condensed systems exert a specific steric influence on the keto-group:



The plane of these substituents has "become detached" from the plane of the keto-group and therefore the *o,o'*-methyl groups of the mesityl substituent, the *peri*-protons of the anthryl substituent, and the oxygen atoms of the condensed dibenzoylenepyridine system prevent the intramolecular nucleophilic attack by the XH group directed at right angles to the plane of the C=O bond. For this reason, the amides of 2-(2,4,6-trimethylbenzoyl)-,[78] 2-(9-anthroyl)-,[79] and 2-[2,3(CO),6,5(CO)-dibenzoyleneisonicotinoyl]-benzoic acids[80] have an open-chain structure regardless of the structure of the substituent at the nitrogen atom and do not cyclise under the conditions of alkaline catalysis. Similar examples are known also for carboxylic acids—2-(2,4,6-trimethylbenzoyl)benzoic and 8-(2,4,6-trimethylbenzoyl)-naphthoic acids[81] and also for the substituted carbinols $2\text{-}R^1COC_6H_4CR_2OH$, where R = Me or Ph and R^1 = 2,4,6-trimethylphenyl[82] or 9-anthryl[83], and for 2-hydroxy-1,4-di-(2,4,6-trimethylphenyl)butane-1,3,4-trione[84].

An increase in the length and branching of the alkyl substituents at the azomethine linkage [R^1 and R^2 in formulae (III)–(VI)] also destabilise the cyclic structure. For example, the ring–chain equilibrium constants for the *N*-(1-hydroxy-1-phenyl-2-propyl)-*N*-methylhydrazones of aliphatic aldehydes[85] decrease with increase of the bulk of the alkyl substituent in the sequence Me < Et < iso-Pr < t-Bu. The same behaviour is observed also for the *N*-2-hydroxy-[50] and 2-mercapto-alkylhydrazones of aldehydes and ketones[53,65] and for the *N*-alkylimines of hydroxycarbonyl compounds[51,55].

IV. THE INFLUENCE OF THE STRUCTURE OF THE CONNECTING UNIT

In order to elucidate the influence of the structure of the connecting unit, systematic studies on the equilibria and rates of the intramolecular reactions between the same two functional groups, while the structure of the carrier system is varied within wide limits, are necessary. Unfortunately, few such investigations, embracing a large set of different structures, have been described in the literature. The ring–chain equilibrium constants have been determined in different investigations under different conditions and by different methods[23], which reduces the value of the information obtained on comparing them.

The problem of the estimation of the influence of the structure of the connecting unit on the ease of formation of the ring and its stability is extremely complex. Two approaches are possible: (1) estimation of the structural possibilities for the mutual approach of the reacting groups in the steric orientation optimum for the intramolecular reaction; (2) assessment of the structure from the standpoint of the entropy and enthalpy contributions (deformation of the bond lengths and angles, non-bonding and electrostatic interactions, strain, etc.) to the energy of formation of the ring[24].

The aim of the expansion of research on these lines was to create a model system whereby one could explain the enormous rates of enzymatic reactions compared with the usual

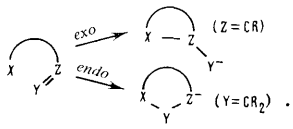
bimolecular reactions. New concepts such as "stereopopulation control"[86-90] and "orbital steering"[91-93] appeared in this connection.

According to the concept of stereopopulation control, the very considerable acceleration of the lactonisation reactions of *o*-hydroxyhydrocinnamic acids, observed after the introduction of methyl groups into the chain and into the benzene ring, can be explained by the increase of the content of the reactive conformer in which both reaction centres have the optimum orientations. It was shown later[94,95] that this effect cannot ensure such a large increase of the rate of reaction and that the increase of the strain energy in the open-chain structure after the introduction of the methyl group plays the most significant role in this phenomenon.

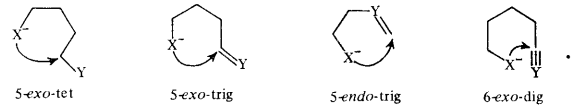
The concept of orbital steering explains the enormous increase of the rate of intramolecular lactonisation of hydroxyacids, achieved by a specific alteration of the structure of the connecting unit, by creating steric conditions for the optimum mutual angular orientation of the reacting centres. This concept has been criticised[96-98] for simplifying the complex pattern of enzymatic reactions and for the clear overestimate of the factor associated with the optimum geometrical orientation of the reacting groups.

Another approach to the solution of this problem[27,99-101] is based on the use of X-ray diffraction data for the crystal structures of specially selected bifunctional compounds in order to elucidate the optimum geometry of the mutual approach of the reacting groups for the minimum-energy reaction. Thus it has been shown on the basis of X-ray diffraction studies on a series of aminoketones that the optimum angle at which the nucleophilic nitrogen atom approaches the C=O bond ($\angle N...C{=}O$) in nucleophilic addition to the keto-group is ~107° and not 90° as was suggested previously. For the oxygen atom as a nucleophile, this angle is in the range 100–110°.[102]

On the basis of simple considerations concerning the stereochemical requirements of intramolecular reactions, simple empirical laws governing the preferential occurrence of different types of cyclisation have been proposed[103-107]. A convenient classification of such reactions was introduced. The formation of the smaller of the two possible rings is called *exo*-cyclisation and the formation of the larger ring is *endo*-cyclisation:



The prefixes "tet", "trig", and "dig" denote tetrahedral, trigonal, and digonal geometries of the carbon atom attacked by the nucleophile and the numeral denotes the number of members in the ring formed, for example:

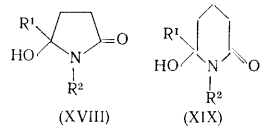


If X is an atom of an element in the Second Period, then 3-, 4-, 5-, 6-, and 7-*exo*-tet-, 3-, 4-, 5-, 6-, and 7-*exo*-trig-, 6- and 7-*endo*-trig-, 5-, 6, and 7-*exo*-dig- and 3-, 4-, 5-, 6-, and 7-*endo*-dig-cyclisation processes are favourable. The 3-, 4-, and 5-*endo*-trig- and 3- and 4-*exo*-dig-cyclisation processes are unfavourable but nevertheless feasible under certain conditions[103].

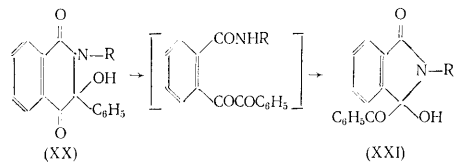
Clearly these rules are most general and the possibility of their practical application is extremely limited, because in the determination of whether or not the cyclisation process is favourable no account is taken of important factors such as the structure of the connecting unit, the presence of the substituents in it, and the nature of the reacting groups. Table 1 presents an example of an unfavourable 5-*endo*-trig-cyclisation, which nevertheless occurs as a ring–chain tautomeric process: aromatic aldehyde *N*-2-hydroxyalkylimine ⇌ oxazolidine#[34].

The rate of formation and higher stability of the five-membered or six-membered cyclic system depend on the nature of the reacting functional groups and the structure of the unit connecting them.

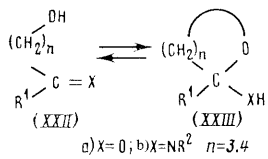
With an appropriate choice of substituents R^1 and R^2, the amides of 3-acylpropionic acids form stable five-membered hydroxylactams (XVIII),[39,108] while it is altogether impossible to obtain the six-membered hydroxylactams (XIX) from similarly substituted amides of 4-acylbutyric acids:



The higher stability of five-membered hydroxylactams compared with the six-membered compounds is confirmed by their ready isomerisation with ring contraction: (XX) → (XXI):[109,110]



On the other hand, in the series of 3-acylpropanols and 4-acylbutanols [(XXIIa) ⇌ (XXIIIa)], the ring–chain equilibrium constants are higher[111] for the closure of the six-membered ring. This also applies to their *N*-alkylimines [(XXIIb) ⇌ (XXIIIb)]:[51]

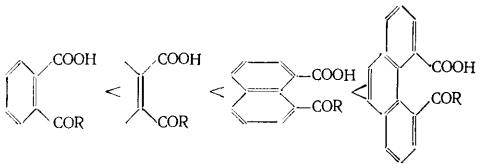


It is seen from a comparison of the rate constants for a large set of cyclisation reactions (see Table 13 in the monograph of Capon and McManus[7]) that a five-membered ring is formed more readily than a six-membered ring in the intramolecular substitution at a tetrahedral carbon atom when the connecting unit consists of sp^3-carbon atoms. The relative ease of closure of the six-membered ring increases after the introduction of sp^2-carbon atoms in the chain and also for reactions involving intramolecular addition to a trigonal carbon atom.

A series of acyl-substituted carboxylic acids, in which the stability of the cyclic form increases for identical substituents R in each respective instance have been proposed[33];

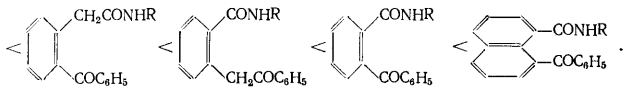
#An example of the faster "unfavourable" 5-*endo*-trig-cyclisation compared with the "favourable" 6-*endo*-trig-cyclisation process has also been observed by J.B.Lambert and M.V.Majchrzak (J.Amer.Chem.Soc., 1980, **102**, 3588).

the ring–chain equilibrium constants have been published in a monograph[23] (Table 3):



An increase in the stability of the cyclic form in an analogous series has been observed[23,38] for the amides of 3- and 4-benzoyl-substituted carboxylic acids:

$C_6H_5CO(CH_2)_3CONHR < C_6H_5CO(CH_2)_2CONHR <$



The influence of the structure of the connecting unit on the equilibrium and rate constants for the lactonisation and thiolactonisation reactions of hydroxy- and mercapto-acids has been examined (Table 2)[92,93]; these data have been compared with the rate constants for the corresponding intermolecular reactions. It can be easily shown that insignificant changes in the structure of the connecting unit can have an enormous influence on the rate and equilibrium of the intramolecular reaction. Comparison of lactonisation and thiolactonisation (Table 2) shows clearly that the same structure of the carrier system has different effects on the rates of these reactions: the ratio of the lactonisation and thiolactonisation rate constants varies within the limits of two orders of magnitude, although the overall trend is maintained.

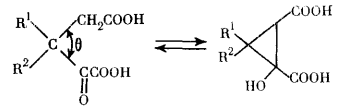
It is seen from the examples presented that the ease of formation and the stability of the cyclic form (the heterocycle) increase with increase of the rigidity of the connecting unit, i.e. with decrease of its conformational mobility, provided that the possibility of the mutual approach of the reacting groups in space and their optimum mutual orientation are maintained. Thus, in the structures of carboxylic ketoacids and their amides which have been examined, the keto-group is capable of free rotation about the C–CO bond and of assuming a conformation in which the nucleophile (O or N) can approach its plane in a perpendicular direction. The failure of this condition in the molecules of anthraquinone-1-carboxylic acid[116] prevents cyclisation.

The elucidation of the general characteristics of the influence of the structure of the connecting unit on the rate and equilibrium constants for the intramolecular reactions is difficult owing to the difference between the steric requirements of different reacting groups. The examples considered and the data in Table 2 show that there are no direct correlations between the structure of the connecting unit and the $\lg K$ and $\lg k$ for intramolecular reactions when pairs of reacting groups are replaced.

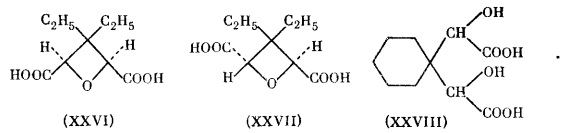
V. STERIC EFFECTS OF SUBSTITUENTS IN THE CONNECTING UNIT

1. The Thorpe–Ingold Effect

The introduction of alkyl groups at carbon atoms in the chain between the reacting groups and particularly the introduction of two groups at the same atom increase the rate of cyclisation and shift the equilibrium in the direction of the cyclic structure. This effect is usually called the "*gem*-dimethyl", "*gem*-dialkyl", or "Thorpe–Ingold" effect[1,2,7–9,16]. The first theoretical explanation has been given by Thorpe and Ingold[117,118], who observed the effect in a ring–chain isometric system which they suggested involved the (XXIV) ⇌ (XXV) transformation. A sharp increase of the content of the cyclic isomer was observed after the introduction of two alkyl groups R^1 and R^2 and the increase of their bulk[119]. The authors explained this phenomenon by the decrease of the valence angle θ.



(XXIV) (XXV)



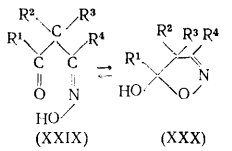
(XXVI) (XXVII) (XXVIII)

However, structures (XXIV) and (XXV) were later disproved by ^1H NMR and the corrected structures (XXVI)–(XXVIII) were proposed in their place[120,121]; this greatly reduced the popularity of Ingold's concept. The study of the intramolecular hydrogen bond in 2-substituted propane-1,3-diols by infrared spectroscopy showed[18] that, after the introduction of substituents at the middle carbon atom, the C–C–C angle decreases somewhat, but this decrease cannot play a significant role in the closure of five- and six-membered rings.

Hammond[1] saw a more important cause of the influence of the *gem*-dialkyl group on the cyclisation reaction in the restriction of the free rotation about the C–C–C bonds in the open-chain isomer after the introduction of two bulky groups at the middle carbon atom and hence in the appearance of entropy factors favouring cyclisation. As a development of this idea, a thermodynamic concept based on a comparison of the enthalpies and entropies of linear and cyclic structures was proposed[122]. It has been shown for hexanes and cyclohexanes that, in the presence of alkyl substituents, there is a smaller number of non-bonding *gauche*-interactions in the rings than in open chains. This implies that the enthalpy factors favour cyclisation of the methyl-substituted chain to a greater extent than the unsubstituted chain. Furthermore, branching reduces the entropy of open-chain compounds by restricting the internal rotation, but cannot alter significantly the entropies of cyclic compounds, because they are capable of free internal rotation. The decrease of ΔH and the increase of ΔS for the cyclisation reactions of pentane and hexane in the gas phase after the introduction of two methyl groups at the same carbon atom lead to an increase of the equilibrium constant by 2–3 orders of magnitude[7] (p.59).

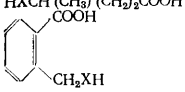
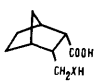
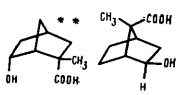
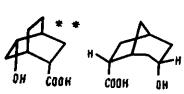
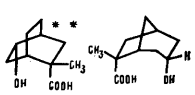
In a study of the ring–chain tautomerism of 1-hydroxyimino-3-propanones [(XXIX) ⇌ (XXX)], it was observed[37] that in solutions of 3-methyl-4-spiropropano-5-hydroxy-5-phenyl-Δ^2-isoxazoline [XXX, R^1 = Ph, R^2, $R^3 = -(CH_2)_2$, R^4 = Me] and the corresponding 4,4-dimethyl derivative (XXX, R^1 = Ph, $R^2 = R^3 = R^4$ = Me) the open-chain tautomeric form is absent within the limits of the sensitivity of the infrared spectroscopic and ^1H NMR methods. Since the equilibrium (XXIX) ⇌ (XXX) has been observed for the 4-unsubstituted derivative, this finding disproves Ingold's concept, since $(CH_2)_2C$ ⟨ angle has not been reduced and has even been increased conpared with the H_2C⟨ angle. The stabilisation

of the cyclic isomer (XXX) on spirocyclopropane substitution in the 4-position can be accounted for only by the restriction of the freedom of rotation or by the appearance of steric strain in the open-chain isomer of isoxazoline (XXIX):



(XXIX) (XXX)

Table 2. The influence of the structure of the connecting unit on the equilibrium and rate constants for the lactonisation of carboxylic hydroxy- and mercapto-acids under the conditions of acid catalysis[92,93].

Carboxylic hydroxy- or mercapto-acid	X = O		X = S	
	K	$\lg k_{rel}$	K	$\lg k_{rel}$
$CH_2CH_2XH + CH_3COOH$ *	$7\cdot10^{-2}$	0.00	$6.6\cdot10^{-4}$	0.00
$HX(CH_2)_2COOH$	6.15	1.90	2.44	2.58
$HXCH(CH_3)(CH_2)_2COOH$	11.13	2.07	—	—
	—	2.50	—	2.97
	2810	3.82	110	1.95
	—	5.14	63	3.67
	12740	6.01	>100	5.91
	—	2.44	—	—
	—	2.94		
	—	4.99		
	—	3.96		
	—	5.68		

*The rate constants adopted as unity actually amount to $k = 1.09 \times 10^{-3}$ litre mol^{-1} min^{-1} for X = O and $k = 3.2 \times 10^{-6}$ litre mol^{-1} min^{-1} for X = S.

**These structures shown in brackets proved to be erroneous in a reinvestigation[112–115]; the corrected structures are shown next to them.

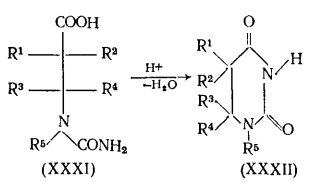
The positive influence of alkyl substituents in the connecting unit on the rate and equilibrium constants has been observed in the conversion of succinic acids[123] and their *N*-phenyl monoamides[124] into anhydrides [and imides respectively?], the lactonisation of 4-hydroxybutyric and 5-hydroxyvaleric acids[125], in the ring–chain tautomerism of levulinic acids[126], many other ring–chain tautomeric systems[20, 23,50], addition reactions with intramolecular cyclisation[127], intramolecular catalysis proceeding via a cyclic transition state[5–9], and the formation of an intramolecular hydrogen bond[17].

The influence of alkyl substituents on the rate and equilibrium constants for cyclisation reactions depends on their bulk, their position in the connecting unit, and the conformational mobility of the connecting unit itself. If the reacting groups are separated by a chain of three sp^3-carbon atoms, the introduction of alkyl substituents at the middle atom has the greatest influence[125,128]. The methyl groups at the carbon atom in the α-position relative to the reacting group, particularly the C=O group, can have the opposite influence owing to the steric shielding of the reaction centre. The influence of the position of the methyl substituent can be followed in relation to the cyclisation of methyl-substituted 3-ureidopropionic acids [(XXXI) → (XXXII)] (Table 3)[129].

Table 3. The influence of methyl substituents on the rate constants for the cyclisation of 3-ureidopropionic acids [(XXXI) → (XXXII)].[129]

R^1	R^2	R^3	R^4	R^5	$\lg k_{rel}$
H	H	H	H	H	0.00
Me	H	H	H	H	0.07
H	H	Me	H	H	0.45
erythro-Me	H	Me	H	H	−0.08
threo-Me	H	H	Me	H	0.47
Me	Me	H	H	H	−0.46
H	H	Me	Me	H	1.25
H	H	H	H	Me	1.66

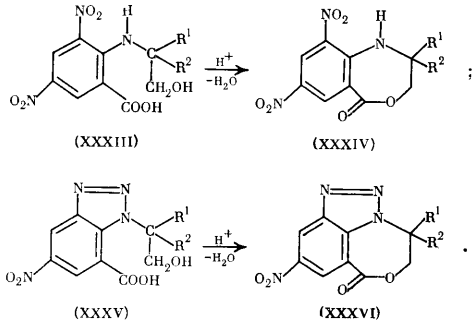
The introduction of two methyl groups in the α-position relative to the carboxy-group actually retards cyclisation, while two methyl groups at the β-carbon atom greatly accelerate it.



(XXXI) (XXXII)

The destabilisation of the cyclic structure after the introduction of the methyl group at the carbon atom in the α-position relative to the C=O group has been observed in the ring–chain tautomerism of *N*-(3-oxoalkyl)-*N'*-substituted thioureas[70] and 3-aryl-1-(2-oxoalkyl)triazenes[29].

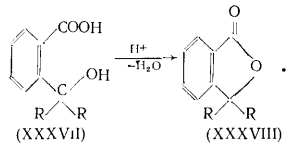
The influence of alkyl substituents at an sp^3-carbon atom intensifies following the increase of the conformation rigidity of the connecting unit, which is readily seen in relation to the lactonisation reactions (XXXIII) → (XXXIV) and (XXXV) → (XXXVI) (Table 4)[130].



(XXXIII) (XXXIV)

(XXXV) (XXXVI)

The introduction of two methyl groups in the methylene group of 2-hydroxymethylbenzoic acid (XXXVII, R = Me) accelerates the lactonisation reaction (XXXVII) → (XXXVIII) by four orders of magnitude[87] compared with the unsubstituted analogue (XXXVII, R = H), which greatly exceeds the *gem*-dimethyl effect in connecting units containing only sp^3-carbon atoms[131]:



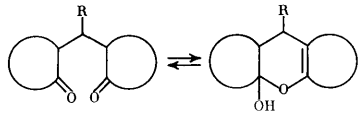
(XXXVII) (XXXVIII)

Table 4. The influence of alkyl substituents on the rate constants for the cyclisation of hydroxyethyl derivatives of nitroanthranilic acids [(XXXIII) → (XXXIV)] and nitrotriazolobenzoic acids [(XXXV) → (XXXVI)].[130]

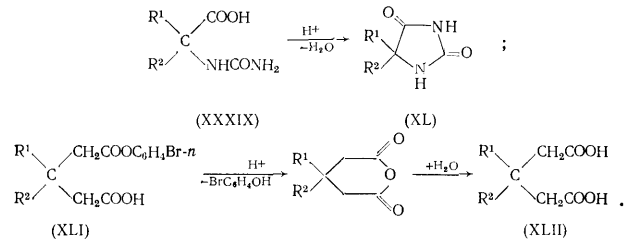
R¹	R²	$\lg k_{rel}$ (XXXIII) → (XXXIV)	$\lg k_{rel}$ (XXXV) → (XXXVI)
H	H	0.00	0.00*
H	Et	0.57	0.04
Me	Me	1.38	4.86 (I)

*$k_{(XXXV)}/k_{(XXXIII)} = 0.52$ ($R^1 = R^2 = H$).

The intense stabilisation of the cyclic structure after the introduction of two methyl groups in a connecting unit of the type $o\text{-}C_6H_4CR_2$ was noted in a study of the ring–chain tautomerism of 2-acylmethylbenzoic and 2-acylphenylacetic acids[132,133] as well as their derivatives[134]. The same thing occurs when at least one substituent R is introduced at the bridgehead carbon atom in bicyclic ring–chain tautomeric systems[135–139]:



In the cyclisation reactions of substituted ureidoacetic acids [(XXXIX) → (XL)][140] and in the hydrolysis of 4-bromophenyl esters of 3-substituted glutaric acids, which takes place with the intermediate formation of the anhydride [(XLI) → (XLII)],[131] a satisfactory additivity of the influence of the substituents was observed and for the last reaction also a satisfactory correlation with the steric substituent constants E_S. The possibility of such correlation was nevertheless criticised[141]. The accelerating effect increases with increasing bulk of the substituent (Table 5). The influence of the substituents changes very considerably on passing from one reaction series to another:



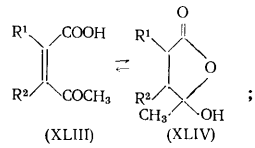
(XXXIX) (XL)

(XLI) (XLII)

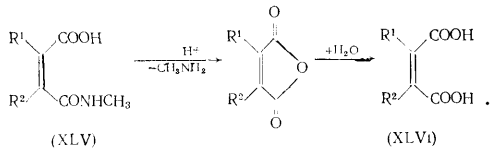
Table 5. The influence of substituents on the rate constants for the cyclisation reactions (XXXIX) → (XL) and (XLI) → (XLII).[131,140]

R¹	R²	$\lg k_{rel}$ (XXXIX)→(XL)	$\lg k_{rel}$ (XLI)→(XLII)	R¹	R²	$\lg k_{rel}$ (XXXIX)→(XL)	$\lg k_{rel}$ (XLI)→(XLII)
H	H	0.00	0.00	Ph	Et	—	2.33
Me	H	1.05	0.68	Ph	Ph	1.38	2.43
iso-Pr	H	0.53	1.52	Me	Me	1.80	1.36
Ph	H	0.63	0.61	Me	iso-Pr	—	2.34
Ph	Me	—	1.51	Me	t-Bu	—	3.02

The introduction of alkyl substituents at sp^2-carbon atoms in the connecting unit also stabilises the cyclic structure, evidently as a result of the increase of the steric strain in the open-chain structure[142]. This effect is clearly shown in the ring–chain tautomerism of *cis*-3-acetylacrylic acids [(XLIII) ⇌ (XLIV)][143] and in the hydrolysis of *N*-methylmaleic acids [(XLV) → (XLVI)], which proceeds under the conditions of intramolecular catalysis with the intermediate formation of the anhydride[142] (Table 6). The acceleration of the last reaction takes place also with increase of the bulk of the substituent R^1 (Me < Et < iso-Pr < t-Bu). The introduction of a polymethylene chain as the substituents R^1 and R^2 in maleamic acid (XLV) led to the determination of the influence of ring size on the accelerating effect of the presence of the carboxy-group in the hydrolytic reaction, i.e. on the ability to form cyclic transition states. In the case of the cyclohexene derivative [XLV, R^1, $R^2 = (CH_2)_4$], an appreciable acceleration is observed, but it does not nevertheless reach the level which obtains in the presence of two methyl substituents:



(XLIII) (XLIV)

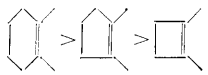


(XLV) (XLVI)

Table 6. The influence of alkyl substituents at the sp^2-carbon atoms on the ring–chain equilibrium constants K for *cis*-3-acetylacrylic acids [(XLIII) → (XLIV)] [143] and the hydrolysis rate constants k_{rel} for *N*-methylmaleamic acids [(XLV) → (XLVI)]. [142]

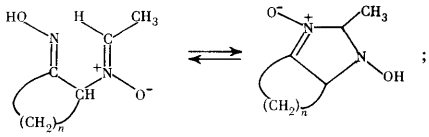
R^1	R^2	lg K (XLIII) ⇄ (XLIV)	lg k_{rel} (XLV) → (XLVI)
H	H	1.2	0.00
Me	H	1.9	1.49
H	Me	3.6	—
Me	Me	5.2	4.37
	$(CH_2)_4$	—	2.73
	$(CH_2)_3$	—	—4.38
	$(CH_2)_2$	—	—5.38

On passing to cyclopentene and cyclobutene systems, the catalytic effect of the carboxy-group disappears, which can be explained by the alteration of the valence angles in the sequence



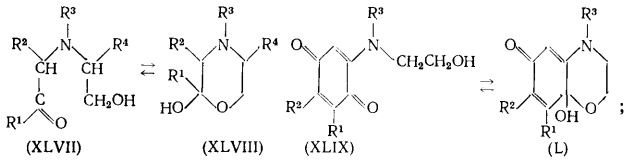
which is unfavourable for the formation of a cyclic transition state.

An analogous influence of ring size has been observed[144] in the ring–chain tautomerism of *N*-(2-hydroxyiminocycloalkyl) nitrones:

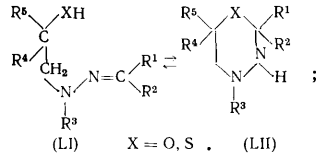


$n = 5$, $K > 100$; $n = 4$, $K = 9$; $n = 3$, $K = 0$.

The introduction of an alkyl group at the nitrogen atom in the connecting unit leads to a marked stabilisation of the cyclic structure (Table 3), which has been demonstrated in relation to the ring–chain tautomerism of *N*-alkyl-*N*-(2-hydroxyalkyl)-*N*-(2-oxoalkyl)amines [(XLVII) ⇌ (XLVIII)], [145, 146] 2-*N*-alkyl-*N*-(2-hydroxyethyl)amino-1,4-benzoquinones [(XLIX) ⇌ (L)], [147] and *N*-alkyl-*N*-(2-hydroxy- or 2-mercapto-alkyl)hydrazones of aldehydes and ketones [(LI) ⇌ (LII)]: [50,52,53,65,148,149]



(XLVII) (XLVIII) (XLIX) (L)



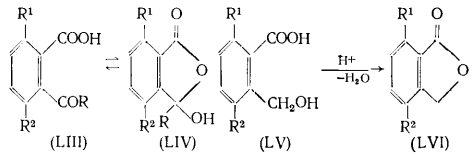
(LI) X = O, S . (LII)

The introduction of alkyl substituents R^3 and the increase of their bulk displace the equilibrium towards the cyclic form, while in the absence of a substituent at the nitrogen atom (i.e. for R^3 = H), compounds (XLVII), (XLIX), and (LI) exist preferentially in the stable open-chain form and a tautomeric equilibrium is not observed.

Potekhin and Bogan'kova[149] suggest the weakening of the intramolecular hydrogen bond X–H...NR^3 as one of the possible causes of the destabilisation of the open-chain structure (LI) with increase of the bulk of the substituent R^3 in addition to the entropy factor, but they do not present any experimental evidence for this hypothesis.

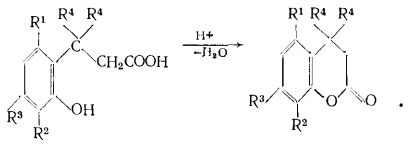
2. The "Supporting" or Steric Cooperation Effect

If the reacting groups are in the *ortho*-positions in an aromatic ring, then the neighbouring alkyl or other substituents give rise to a steric strain, which favours intramolecular cyclisation[150]. Such influence is called the "supporting" or steric cooperation effect. Table 7 presents the quantitative characteristics of this effect for the ring–chain tautomerism of 2-acetylbenzoic[151] and 2-benzoylbenzoic[152] acids [(LIII) ⇌ (LVI)] and also for the lactonisation of 2-hydroxymethylbenzoic acid [(LV) → (LIV)], [153]



(LIII) (LIV) (LV) (LVI)

and 3-(2-hydroxyphenyl)propionic acid [(LVII) → (LVIII)]: [86,87]



(LVII) (LVIII)

The gradual introduction of methyl groups into the molecule of 3-(2-hydroxyphenyl)propionic acid (LVII) makes it possible to discover the influence of the location of the methyl substituents on the lactonisation rate constants under the conditions of acid catalysis; the maximum acceleration attained under these conditions is by 11 orders of magnitude. The main driving force of the acceleration of lactonisation after the introduction of methyl substituents is steric strain in the ground state of the initial molecule and from this standpoint there is no fundamental difference between the Thorpe–Ingold effect [as in compound (LVII, R^4 = Me)] and the steric cooperation effect [as in compound (LVII, $R^1 = R^2$ = Me)].

It is seen from Table 7 that the accelerating effect depends on the bulk of the substituent in the *ortho*-position with respect to the position where the methyl group is to be introduced. The introduction of the methyl group in the

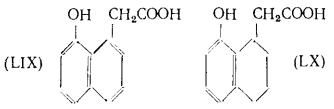
ortho-position with respect to the OH group or the introduction of two methyl groups in the *ortho*-positions with respect to the OH and CH_2CH_2COOH groups accelerates lactonisation by a factor of 3–7, while the methyl group in the *ortho*-position with respect to the CMe_2CH_2COOH group accelerates the lactonisation reaction by 7 orders of magnitude. The extremely high acceleration of the lactonisation reaction (LVII) → (LVIII) has been explained by the fact that the methyl substituents R^1, R^2, and R^4 restrict the freedom of rotation about the C–C bonds and favour the preferential formation of the conformation in which both reacting groups are in the optimum position for reaction between them[86,87].

Table 7. The steric cooperation of the *ortho*-substituents in cyclisation reactions.

R^1	R^2	K ((LIII) ⇄ (LIV))		$\lg k_{rel}$ ((LV)→(LVI)) [153]	$\lg k_{rel}$ ((LVII)→(LVIII)) [86,87]	
		R=Me [151]	R=Ph [152]		R^4=H	R^4=Me
H	H	3.2	<0.1	0.00	0.00*	3.65*
Me	H	16	2.85	1.19	—	10.93**
H	Me	0.52	0.22	1.72	—	4.22*
Me	Me		13.3	2.50	0.83**	11.41*
						11.53**

*R^3 = H.
**R^3 = Me.

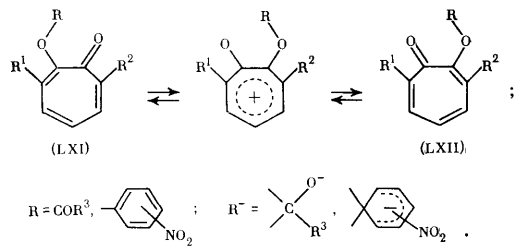
It has been shown[94] that such high acceleration of cyclisation on passing from compound (LVII, $R^1 = R^2 = R^3 = R^4 = H$), i.e. compound (LVIIa), to the trimethyl-substituted compound (LVII, $R^1 = R^2 = R^4 = Me$, $R^3 = H$), i.e. compound (LVIIb), which is by a factor of 10^{11}, cannot be caused solely by the presence of the optimum conformation (this has been confirmed by X-ray diffraction analysis[90]); the steric strain in the initial molecule plays a more significant role here. Comparison of the rate constant for the lactonisation of the acid (LVIIa) with the lactonisation constants for 8-hydroxynaphthylacetic acid (LIX) and 8-hydroxy-1,2,3,4-tetrahydronaphthylacetic acid (LX),



(LIX) (LX)

which model the fixed most favourable conformation for the lactonisation reaction ($k_{(LIX)}/k_{(LVIIa)} = 2.1 \times 10^4$; $k_{(LX)}/k_{(LVIIa)} = 1.5 \times 10^2$) shows that acceleration by a factor of only 10^4 is ensured by the most favourable conformation. The remaining contribution to the acceleration of the cyclisation reaction on passing from compound (LVIIa) to (LVIIb), amounting to a factor of ~10^7, is due to the enthalpy effect of the steric strain in the initial molecule, which has been confirmed by empirical force field calculations[95].

The steric cooperation effect is clearly manifested in the acylo- and arylo- tropic tautomerism of the tropolone system [(LXI) ⇌ (LXII)]:[12,154–156]


(LXI) (LXII)

The introduction of methyl or benzyl substituents in the 3- and 7-positions in the tropolone ring has a favourable steric effect on the formation of a cyclic dipolar transition state or intermediate and accelerates the migration of acyl or aryl groups. In the presence of only one methyl substituent (R^1 = Me, R^2 = H, R = Me_2NCO), the equilibrium (LXI) ⇌ (LXII) is displaced towards the sterically less encumbered tautomer (LXII) (K = 4).[156]

It is seen from the examples considered (see also Capon and McManus[7]) that the influence of the alkyl substituents in the connecting unit on the cyclisation reactions depends on many factors and is difficult to predict quantitatively. Progress in this field resulting from the employment of computational methods has been noted recently.

A satisfactory linear correlation (r = 0.932–0.993) between the free energies of activation for the cyclisation reactions of methyl-substituted ureidopropionic acids [(XXXI) → (XXXII)] and also a number of previously investigated anhydride formation reactions of succinanilic[124] and succinic[123] acids, the hydrolysis of p-bromophenylglutarates [(XLI) → (XLII)],[131] and the lactonisation of 4-hydroxybutyric and 5-hydroxyvaleric acids[125], on the one hand, and the energies of the steric strain estimated on the basis of the enthalpies of formation of homomorphous hydrocarbons[157], on the other, has been observed recently[129].

Empirical force field calculations[150,158–163] have been used successfully for the quantitative prediction of the acceleration of the lactonisation of carboxylic hydroxyacids when the structure of the connecting unit is altered and methyl substituents are introduced[95,164].

The possibilities of the computational methods have been satisfactorily demonstrated[165,166] for the cyclisation reactions of bromoalkylamines and their derivatives substituted by alkyl groups in the chain. A satisfactory agreement between the calculated and experimental rates of cyclisation was observed; the enthalpies of activation were calculated by the empirical force field method and the entropies of activation were obtained from the analogous formal cyclisation reactions of homomorphous alkanes.

It has been confirmed by computational methods that the driving force of the Thorpe–Ingold effect is mainly the enthalpy factor and not the entropy factor as was believed previously[86,87].

REFERENCES

1. G.S.Hammond, in "Steric Effects in Organic Chemistry" (Translated into Russian), Inostr.Lit., Moscow, 1960, p.431.
2. E.L.Eliel, in "Stereochemistry of Carbon Compounds" (Translated into Russian), Izd.Mir, Moscow, 1965, p.185.
3. K.Reid, in "Textbook of Physical Organic Chemistry" [possibly K.F.Reid, "Properties and Reactions of Bonds in Organic Molecules", 1968 (Ed. of Translation)] (Translated into Russian), Izd.Mir, Moscow, 1972, p.521.

4. H.C.Van der Plas, "Ring Transformation of Heterocycles", Acad.Press, London–New York, 1973, Vols.1 and 2.
5. B.Capon, Quart.Rev., 1964, **18**, 45.
6. B.Capon, Quart.Rev., 1964, **18**, 85.
7. B.Capon and S.T.McManus, "Neighbouring Groups Participation", Plenum Press, New York–London, 1976, Vol.1.
8. T.C.Bruice and S.J.Benkovic, "Bioorganic Mechanisms" (Translated into Russian), Izd.Mir, Moscow, 1970.
9. W.P.Jencks, "Catalysis in Chemistry and Enzymology" (Translated into Russian), Izd.Mir, Moscow 1972.
10. L.V.Pavlova and F.Yu.Rachinskii, Uspekhi Khim., 1968, **37**, 1369 [Russ.Chem.Rev., 1968(12)].
11. R.M.Acheson, Acc.Chem.Res., 1971, **4**, 177.
12. V.I.Minkin, L.P.Olekhnovich, and Yu.A.Zhdanov, "Molekulyarnyi Dizain Tautomernykh Sistem" (Molecular Design of Tautomeric Systems), Izd.Rostov. Univ., Rostov-on-Don, 1977.
13. M.I.Page, Angew.Chem.Int.Ed. 1977, **16**, 449.
14. I.V.Berezin and K.Martinek, "Osnovy Fizicheskoi Khimii Fermentativnogo Kataliza" (Fundamentals of the Physical Chemistry of Enzyme Catalysis), Izd. Vysshaya Shkola, Moscow, 1977.
15. A.R.Fersht, "Enzyme Structure and Mechanism" (Translated into Russian), Izd.Mir, Moscow, 1980, p.57.
16. I.Hine, "Structural Effects on Equilibria in Organic Chemistry", Wiley-Intersci., New York, 1975, p.284.
17. M.Tichy, in "Advances in Organic Chemistry" (Translated into Russian), Izd.Mir, Moscow, 1968, Vol.5, p.116.
18. P.von R.Schleyer, J.Amer.Chem.Soc., 1961, **83**, 1368.
19. L.P.Kuhl, P.von R.Schleyer, W.F.Baitinger, and L.Eberson, J.Amer.Chem.Soc., 1964, **86**, 650.
20. P.R.Jones, Chem.Rev., 1963, **63**, 461.
21. R.Valters, Uspekhi Khim., 1973, **42**, 1060 [Russ. Chem.Rev., 1973(6)].
22. R.Valters, Uspekhi Khim., 1974, **43**, 1417 [Russ. Chem.Rev., 1974(8)].
23. R.Valters, "Kol'chato-Tsepnaya Izomeriya v Organicheskoi Khimii" (The Ring–Chain Isomerism in Organic Chemistry), Izd.Zinatne, Riga, 1978.
24. M.I.Page, Chem.Soc.Rev., 1973, **2**, 295.
25. L.Yu.Yuzefovich, B.M.Sheiman, T.M.Filippova, and V.G.Mairanovskii, Khim.Geterotsikl.Soed., 1978, 758.
26. L.Yu.Yuzefovich, B.M.Sheiman, V.G.Mairanovskii, and T.M.Filippova, Khim.Geterotsikl.Soed., 1979, 616.
27. D.J.Chadwick and J.D.Dunitz, J.Chem.Soc., Perkin Trans.II, 1979, 276.
28. W.P.Jencks, in "Modern Problems in Physical Organic Chemistry" (Translated into Russian), Izd. Mir, Moscow, 1967, p.342.
29. C.E.Olsen and C.Pedersen, Acta Chem.Scand., 1973, **27**, 2279.
30. B.M.Sheiman, L.Yu.Yuzefovich, L.Ya.Denisova, T.M.Filippova, V.G.Mairanovskii, and V.M.Berezovskii, Khim.Geterotsikl.Soed., 1977, 634.
31. M.V.Bhatt and K.M.Kamath, J.Chem.Soc.(B), 1968, 1036.
32. R.Bowden and M.P.Henry, J.Chem.Soc., Perkin Trans.II, 1972, 201.
33. K.Bowden and A.M.Last, J.Chem.Soc., Perkin Trans.II, 1973, 1144.
34. J.V.Paukstelis and L.L.Lambing, Tetrahedron Letters, 1970, 299.
35. A.F.McDonagh and H.E.Smith, J.Org.Chem., 1968, **33**, 1.
36. R.Valters and V.Ciekure, Khim.Geterotsikl.Soed., 1975, 1476.
37. R.Escale, R.Jacquier, B.Ly, F.Petrus, and J.Verducci Tetrahedron, 1976, **32**, 1369.
38. R.Valters, Abstract of Doctoral Thesis in Chemical Sciences, Riga Polytechnic Institute, Riga, 1975.
39. R.Chiron and Y.Graff, Bull.Soc.chim.France, 1970, 575.
40. M.V.Bhatt and M.Ravindranathan, J.Chem.Soc., Perkin Trans.II, 1973, 1160.
41. R.Valters and V.R.Zin'kovskaya, Izv.Akad.Nauk Latv.SSR, Ser.Khim., 1973, 310.
42. W.Walter and Ck.Rohloff, Annalen, 1977, 485.
43. M.Uda and S.Kubota, J.Heterocycl.Chem., 1978, **15**, 807.
44. M.P.Nemeryuk and T.S.Safonova, Khim.Geterotsikl. Soed., 1971, 73.
45. T.S.Safonova, J.N.Sheinker, M.P.Nemerjuck, E.M.Peresleni, and G.P.Syrova, Tetrahedron, 1971, **27**, 5455.
46. E.M.Peresleni, L.A.Myshkina, K.F.Turchin, T.Ya.Filipenko, T.S.Safonova, and Yu.N.Sheinker, Khim.Geterotsikl.Soed., 1979, 103.
47. R.Valters, Izv.Akad.Nauk Latv.SSR, Ser.Khim., 1970, 223.
48. R.Valters, Izv.Akad.Nauk Latv.SSR, Ser.Khim., 1970, 339.
49. H.Alper and B.H.Lipshutz, J.Org.Chem., 1973, **38**, 3742.
50. B.V.Ioffe, M.A.Kuznetsov, and A.A.Potekhin, "Khimiya Organicheskikh Proizvodnykh Gidrazina" (The Chemistry of Organic Derivatives of Hydrazine), Izd.Khimiya, Leningrad, 1979, p.187.
51. A.A.Potekhin and S.L.Zhdanov, Khim.Geterotsikl. Soed., 1979, 1317.
52. A.A.Potekhin, Zhur.Org.Khim., 1971, **7**, 16.
53. S.M.Shevchenko, Abstracts of Candidate's Thesis in Chemical Sciences, Zhdanov Leningrad State University, Leningrad, 1980.
54. A.A.Potekhin, S.L.Zhdanov, V.A.Gindin, and K.A.Ogloblin, Zhur.Org.Khim., 1976, **12**, 2090.
55. S.L.Zhdanov, Abstract of Candidate's Thesis in Chemical Sciences, Zhdanov Leningrad State University, Leningrad, 1976.
56. R.Valters, D.Balode, R.Kampare, and S.Valtere, Khim.Geterotsikl.Soed., 1981, 1209.
57. R.Valters and G.Karlivans, Izv.Akad.Nauk Latv. SSR, Ser.Khim., 1974, 705.
58. G.Karlivans, R.Valters, and S.Valtere, Zhur.Org. Khim., 1977, **13**, 805.
59. R.Kampare, R.Valters, E.Liepins, and G.Karlivans, Izv.Akad.Nauk Latv.SSR, Ser.Khim., 1981, 244.
60. G.Karlivans and R.Valters, Zhur.Org.Khim., 1978, **14**, 890.
61. G.Karlivans, R.Valters, R.Kampare, and V.Ciekure, Khim.Geterotsikl.Soed., 1979, 780.
62. G.Karlivans and R.Valters, Khim.Geterotsikl.Soed., 1980, 335.
63. D.E.Balode and R.Valters, Izv.Akad.Nauk Latv. SSR, Ser.Khim., 1980, 227.
64. D.E.Balode and R.Valters, Izv.Akad.Nauk Latv. SSR, Ser.Khim., 1979, 588.
65. S.M.Shevchenko and A.A.Potekhin, Khim. Geterotsikl.Soed., 1979, 1637.
66. C.D.Johnson, "The Hammett Equation" (Translated into Russian), Izd.Mir, Moscow, 1977, p.178.

67. R.Valters and S.Valtere, Izv.Akad.Nauk Latv.SSR, Ser.Khim., 1969, 704.
68. R.Valters, S.Valtere, and A.Kipina, Symposium, "Biologicheski Aktivnye Soedineniya" (Biologically Active Compounds), Izd.Nauka, Leningrad, 1968, p.213.
69. G.Karlivans, V.Ciekure, and R.Valters, Izv. Akad.Nauk Latv.SSR, Ser.Khim., 1980, 732.
70. B.V.Unkovskii, L.A.Ignatova, and M.G.Zaitseva, Khim.Geterotsikl.Soed., 1969, 889.
71. R.W.Lamon, W.J.Humphlett, and W.P.Blum, J.Heterocycl.Chem., 1967, **4**, 349.
72. R.Valters, Khim.Geterotsikl.Soed., 1973, 762.
73. R.Valters and G.Karlivans, Zhur.Org.Khim., 1976, 12, 238.
74. R.Valters and G.Karlivans, Khim.Geterotsikl.Soed., 1976, 1207.
75. K.Bowden and M.P.Henry, J.Chem.Soc., Perkin Trans.II, 1972, 206.
76. K.Bowden and G.R.Taylor, J.Chem.Soc.(B), 1971, 1390.
77. H.Alper, E.C.H.Keung, and R.A.Partis, J.Org. Chem., 1971, **36**, 1352.
78. R.Valters and A.Bace, Izv.Akad.Nauk Latv.SSR, Ser.Khim., 1971, 335.
79. R.Valters, A.Bace, A.Burkevica, and R.Kampare, Zhur.Org.Khim., 1976, 12, 173.
80. G.Duburs and G.Vanags, Izv.Akad.Nauk Latv.SSR, Ser.Khim., 1961, 235.
81. L.Christiaens and M.Renson, Bull.Soc.chim.Belge, 1969, **78**, 359.
82. D.A.Oparin, T.G.Melent'eva, and L.A.Pavlova, Zhur.Org.Khim., 1980, **16**, 1530.
83. L.Yu.Yuzefovich et al., Khim.Geterotsikl.Soed., 1978, 758.
84. Y.Miyagi, S.Kimura, and R.Goto, Bull.Chem.Soc. Japan, 1968, **41**, 2927.
85. L.C.Dorman, J.Org.Chem., 1967, **32**, 255.
86. S.Milstien and L.A.Cohen, Proc.Nat.Acad.Sci.USA, 1970, **67**, 1143.
87. S.Milstien and L.A.Cohen, J.Amer.Chem.Soc., 1972, **94**, 9158.
88. R.T.Borchardt and L.A.Cohen, J.Amer.Chem.Soc., 1972, **94**, 9166.
89. R.T.Borchardt and L.A.Cohen, J.Amer.Chem.Soc., 1972, **94**, 9176.
90. J.M.Karle and I.L.Karle, J.Amer.Chem.Soc., 1972, **94**, 9182.
91. A.Dafforn and D.E.Koshland, Proc.Nat.Acad.Sci. USA, 1971, **68**, 2463.
92. D.R.Storm and D.E.Koshland, J.Amer.Chem.Soc., 1972, **94**, 5805.
93. D.R.Storm and D.E.Koshland, J.Amer.Chem.Soc., 1972, **94**, 5815.
94. C.Danforth, A.W.Nicholson, J.C.James, and G.M.Loudon, J.Amer.Chem.Soc., 1976, **98**, 4275.
95. R.E.Winans and Ch.F.Wilcox, J.Amer.Chem.Soc., 1976, **98**, 4281.
96. B.Capon, J.Chem.Soc.(B), 1971, 1207.
97. Th.C.Bruice, H.Brown, and D.O.Harris, Proc. Nat.Acad.Sci.USA, 1971, **68**, 658.
98. M.I.Page and W.P.Jenks, Proc.Nat.Acad.Soc.USA, 1971, **68**, 1678.
99. H.B.Bürgi, J.D.Dunitz, and E.Shefter, J.Amer. Chem.Soc., 1973, **95**, 5065.
100. H.B.Bürgi, J.D.Dunitz, J.M.Lehn, and G.Wipf, Tetrahedron, 1974, **30**, 1563.
101. H.B.Bürgi, Angew.Chem., 1975, **87**, 461.
102. H.B.Bürgi, J.D.Dunitz, and E.Shefter, Acta Cryst., 1974, **30**, 1517.
103. J.E.Baldwin, Chem.Comm., 1976, 734.
104. J.E.Baldwin, J.Cutting, W.Dupont, L.Kruse, L.Siberman, and R.C.Thomas, Chem.Comm., 1976, 736.
105. J.E.Baldwin and J.A.Reiss, Chem.Comm., 1977, 77.
106. J.E.Baldwin and L.I.Kruse, Chem.Comm., 1977, 233.
107. J.E.Baldwin, R.C.Thomas, and L.I.Kruse, J.Org. Chem., 1977, **42**, 3846.
108. R.Chiron and Y.Graff, Bull.Soc.chim.France, 1971, 2145.
109. R.Valters and S.Valtere, Izv.Akad.Nauk Latv.SSR, Ser.Khim., 1971, 213.
110. J.L.Moniot, D.M.Hindenlang, and M.Shamma, J.Org. Chem., 1979, **44**, 4343.
111. J.E.Whiting and J.T.Edward, Canad.J.Chem., 1971, **49**, 3799.
112. R.M.Moriarty and T.Adams, J.Amer.Chem.Soc., 1973, **95**, 4070.
113. T.Adams and R.M.Moriarty, J.Amer.Chem.Soc., 1973, **95**, 4071.
114. R.M.Moriarty, Ch.C.Chien, and T.B.Adams, J.Org. Chem., 1979, **44**, 2206.
115. R.M.Moriarty, Ch.C.Chien, and T.B.Adams, J.Org. Chem., 1979, **44**, 2210.
116. R.Valters and J.Mednis, Zhur.Org.Khim., 1974, 10, 1248.
117. R.M.Beesley, C.K.Ingold, and J.F.Thorpe, J.Chem. Soc., 1915, **107**, 1080.
118. C.K.Ingold, J.Chem.Soc., 1921, **119**, 305.
119. E.W.Lanfear and J.F.Thorpe, J.Chem.Soc., 1923, **123**, 1683.
120. H.W.Holmquist and K.B.Wiberg, J.Org.Chem., 1959, **24**, 578.
121. H.O.Larson and G.S.K.Sung, Austral.J.Chem., 1962, **15**, 261.
122. N.L.Allinger and V.Zalkov, J.Org.Chem., 1960, **25**, 701.
123. L.Eberson and H.Welinder, J.Amer.Chem.Soc., 1971, **93**, 5821.
124. T.Higuchi, L.Eberson, and A.K.Herd, J.Amer. Chem.Soc., 1966, **88**, 3805.
125. O.H.Wheeler and E.De Rodriguez, J.Org.Chem., 1964, **29**, 1227.
126. R.P.Bell and A.D.Covington, J.Chem.Soc., Perkin Trans.II, 1975, 1343.
127. V.I.Staninets and E.A.Shilov, Uspekhi Khim., 1971, **40**, 491 [Russ.Chem.Rev., 1971(3)].
128. T.C.Bruice and U.K.Pandit, J.Amer.Chem.Soc., 1960, **82**, 5858.
129. I.B.Blagoeva, B.J.Kurtev, and I.G.Pajarlieff, J.Chem.Soc., Perkin Trans.II, 1979, 1115.
130. J.Turk, W.M.Haney, G.Heid, R.E.Barlow, and L.B.Clapp, J.Heterocycl.Chem., 1971, **8**, 149.
131. T.C.Bruice and W.C.Bradbury, J.Amer.Chem.Soc., 1965, **87**, 4846.
132. M.Renson and L.Christiaens, Bull.Soc.chim.Belg., 1962, 71, 379.
133. M.Renson and L.Christiaens, Bull.Soc.chim.Belg., 1962, 71, 394.
134. V.R.Zin'kovskaya and R.E.Valter, Izv.Akad.Nauk Latv.SSR, Ser.Khim., 1976, 65.
135. V.I.Vysotskii, N.V.Vershinina, and M.N.Tilichenko, Khim.Geterotsikl.Soed., 1975, 898.
136. N.V.Vershinina, V.I.Vysotskii, L.M.Eremeeva, V.A.Kaminskii, and M.N.Tilichenko, Khim. Geterotsikl.Soed., 1977, 1315.

137. I.Lielbriedis and E.Gudriniece, Izv.Akad.Nauk Latv. SSR, Ser.Khim., 1966, 684.
138. J.Lemba and I.Lielbriedis, Izv.Akad.Nauk Latv. SSR, Ser.Khim., 1973, 598.
139. V.G.Kharchenko and S.N.Chalaya, "1,5-Diketony" (1,5-Diketones), Izd.Saratov.Gos.Univ., Saratov, 197... [?Ed. of Translation], p.36.
140. V.Stella and T.Higuchi, J.Org.Chem., 1973, **38**, 1527.
141. V.Palm, "Osnovy Kolichestvennoi Teorii Organicheskikh Reaktsii" (Fundamentals of a Quantitative Theory of Organic Reactions), Izd.Khimiya, Leningrad, 1977, p.236.
142. A.J.Kirby and P.M.Lancaster, J.Chem.Soc., Perkin Trans.II, 1972, 1206.
143. R.Scheffold and P.Dubs, Helv.Chim.Acta, 1967, **50**, 798.
144. Yu.G.Tsutsykin and L.B.Volodarskii, Izv.Sibir. Otd.Akad.Nauk SSSR, Ser.Khim., 1969, **9**(4), 86.
145. N.H.Cromwell and K.-Ch.Tsou, J.Amer.Chem.Soc., 1949, **71**, 993.
146. R.E.Lutz and C.E.Griffin, J.Org.Chem., 1960, **25**, 928.
147. H.-P.Rettig and H.Berg, Z.phys.Chem.(Leipzig), 1963, **222**, 193.
148. A.A.Potekhin and B.D.Zaitsev, Khim.Geterotsikl. Soed., 1971, 301.
149. A.A.Potekhin and E.A.Bogan'kova, Khim.Geterotsikl. Soed., 1973, 1461.
150. F.Westheimer, in "Steric Effects in Organic Chemistry" (Translated into Russian), Inostr.Lit., Moscow, 1960, p.529.
151. R.P.Bell, D.W.Earls, and J.B.Henshall, J.Chem.Soc., Perkin Trans.II, 1976, 39.
152. M.S.Newman and C.Courduvelis, J.Org.Chem., 1965, **30**, 1795.
153. J.T.Bunnett and C.F.Hauser, J.Amer.Chem.Soc., 1965, **87**, 2214.
154. V.I.Mimkin, L.P.Olekhnovich, Yu.A.Zhdanov, Z.N.Budarina, V.P.Metlushenko, and Z.B.Orenshtein, Zhur.Org.Khim., 1977, **13**, 777.
155. L.P.Olekhnovich, Abstract of Doctoral Thesis in Chemical Sciences, Rostov State University, Rostov-on-Don, 1981.
156. Z.N.Budarina, Abstract of Candidate's Thesis in Chemical Sciences, Rostov State University, Rostov-on-Don, 1979.
157. B.I.Istomin and V.Palm, Reakts.Sposobn.Org.Soed., 1972, **9**, 433.
158. E.M.Engler et al., J.Amer.Chem.Soc., 1973, **95**, 8005.
159. N.L.Allinger, M.T.Tribble, M.A.Miller and D.H.Wertz, J.Amer.Chem.Soc., 1971, **93**, 1637.
160. R.H.Boyd, J.Chem.Phys., 1968, **49**, 2574.
161. D.F.De Tar, J.Amer.Chem.Soc., 1974, **96**, 1254.
162. D.F.De Tar and C.J.Tenpas, J.Org.Chem., 1976, **41**, 2009.
163. D.F.De Tar, D.F.McMullen, and N.P.Luthra, J.Amer.Chem.Soc., 1978, **100**, 2484.
164. D.F.De Tar, J.Amer.Chem.Soc., 1974, **96**, 1255.
165. D.F.De Tar and N.P.Luthra, J.Amer.Chem.Soc., 1980, **102**, 4505.
166. D.F.De Tar and W.Brooks, J.Org.Chem., 1978, **43**, 2245.

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