U.D.C. 541.571.9

The Intramolecular Hydrogen Bond and the Reactivity of Organic Compounds

I.D.Sadekov, V.I.Minkin, and A.E.Lutskii

Numerous new data on the effect of intramolecular hydrogen bonds on the reactivity of organic compounds are reviewed systematically.
The bibliography comprises 200 references.

CONTENTS

1. Introduction
2. Effect of the intramolecular hydrogen bond on the acidity of the hydroxy-group
3. Alkylation of hydroxy-compounds
4. The strength of carboxylic acids
5. Esterification reactions
6. Hydrolysis of esters
7. Decarboxylation reactions
8. Intramolecular hydrogen bonds and basicity
9. Reduction reactions
10. Substitution reactions
11. Reactions of *o*-hydroxy-aldehydes
12. Intramolecular hydrogen bonds and certain specific reactions
13. Inhibition of chemical reactions by intramolecular hydrogen bonds
14. The role of intramolecular hydrogen bonds in the stabilisation of organic molecules

1. INTRODUCTION

An enormous number of investigations have been made recently on the nature and properties of hydrogen bonds. In the vast majority of these the effects of hydrogen bonds on different physical properties (on electronic, vibration, and NMR spectra, dipole moments, etc.) are investigated. A number of monographs and reviews are devoted to data obtained in this field. There is much less information about the effect of hydrogen bonds on the chemical properties of the molecules involved in them. Such information is scattered in various sources and only two attempts have been made to review it [1,2]. Subsequently many new communications on the role of hydrogen bonds in various chemical reactions appeared. The principal aim of the present review is to give a general and systematic account of these data.

In view of the large number of new facts, the scope of the review had to be restricted to only one type of hydrogen bond—the intramolecular hydrogen bond (i.h.b.). The qualitative nature of the available literature data on the effect of intramolecular hydrogen bonds on the reactivity of organic compounds and as a rule the lack of sufficiently systematic studies precludes the treatment of these data on the basis of any one general concept. Numerous conclusions concerning the effect of intramolecular hydrogen bonds on chemical properties arrived at in this review or by the authors of the papers quoted are based on comparisons and analogies, the generality of which cannot always be demonstrated, for example those based on the identification of the properties of hydroxy- and alkoxy-derivatives, *o*- and *p*-substituted benzenes, etc.

However, this approach reflects not only the level attained in the modern analysis of the effect of intramolecular hydrogen bonds on reactivity but also the exceptional complexity of the problem. In principle, the difficulty of investigating this problem consists in the fact that the intramolecular hydrogen bond, the effect of which on reactivity has to be elucidated, should be regarded as a comparatively small perturbation in relation to factors which determine the mode and type of reaction, since usually the energy of the intramolecular hydrogen bond is almost ten times smaller than the energy of activation for the corresponding chemical reactions.

Bearing this in mind, our aim was to collect the principal facts relevant to the problem under consideration and to describe them systematically.

2. EFFECT OF THE INTRAMOLECULAR HYDROGEN BOND ON THE ACIDITY OF THE HYDROXY-GROUP

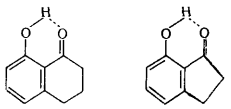
The hydrogen atom of the hydroxy-group involved in an intramolecular hydrogen bond is linked to the molecule much more strongly than in the absence of such a bond. As a result, the removal of such a proton from the molecule is more difficult than in the case of a non-chelated hydrogen atom. For this reason *ortho*- or *peri*-hydroxy-compounds with substituents capable of functioning as electron acceptors are weaker acids than the analogous compounds with *para*-substituents. Salicylaldehyde which contains a strong intramolecular hydrogen bond [3,4] has $pK_a = 8.14$ (in water), while the pK_a of the isomeric *p*-hydroxybenzaldehyde is 7.45. [5,6] If it is assumed that the transmission of electronic effects from the *ortho*- and *para*-positions is approximately the same, it becomes clear why 4-chloro-2-hydroxybenzaldehyde ($pK_a = 7.18$) is a weaker acid than 2-chloro-4-hydroxybenzaldehyde ($pK_a = 6.60$), which has no hydrogen bond [7].

The acidity of *o*-hydroxyacetophenone is lower than that of *p*-hydroxyacetophenone (their pK_a's are 10.07 and 7.87 respectively [6,8]). The higher dissociation constant of

salicylaldehyde compared with *o*-hydroxyacetophenone is consistent with the relative strengths of the intramolecular hydrogen bonds, which can be estimated from the infrared spectra ($\Delta\nu_{C=O}$, determined by the intramolecular hydrogen bond, is 38 cm^{-1} for the first compound and 45 cm^{-1} for the second). The relative pK_a's of α-naphthol derivatives have been determined [9]. 1-Hydroxy-2-naphthaldehyde (pK_a = 8.85) and 1'-hydroxy-2'-acetonaphthone (pK_a = 10.9), which have powerful intramolecular hydrogen bonds [2], are weaker acids than 1-hydroxy-4-naphthaldehyde (pK_a = 8.75) and 1'-hydroxy-4'-acetonaphthone (pK_a = 9.6) where a hydrogen bond is impossible.

Although the acid dissociation constants of the *o*-hydroxycarbonyl compounds were measured by different investigators and under different conditions, nevertheless it is clear that the *o*-hydroxycarbonyl derivatives of naphthalene are usually weaker acids than the corresponding benzene derivatives. The explanation of this should be sought in the greater strength of the hydrogen bond in the naphthalene series compared with benzene derivatives.

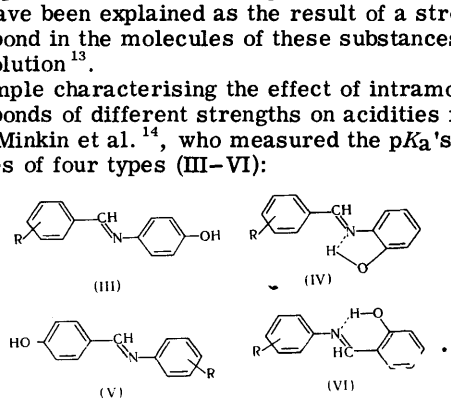
The strong intramolecular hydrogen bond in 8-hydroxy-1-tetralone(I) is the reason why this compound is a weaker acid (pK_a = 11.14) than 6-hydroxy-1-tetralone (pK_a = 7.74) and similarly 7-hydroxy-1-indanone (II) is a weaker acid (pK_a = 8.43) than 5-hydroxy-1-indanone (pK_a = 7.53):[10]



(I) (II)

As a result of the strong intramolecular hydrogen bond between hydroxy- and nitro-groups, the acidity of 2-nitro-1-naphthol is lower than that of 4-nitro-1-naphthol [5]. According to spectrophotometric determinations [11,12], the pK_a of 2-nitro-1-naphthol is 8.72, which corresponds to a dissociation constant 8 times higher than for 1-naphthol, while the pK_a of 1-nitro-2-naphthol is 9.02, i.e. the dissociation constant is 14 times higher than that of 2-naphthol. This non-equivalent increase of acidity has been attributed to a stronger intramolecular hydrogen bond in 1-nitro-2-naphthol compared with its isomer. It is noteworthy that, apart from the intramolecular environment, acid dissociation constants are greatly influenced by the solvent in which the pK_a is determined. Thus, the anomalously low acid dissociation constants of 2,4- and 2,5-dinitrophenols in benzene compared with their values in water have been explained as the result of a stronger hydrogen bond in the molecules of these substances in benzene solution [13].

An example characterising the effect of intramolecular hydrogen bonds of different strengths on acidities is quoted by Minkin et al. [14], who measured the pK_a's of Schiff bases of four types (III–VI):



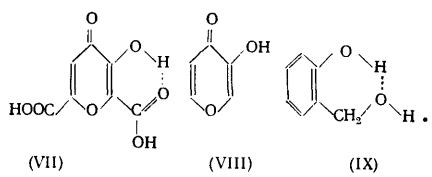
(III) (IV) (V) (VI)

The corresponding pK_a's (in 98% methanol) are listed in Table 1. The reduced acidity of (VI) compared with (V) and of (IV) compared with (III) is undoubtedly associated with the effect of the hydrogen bond. The order of magnitude of the pK_a values is consistent with the concept of the greater strength of the hydrogen bond in the six-membered ring of (VI) [15,16,17] compared with the five-membered ring of (IV). [18,19,20]

Table 1.

Type of Schiff base	pK_a					
	R=N(CH₃)₂	R=OCH₃	R=H	R=CH₃	R=I	R=NO₂
III	10.60	10.49	10.42	—	10.33	10.18
IV	11.02	—	10.88	10.92	—	10.71
V	—	9.84	9.73	9.79	9.63	—
VI	—	—	11.03	11.09	10.95	10.82

The presence of intramolecular hydrogen bonds in hydroxy-acids increases the dissociation constant of the carboxy-group but significantly lowers that of the chelated hydroxy-group. Whereas $K_a = 3.5 \times 10^{-10}$ for the phenolic hydroxy-group in *p*-hydroxybenzoic acid, salicylic acid, in which there is a strong intramolecular hydrogen bond, has $K_a = 1.5 \times 10^{-14}$. The same thing is also observed for the esters of *p*- and *o*-hydroxy-benzoic acids: the pK_a's of the *o*- and *p*-isomers are 9.2 and 8.34 respectively [21]. The sharply reduced ionisation constant of the phenolic hydroxyl in meconic acid (VII) ($K_a = 1.5 \times 10^{-10}$) compared with pyromeconic acid (VIII) ($K_a = 2.2 \times 10^{-8}$) is evidence [22] of the presence of intense chelation in the first compound between the OH and COOH groups:



(VII) (VIII) (IX)

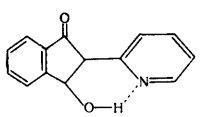
The *peri*-sulpho-groups in phenylazonaphthols behave similarly [23].

It has been found that not only powerful electron-accepting groups such as >C=O, $-NO_2$, >C=N–, and –COOH, which form strong hydrogen bonds, are capable of reducing the acid strength. Even a weak electron-accepting substituent, such as the hydroxymethyl group, forms an intramolecular hydrogen bond with the phenolic hydroxyl in (IX) and weakens its acid properties. The pK_a of *p*-hydroxymethylphenol is lower by 0.1–0.15 units than the pK_a of phenol itself. (9.94 for phenol and 9.82 for *p*-hydroxymethylphenol) [24]. If the effect of the hydroxymethyl group in compound (IX) were mainly inductive, one might expect that the pK_a value for this compound would be approximately the same as for the *para*-isomer. However, the pK_a of *o*-hydroxymethylphenol (IX) is lower by only 0.02–0.05 units than the value for phenol itself. The reason for this is the presence of an intramolecular hydrogen bond in compound (IX). [25,26]

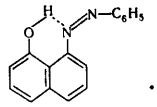
A similar situation exists also in di-(*o*-hydroxyphenyl)-methanes [27,28]. The behaviour of 2,2'-dihydroxybiphenyl is very similar to that discussed above. Whereas the higher value of the first ionisation constant of this compound ($pK_{a_1} = 7.56$) [29] compared with *o*-phenylphenol ($pK_a = 9.97$) [30] may be attributed to an intramolecular hydrogen bond in the neutral molecule [31], the much lower value of the second ionisation constant ($K_{a_1}/K_{a_2} = 106$) can

be accounted for by a strong hydrogen bond in the mono-anion.

The effect of the intramolecular hydrogen bond is shown in the fact that many phenols with such a bond do not form normal salts under the usual conditions. Thus 2-(2′-pyridyl)indane-1,3-dione (X) is insoluble in aqueous sodium bicarbonate and is not titrated with alkali in an aqueous dioxan mixture [32]. Certain *peri*-hydroxyazo-dyes (XI) behave similarly. They are all insoluble in aqueous solutions of alkali [33]. Many other examples of similar behaviour of phenols have been quoted [1-4,34]:



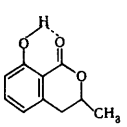
(X)



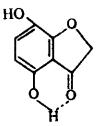
(XI)

3. ALKYLATION OF HYDROXY-COMPOUNDS

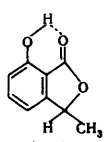
The presence of an intramolecular hydrogen bond in the molecule is the reason for the difficulty and sometimes the impossibility of obtaining ethers derived from the hydroxy-groups involved in the hydrogen bond by treatment with diazomethane under the usual conditions. This property of chelated groups is sometimes used to establish the structures of hydroxyanthraquinones, hydroxyflavones, hydroxyxanthones, etc., although in certain cases such *peri*-chelated hydroxyls may be methylated by prolonged heating with a large excess of diazomethane. A particular example of such "normally" methylated compounds, is mellein—3,4-dihydro-8-hydroxy-3-methylisocoumarone (XII). [35] Under the action of diazomethane, it is readily converted into the methoxy-derivative, although its OH group is involved in a strong hydrogen bond:



(XII)

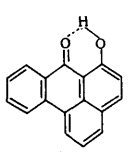


(XIII)

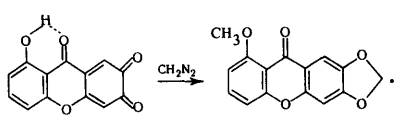


(XIV)

Other compounds where the proton of a chelated hydroxy-group can be comparatively readily replaced by methyl under the action of an ethereal solution of diazomethane are 4,6-dihydroxy-3-coumarone (XIII), [36] 7-hydroxy-3-methylphthalide (XIV), [37] 3,6-dihydroxyphthalic anhydride, 3,6-dihydroxyphthalimide, [38] 1-benzoyl-2-naphthol, and 6-hydroxymesobenzanthrone (XV): [39]



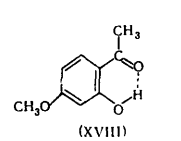
(XV)



(XVI) (XVII)

8-Hydroxy-2,3-quinoxanthone (XVI) is methylated in an unusual way, being converted under the action of diazomethane in an ethereal solution into compound (XVII). [40] It is interesting that in the majority of the normally methylated compounds the carbonyl group is located in a five-membered ring.

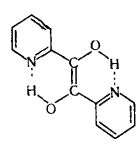
The vast majority of chelated phenols are not methylated, and in the presence of several hydroxy-groups in the molecule only those not involved in hydrogen bonding are substituted. *o*-Hydroxyacetophenone, *o*-hydroxybenzophenone, 2-hydroxy-4-methoxyacetophenone (XVIII), [39] 1-hydroxy-9-xanthone (XIX), [41] and the diethyl ester of meconic acid [22] are not methylated at all by diazomethane in ethereal solution:



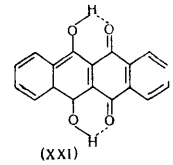
(XVIII) (XIX)

All attempts to methylate 2-pyridoin (XX) [42,43] were also unsuccessful. Diazomethane in ether has altogether no effect on this compound and in the reaction with sodium and methyl iodide or with dimethyl sulphate and alkalies, the only products are picolinamide in the first case and methyl picolinate in the second.

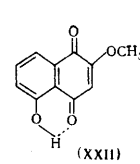
Examples of this kind among quinones are fairly numerous. The hydroxy-groups of alizarin methylated in the 2-position [1], 6,11-dihydroxy-5, 12-naphthacenequinone (XXI), [44] and 2-methoxyjuglone (XXII) [45] do not react with diazomethane:



(XX)

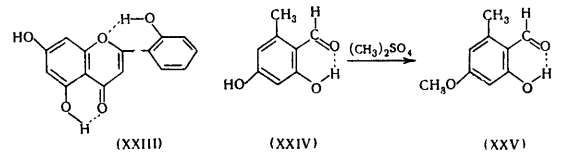


(XXI)



(XXII)

A very characteristic feature of polyhydroxy-compounds is selective alkylation of the free hydroxyls. In chromanone, flavanone [46], and polyhydroxyflavone [40] derivatives diazomethane methylates all the hydroxy-groups with the exception of the group in the 5-position. Similar results were obtained in the reaction with dimethyl sulphate in alkali at room temperature [46]. It has been shown [47] that the 2′-hydroxy-group in flavanones behaves similarly to the 5-hydroxy-group. Thus methylation of 2′,5,7-trihydroxyflavanone (XXIII) with dimethyl sulphate in acetone in the presence of potassium carbonate gives only 2′,5-dihydroxy-7-methoxyflavanone:



(XXIII) (XXIV) (XXV)

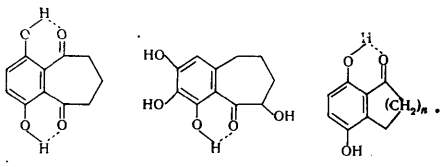
The only product of the methylation of 2,4,5-trihydroxyacetophenone with dimethyl sulphate is 2-hydroxy-4,5-dimethoxyacetophenone [48], while 2,4-dihydroxydeoxybenzoin yields only 2-hydroxy-4-methoxydeoxybenzoin [49]. A similar situation exists in substituted resacetophenones and nitroresorcinols where methylation with dimethyl sulphate of the hydroxyl chelated with the nitro- or carbonyl group is very difficult [49,50]. Methylation with dimethyl sulphates of the *o*-orsellinaldehyde (XXIV) leads to everninaldehyde (XXV). [51]

Sometimes the inability of chelated hydroxy-groups to be methylated is used for their protection in many syntheses. Thus Baker and Savage [52] showed that the 1,2-methylene ether of pyrogallol can be obtained by converting pyrogallol into pyrogallol-4-carboxylic acid, which yields 2-hydroxy-3,4-methylenedioxybenzoic acid under the action of dimethyl sulphate. The decarboxylation of this compound on heating with copper chromite gave the required product. The 1,2-dimethyl ether of pyrogallol was synthesised similarly.

Similar results were obtained in the study of the methylation [45] of a series of derivatives of polyhydroxy-1,4-naphthoquinones: juglone (5-hydroxy-1,4-naphthoquinone) and

naphthazarin (5,8-dihydroxy-1,4-naphthoquinone). Under all the conditions investigated, the *peri*-hydroxy-groups in the 5- and 8-positions, which are linked by strong hydrogen bonds, are not methylated by diazomethane, while all other hydroxy-groups are readily converted into methoxy-groups. Thus, in the reaction with diazomethane 2-hydroxyjuglone gives 2-methoxyjuglone, 3-hydroxyjuglone gives 3-methoxyjuglone, and 6-ethyl-7-hydroxy-2-methoxyjuglone gives 6-ethyl-2,7-dimethoxyjuglone. Hydroxynaphthazarins behave similarly.

The behaviour of polyhydroxyindanones, tetralones, and 1,2-benzocycloheptanones is unusual. Like all *peri*-chelated hydroxy-ketones, 1′,4′-dihydroxy-1,2-benzocyclohepta-3,7-dione (XXVI) does not react with diazomethane[53]. However, 1′,2′,3′,4′-tetrahydroxy-1,2-benzocycloheptan-3-one (XXVII) is readily converted into the 2′,3′,4′-trimethyl ether, the *peri*-hydroxy group of which cannot be alkylated,[54]:



(XXVI) (XXVII) (XXVIII)

At the same time, 5,8-dihydroxytetralone is not methylated with diazomethane even at the free hydroxy-groups in the 5-position[55]. An anomalous feature is that the reaction of diazomethane with 4,7-dihydroxyindanones (XXVIII, $n = 1$), 4,7-dihydroxytetralones (XXVIII, $n = 2$), and 4,7-dihydroxybenzocycloheptanones (XXVIII, $n = 3$) does not result in the methylation of any of the hydroxy-groups even on prolonged contact at low temperatures in various solvents[38]. The behaviour of these compounds in reactions with phenyl isocyanate is also anomalous[38].

4. THE STRENGTH OF CARBOXYLIC ACIDS

When hydrogen bonds are formed in molecules of organic carboxylic acids, the dissociation constants of the latter may increase or decrease. They increase when the carboxy-group behaves as a proton acceptor (by virtue of its carbonyl oxygen) and they decrease in those cases where the hydroxyl of the carboxy-group behaves as a proton donor in the hydrogen bond. Examples of compounds of the first type are the *o*-hydroxy-acids of the benzene and naphthalene series. Salicylic acid is much stronger than the *m*- and *p*-isomers[21,56-58]. The introduction of a second hydroxy-group in the *o*-position results in an even greater increase of the dissociation constant. 2,6-Dihydroxybenzoic acid is stronger than phosphoric acid. The acid dissociation constants K_a in water are listed in Table 2.

The much higher dissociation constant of salicylic acid [compared with isomers (Ed. of Translation)] cannot be explained by the electronic effect of the hydroxy-group, since it should be approximately the same for the *o*- and *p*-positions. Nor can one invoke the *ortho*-effect to account for this phenomenon[59]. Although the higher dissociation constants K_a of the *o*-substituted benzoic acids compared with the *p*-isomers due to the destabilisation of the unionised acid by steric factors[57] is observed also on introduction of other *o*-substituents, incapable of formation of hydrogen bonds, the increase is much less. Thus, whereas the K_a values for the *o*-isomers of toluic and chlorobenzoic acids, for example, exceed the values for the *p*-isomers by factors of 2.9 and 10.5,[60] K_a for *o*-monohydroxybenzoic acid is higher than the corresponding value for the *p*-isomer by a factor of 40. Nor should one forget that the bulk of the hydroxy-group is much smaller than that of the majority of other *o*-groups and yet its effect on K_a is much greater. The polar effect is itself too small to account for the considerable difference between the dissociation contants of *o*- and *p*-hydroxybenzoic acids. This is evident from the fact that the K_{a1} for *o*- and *p*-phthalic acids, which are 1.1×10^{-3} and 2.9×10^{-4}, and for *o*- and *p*-aminobenzoic acids, 1.1×10^{-5} and 1.4×10^{-5}, differ much less than in the case of hydroxy-acids[60].

Table 2.

Acid	$10^5 K_a$	$K_a/K_{a(C_6H_5COOH)}$
Benzoic	6.30	1
m-Hydroxybenzoic	8.33	1.32
p-Hydroxybenzoic	2.62	0.42
o-Hydroxybenzoic	105	16.7
2,6-Dihydroxybenzoic	6000	952

The only acceptable explanation of the anomalously high K_a value for salicylic acid is the existence of an intramolecular hydrogen bond in its molecule[3]. The intramolecular hydrogen bond is of course present both in the undissociated acid and in the anion[61,62]. However, since it is to be expected that it is stronger in the anion than in the acid, the stabilisation of the former will be significant and the equilibrium will be displaced towards the dissociated form. An indirect confirmation of this hypothesis is provided by the dissociation constants of methoxybenzoic and 3-methoxy-2-naphthoic acids[21] listed in Table 3.

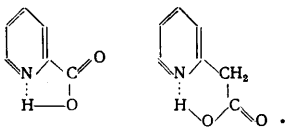
Table 3.

Acid	$10^5 K_a$	$K_{a(OH)}/K_{a(OCH_3)}$
p-Methoxybenzoic	3.20	0.81
o-Methoxybenzoic	8.06	13.00
3-Methoxy-2-naphthoic	15	13.1

It should be noted, that on the basis of K_a measurements for substituted salicylic acids in benzene, Dunn and Penner[63] regard the above explanation of the unusual strength of salicylic acid as a serious oversimplification.

The anomalously high pK_a values for methylsubstituted pyrrole-2-carboxylic acid compared with the 3-isomers (Table 4)[64,65] have been attributed to the existence of intramolecular hydrogen bonds in the anions of the former compounds. Although intramolecular hydrogen bonds of this kind have not been found in the corresponding ester or in 2-acetylpyrrole, the more pronounced nucleophilic properties of the carboxylate anion may result in this type of interaction[64].

While in the examples considered above the intramolecular hydrogen bond is responsible for the increase of the acid dissociation constant, in many 2-substituted acids with heterocyclic substituents the hydrogen bond has the opposite effect. The σ-constant of the 2-pyridyl group calculated from the K_a of picolinic (XXIX) and pyridine-2-acetic (XXX) acids proved to be anomalously low compared with the σ-values calculated from data for other reaction series. This is explained by the presence of an intramolecular hydrogen bond between the hydrogen atom of the hydroxy-group and the nitrogen atom, which stabilises the acid and increases the pK_a value [66]:

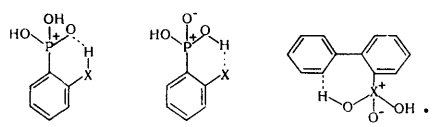


(XXIX) (XXX)

Table 4. pK_a values for substituted pyrrolecarboxylic acids.

Position of COOH	R	pK_a
2	H	4.40
3	H	4.95[18]; 5.00[56]
2	3-CH_3	4.60
2	4-CH_3	5.10
2	5-CH_3	5.00
3	2-CH_3	5.80
3	4-CH_3	5.60
3	5-CH_3	5.35

Jaffe's examination of the acid dissociation constants of *o*-substituted phenylphosphonic acids [67] led to the hypothesis that, depending on the nature of the *o*-substituent, the P=O group can behave as an acceptor [compound (XXXI)] or a donor [compound (XXXII)] in the hydrogen bond:



(XXXI) (XXXII) (XXXIII)

When the P=O group behaves as an acceptor, the negative charge of its oxygen atom decreases and the acid strength increases. This effect is clearly seen in 2-hydroxy-4-nitrophenylphosphonic acid, where the difference between the experimental pK_a and the value calculated on the assumption that the polar and inductive effects are the same in the *o*- and *p*-positions reaches −0.18 in water and −0.64 in 50% alcohol.

On the other hand, if the P=O group behaves as a donor in the hydrogen bond, its oxygen atom assumes a partial negative charge and therefore the first dissociation constant of the phosphonic acid increases. This effect, which is weaker than the first, obtains in *o*-methoxyphenylphosphonic acid (ΔpK_a in water +0.10 and in alcohol +0.25). The effect of substituents on the second dissociation constants of the above compounds is also interpreted from the standpoint of this mechanism.

Hydrogen bonds with benzene rings as proton acceptors are fairly weak [68–73]. Nevertheless the large differences between the pK_a values of *o*-biphenylylphosphonic (XXXIII, X = P) (pK_a = 3.78) and phenylphosphonic (pK_a = 1.83) acids [67,74] and *o*-biphenylylarsonic (XXXIII, X = As) (pK_a = 4.29) and phenylarsonic (pK_a = 3.47) acids [75] have been attributed to the intramolecular hydrogen bonds between the acid hydroxy-groups and the π electrons of the aromatic system[67].

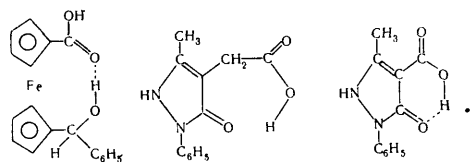
Intramolecular hydrogen bonds have some effect also on the dissociation constants of organic acid salts. When a hydroxy- or amino-group capable of formation of hydrogen-bonded bridges is present in the salt anion, the dissociation constant of the salt is greatly increased. This has been found, in particular, for magnesium, calcium, strontium, and barium salts of glycollic acid, glycine, etc.[76]

5. ESTERIFICATION REACTIONS

The rate and mode of esterification reactions depends significantly on the presence of intramolecular hydrogen bonds in the reactant molecules. Measurements of the rate constants for the interaction of substituted benzoic acids with *p*-tolyldiazomethane in toluene or ethyl acetate solutions showed that salicylic acid is the most reactive [77]:

$$RCOOH + N_2C(C_6H_4CH_3)_2 \rightarrow RCOOCH(C_6H_4CH_3)_2 + N_2.$$

In an analogous reaction with diphenyldiazomethane in toluene at 30°C, among all ferrocenecarboxylic acids with heteroannular CH_3CO, C_2H_5, C_6H_5, $C_6H_5CH_2$, and $C_6H_5CH(OH)$ substituents, 1-(α-hydroxybenzyl)ferrocene-1′-carboxylic acid was esterified with the highest rate constant [78]. It has been shown [79] that diphenyldiazomethane attacks the carboxy-group at the O–H bond. Therefore the high reactivities of salicylic acid [77] and 1-(α-hydroxybenzyl)ferrocene-1′-carboxylic acid (XXXIV) [78] can be explained by the formation of an intramolecular hydrogen bond between the hydroxy-group of the substituent and the carbonyl oxygen, which inhibits the rotation of the COOH group and increases the rate of its reaction with diaryldiazomethanes:



(XXXIV) (XXXV) (XXXVI)

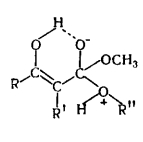
The sharp difference between the reactivities of *cis*- and *trans*-2-hydroxycyclohexane-1-carboxylic acids and their derivatives is attributed to the presence of a hydrogen bond in the *cis*-isomer [80]. The higher rate of reaction with diazomethane of antipyrineacetic acid (XXXV) compared with antipyrinecarboxylic acid (XXXVI) is a consequence, according to the author [81], of the greater lability of the seven-membered chelate ring in compound (XXXV) compared with the six-membered ring in compound (XXXVI). It is believed that the higher reactivity of β-keto-esters in transesterification reactions (RCOOR′ + R″OH → RCOOR″ + R′OH) may be due to a hydrogen bond in the transition state (XXXVII) of the reaction [82,83]. Indeed, while the transesterification of methyl- and ethyl-substituted β-keto-esters takes place under mild conditions in the absence of a catalyst, the transesterification of disubstituted β-keto-esters incapable of enolisation and

hence of the formation of intramolecular hydrogen bonds does not take place under these conditions.

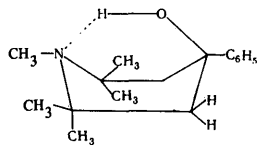
A chelated phenolic hydroxyl is probably more readily acylated than alkylated [40]. However, the formation of esters (particularly under the usual conditions) is also anomalously slow or does not occur at all when the molecule contains hydrogen-bonded hydroxyls. Thus in the benzoylation of phenol and its substituted derivatives it was found that *o*-nitrophenol is esterified at the lowest rate, while the esterification of the *m*- and *p*-isomers is somewhat faster than that of phenol itself [1]. In polyhydroxyanthraquinones the chelated *peri*-hydroxyls are acetylated much more slowly than others [1].

Many compounds with a strong intramolecular hydrogen bond are not acetylated at all under the usual conditions (acetylation with acetic anhydride at room temperature with addition of several drops of pyridine). This has been established for 4-chlorosalicylaldehyde [1], 5-fluoro-2-nitrophenol [1], 2-hydroxy-3-methyl-5-nitrobenzaldehyde [49], 2,3,5-trinitrophenol [49], and α-hydroxybenzylideneacetophenone [49].

The unsuccessful attempts to obtain the acetyl derivatives of compound (XXXVIII) are due to the presence of the strong intramolecular hydrogen bond in the latter ($\Delta\nu_{OH} = 205$ cm^{-1}). [84]

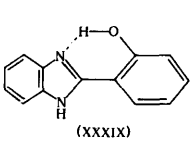


(XXXVII)

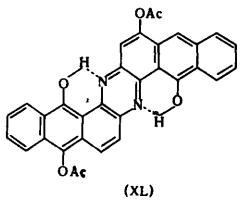


(XXXVIII)

The selective acetylation of hydroxy-groups in polyhydroxy-compounds is also due to the involvement of some of these in intramolecular hydrogen bonds. Thus in the acetylation of 2,4-dihydroxybenzoic acid and the corresponding aldehyde only the 4-acetoxy-2-hydroxy-derivative is obtained [1] and 2,4,6-trihydroxybenzaldehyde gives only the 4,6-diacetyl derivative [1]. Acetylation of polyhydroxy-substituted flavones, isoflavones, chromones, and flavanones under mild conditions does not involve the hydroxy-groups in the 5-position because of its strong hydrogen bond with the *peri*-carbonyl oxygen atom [40] (under more severe conditions—heating at 100°C—this hydroxyl is also acetylated). Acetylation with acetic anhydride of 1′,2′,3′,4-tetrahydroxy-1,2-benzocycloheptan-3-one (XXVII) gives 2′,3′,4-triacetoxy-1-hydroxy-1,2-benzocycloheptan-3-one [84], while the acetylation of 2-(*o*-hydroxyphenyl)benzimidazole (XXXIX) takes place at the nitrogen atom [85] (there is a strong intramolecular hydrogen bond between the hydroxy-group and the imine nitrogen atom [86]):



(XXXIX)



(XL)

The reductive acetylation (with zinc and acetic anhydride) of the non-linear isomer of indanthrone yields only the diacetyl derivative (XL) since the remaining hydroxy-groups are linked by strong hydrogen bonds [87].

To elucidate the effects of intramolecular hydrogen bonds on the rate of acetylation, the kinetics of the reaction of certain cholinolytic substances with acetyl chloride have been investigated [88] at 30°C in chloroform solution. The kinetic data together with infrared spectroscopic data [89] are presented in Table 5. A particularly important feature of these results is that the spectroscopic measurements were made approximately under the same conditions (carbon tetrachloride as a solvent) as the kinetic experiments.

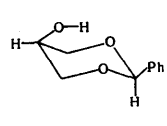
Table 5.

Compound	ν_{OH}, cm^{-1}	$k_{acetylation}$, litre mole^{-1} min^{-1}
(1) $(C_6H_5)_2C(OH)CH_2OC_2H_5$	3484^{*}_{33}	0.50
(2) $(C_6H_5)_2C(OH)C_2H_5$	—	0.50
(3) $(C_6H_5)_2C(OH)COOCH_2CH_2N(C_2H_5)_2$	3534_{21} 3610_{64}	1.42
(4) $(C_6H_5)_2C(OH)COSCH_2CH_2N(C_2H_5)_2$	3534_{57} 3610_{30}	9
(5) $(C_6H_5)_2C(OH)CONHCH_2CH_2N(C_2H_5)_2$	3378_{58} 3623_{73}	1.50
(6) $(C_6H_5)_2C(OH)CON(CH_3)CH_2CH_2N(C_2H_5)_2$	3378_{33} 3610_{80}	1.90
(7) $(C_6H_5)_2C(OH)CH_2OCH_2CH_2N(C_2H_5)_2$	3155_{88} 3610_{75}	0.29
(8) $(C_6H_5)_2C(OH)CH_2CH_2N(C_2H_5)_2$	3226_{34} 3610_{84}	0.35

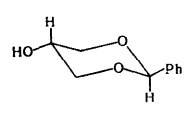
*The subscripts denote the percentage transmission in 0.02 M solutions in carbon tetrachloride.

The complexity of the structures of the compounds chosen and the presence in them of substituents of different electronic types complicates the interpretation of the results. Nevertheless it is clear that the rate of acetylation of the thioester (4) is much higher than that of the ester (3), while the rates for the corresponding amides are much lower. This is fully consistent with the spectroscopic finding that the hydroxyl in (4) is less strongly linked and those in (5) and (6) are more strongly linked by intramolecular hydrogen bonds than the hydroxyl in (3). One cannot of course dismiss the possibility of some influence of the ester, thioester, and amide groups on the lability of the hydrogen atom in the hydroxy-group. Similarly the lower rate of reaction of (7) and (8) compared with (1) and (2) respectively can be explained by stronger intramolecular hydrogen bonds in the latter.

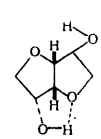
The accelerating effect of hydrogen bonds on the esterification of alcohols has also been described. Such an effect has been noted by Buck et al. [90] in a study of the esterification of 5-hydroxy-1,3-dioxan derivatives with *p*-phenylazobenzoyl chloride. *cis*-5-Hydroxy-2-phenyl-1,3-dioxan (1,3-benzilideneglycerol) and (XLI) reacts with *p*-phenylazobenzoyl chloride almost six times faster than the *trans*-isomer (XLII). This is because the intramolecular hydrogen bond in compound (XLI) (in carbon tetrachloride solutions $\Delta\nu_{OH_{cis}} = 3590$ cm^{-1} and $\Delta\nu_{OH_{trans}} = 3633$ cm^{-1}) increases the basicity of the oxygen atom of the hydroxy-group and thereby increases the rate of esterification:



(XLI)



(XLII)



(XLIII)

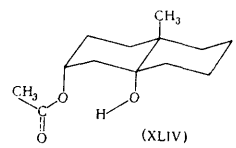
This is confirmed by the behaviour of 4-phenylcyclohexanols. Since only intermolecular hydrogen bonds may exist in solutions of these compounds, the reactivity of both

isomers should be enhanced, but, since in the *cis*-isomer the hydroxy-group is sterically more inaccessible, the greatest increase in rate should be expected for the *trans*-isomer. Indeed, at 37°C *trans*-4-phenylcyclohexanol reacts almost 7 times faster than the *cis*-isomer.

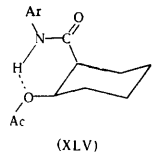
Of the two hydroxy-groups in 1,4,3,6-dianhydro-α-gluticol (XLIII) the 5-hydroxy-group, involved in an intramolecular hydrogen bond, is the more reactive. In particular, the formation of the *p*-toluenesulphonyl derivative involves mainly the 5-hydroxy-group (after interaction with *p*-toluenesulphonyl chloride for 46 h the mixture has the following composition: 11.7% of the 2-monosubstituted derivative, 11.7% of the 2,5-disubstituted derivative, and 45.4% of the 5-monosubstituted derivative [91]); in the esterification with *p*-phenylazobenzoyl chloride the 5-monosubstituted derivative is also mainly formed (after 22 h the reaction mixture contains 12% of the 2-monosubstituted derivative, 9% of the 2,5-disubstituted derivative, and 36% of the 5-mono-substituted derivative [90]).

6. HYDROLYSIS OF ESTERS

Barton [92] established that esters of equatorial alcohols of the cyclohexane series are hydrolysed more readily than the epimeric axial esters. However, this general rule does not hold if the hydroxy- and ester-groups in the monoesters of the diols approach one another under the influence of the molecular environment to such an extent that an intramolecular hydrogen bond is formed. Such a hydrogen bond greatly facilitates the hydrolysis of axial esters compared with the equatorial esters. This phenomenon was discovered for the first time by Henbest and Lovell [93,94]. In a study of the hydrolysis of 3-acetoxy-5-hydroxysteroids in aqueous potassium bicarbonate they found that the *cis*-diaxial hydroxy-esters of the cholestane and coprostane series are hydrolysed (under the same conditions) to a much greater extent than the corresponding equatorial esters. These results were explained by the formation of a six-membered ring with a hydrogen bond between the hydroxyl in the 5-position and the alcoholic oxygen of the axial ester (XLIV):



(XLIV)



(XLV)

According to the authors, such a hydrogen bond increases the reactivity of the ester group in relation to the nucleophilic agent introduced into the reaction [94]. The decrease of the OH and ⩾C–O vibration frequencies and the increase of the carbonyl frequency in the infrared spectra of acetoxy-alcohols of type (XLIV) confirmed the hypothesis that intramolecular hydrogen bonds of this type are present.

A study of the infrared spectra (with high resolution in the region of the hydroxyl stretching vibrations) of certain 1,3-hydroxy-acetates of the bicyclononane and bicyclononene series was carried out by Johnson and coworkers [95]. The authors believe that the slight shift of the hydroxyl band ($\Delta\nu_{OH}$ = 15 cm^{-1}) cannot be assigned to the hydrogen bond with the carbonyl oxygen because, like Henbest and Lovell [93,94], they attribute this shift to the hydrogen bond with the ester oxygen. Furthermore, the >C=O frequency in the intramolecularly hydrogen-bonded compounds investigated is usually enhanced, while involvement in an intramolecular hydrogen bond always reduces it.

The hydrogen bond is also responsible for the higher reactivity of derivatives of *cis*-2-hydroxycyclohexanecarboxylic acid compared with the *trans*-isomers. Thus the *cis*-acetoxy-*p*-toluidide (XLV) is hydrolysed much more rapidly than the corresponding *trans*-isomer [80].

Similarly the base-catalysed methanolysis of 7- and 16-acetoxy-derivatives of germine is facilitated by the presence of hydroxy-groups in the 14- and 20-positions [96], while the methanolysis of the 16-acetoxy-derivative of cevine is facilitated by the hydroxy-group in the 20-position [97].

Table 6.

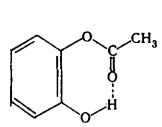
Compound	10^3k, litre $mole^{-1}$ s^{-1}
3β-Methoxycholestan-4β-yl acetate	2.7
4β-Hydroxycholestan-3β-yl acetate	22
3β-Hydroxycholestan-4β-yl acetate	24
Cholestan-3β-yl acetate	1.3

A study has been made [98,99] of the kinetics of the alkaline hydrolysis of cholestan-3β-yl acetates at 30°C in 20% aqueous dioxan containing sodium hydroxide. The results are presented in Table 6, which shows that the rate of hydrolysis of the 3β-acetate increases by a factor of 8 or 9 when a 4β-hydroxy-group is introduced into the molecule. The replacement of the 3β-hydroxy-group by a methoxy-group (the inductive effect of which is approximately the same as that of the hydroxy-group) reduces the rate of hydrolysis of the 4β-acetate by a factor of 19.

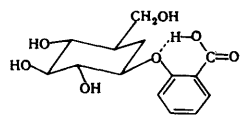
In a study of the rate of alkaline hydrolysis of a number of monoglycyl derivatives of *cis*- and *trans*-tetrahydrofuran-3,4-diols it was found [100] that, whereas the *trans*-hydroxy-group increases the rate of alkaline hydrolysis (at 30°C) by a factor of 2.3, the increase due to the *cis*-hydroxy-group is by a factor of 6.7. However, in contrast to Henbest and Lovell [93,94], the enhanced reactivities of the monoglycinates derived from the *cis*-3,4-diols are attributed [100] to a hydrogen bond with the carbonyl oxygen. It is noteworthy that, although Johnson and coworkers [95] do assert on the basis of infrared spectroscopic measurements that the hydrogen bond in the ground state is formed with the ester oxygen, they believe nevertheless that the kinetically important species may be those where the carbonyl oxygen behaves as the proton acceptor.

The sharp increase of the rate of hydrolysis on formation of a hydrogen bond between a hydroxy-group and a carbonyl or methoxy-carbonyl group was noted in a study of the hydrolysis of indole alkaloids [101,102]. However, because of the complexity of the compounds (yohimbine, corynanthine, methyl reserpate, etc.), the rate of hydrolysis of which is influenced considerably not only by the intramolecular hydrogen bond but also by the concentrations of the conformers and the rates of their interconversions, it is difficult to interpret the quantitative data obtained in this investigation. Examples of the acceleration of alkaline hydrolysis of esters are known also for many other types of compound [103]. Hansen [104] investigated the rate of alkaline hydrolysis of a number of phenols at 25°C in 0.07 M $KClO_4$. The value of $\lg k_2$ (k_2 is a second-order rate constant in litre $mole^{-1}$ s^{-1}) are listed in Table 7.

The much higher rate of hydrolysis of phenyl acetate (by a factor of 700) compared with the *o*-hydroxyphenyl-acetate (XLVI) is due to the presence in the latter of a strong intramolecular hydrogen bond ($\Delta\nu_{C=O}$ in carbon tetrachloride solutions is 30 cm^{-1}). The intramolecular hydrogen bond in *o*-carboxyphenyl-β-D-glucose (XLVII) explains why it is hydrolysed 10^4 times faster than the *p*-carboxyphenyl-derivative [105]:



(XLVI)

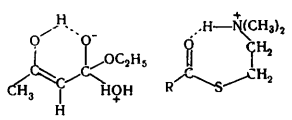


(XLVII)

Table 7.

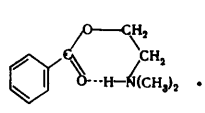
Compound	$\lg k_2$
Phenyl acetate	0.22
o-Methoxyphenyl acetate	0.01
o-Hydroxyphenyl acetate	3.07
o-Phenylene diacetate	0.97

The stabilisation of the transition state (XLVIII) by the intramolecular hydrogen bond is the cause of the rapid hydrolysis of ethyl acetoacetate in water at 90°C:[106]



(XLVIII)

(XLIX)



(L)

Hansen [107] noted an appreciable effect of hydrogen bonds involving a nitrogen atom on the hydrolysis of esters. In the alkaline hydrolysis (pH 7–10) of two thioesters—2-(*NN*-dimethylamino)ethyl thioacetate $CH_3CH_2C(O)SCH_2CH_2NH(CH_3)_2$ (XLIX) and $CH_3CH_2C(O)SCH_2CH_2\overset{+}{N}(CH_3)_3$—it was found that the first ester is hydrolysed 240 times faster than the second. This may be due to a hydrogen bond in (XLIX). The same causes are responsible for the somewhat smaller increase (approximately by a factor of 20) of the rate of hydrolysis of the 2-(*NN*-dimethylamino)ethyl benzoate (L) compared with the 2-(*NNN*-trimethylamino)ethyl ester [108].

The enhanced (by a factor of 20–30) rate of hydrolysis of tertiary 2- and 3-dialkylaminoalkyl acetates compared with the corresponding quaternary compounds is also due to the existence of an intramolecular hydrogen bond in the former, as shown by spectroscopic data [109].

The kinetic data obtained in a comparative study [110] of the alkaline hydrolysis of esters with the general formula $C_6H_5COOCH_2R$ at a constant pH at 25°C in 50% ethanol are presented in Table 8, which shows that the esters capable of forming an intramolecular hydrogen bond with a carbonyl oxygen are hydrolysed many times faster than their analogues without such bonds. Thus compound (2) is hydrolysed 22 times faster than compound (1) and compound (6) is hydrolysed 1000 times faster than compound (5).

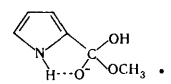
Many other examples of the effect of intramolecular hydrogen bonds on the rate of hydrolysis have been adduced [111,112]. In a spectrophotometric study of the acid hydrolysis of a number of aromatic Schiff bases in aqueous alcohol it was found that the rate constant for the hydrolysis of *o*-hydroxybenzylidene-*p*-toluidine (k_1 = 0.021) is 9.6 times lower than that of *p*-hydroxybenzylidene-*p*-toluidine (k_1 = 0.202). [111] On the other hand, *o*-methoxybenzylidene-*p*-toluidine (k_1 = 0.680) hydrolyses three times faster than *p*-methoxybenzylidene-*p*-toluidine (k_1 = 0.220). Clearly the markedly lower rate of hydrolysis of the *o*-hydroxy-isomer compared with the *p*-isomer is due to an intramolecular hydrogen bond in the former.

Table 8.

Substituent R	Presence of i.h.b.*	k, $mole^{-1}\ min^{-1}$
(1) $-C\equiv C-CH_2-N(C_2H_5)_2$	—	7.46
(2) $-C\equiv C-CH_2-NH-C_2H_5$	+	167
(3) $-C\equiv C-CH_2-\overset{+}{N}(C_2H_5)_2-CH_3$	—	32.1
(4) $-C\equiv C-$	—	12.8
(5) $-CH_2-N(C_2H_5)_2$	—	2.48
(6) $-CH_2-\overset{+}{N}H(C_2H_5)_2$	+	2500
(7) $-CH_2-\overset{+}{N}(C_2H_5)_3$	—	69.8

*A minus sign denotes the absence of a hydrogen bond and a plus sign denotes its presence.

This bond reduces the basicity of the imino-nitrogen and hinders its protonation:



(LI)

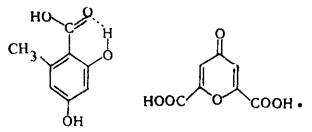
The hydrogen bond has an accelerating effect on the alkaline hydrolysis of methyl pyrrole-2-carboxylate (LI) compared with the isomeric methyl pyrrole-3-carboxylate [64], the rate constants for their hydrolysis in aqueous acetone being 0.41×10^{-3} and 0.059×10^{-3} respectively. The explanation is that the transition state in the hydrolysis of compound (LI) is stabilised by an intramolecular hydrogen bond of the type >N–H...O<.

The ease of hydrolysis of 1-quinolinium derivatives to the corresponding quinolines is attributed [112] to the presence of an intramolecular hydrogen bond in 4-dialkylaminoalkylaminoquinolines [113].

7. DECARBOXYLATION REACTIONS

The decarboxylation reaction requires a weakening of the bond between the carboxyl carbon atom and the atom in the ring (or chain) to which it is linked. This happens to some extent on acid dissociation and the rate of reaction is determined mainly by the rate of decomposition of the anion [114–116]. Since acids with the carbonyl group involved in a hydrogen bond with *o*-hydroxy-groups are much stronger than their isomers, they should be decarboxylated much more readily than the latter. Thus, while benzoic acid is not decarboxylated up to 400°C and

p-hydroxybenzoic acid is decarboxylated at about 300°C, salicylic acid splits off carbon dioxide on heating in water to 220–230°C,[49] 2-hydroxynaphthoic acid, which has a strong intramolecular hydrogen bond[117], is decarboxylated at 120°C,[49] and orsellinic acid (LII) decomposes into orcinol and carbon dioxide even on boiling in methanol[49]:



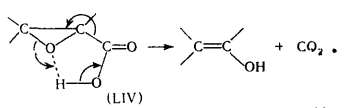
(LII) (LIII)

Similarly, meconic acid, the carboxy-group of which is chelated, splits off carbon dioxide above 120°C, while chelidonic acid (LIII) which does not have a hydrogen bond of this kind is decarboxylated only at 300°C.

Some of these acids, for example, phloroglucinoldicarboxylic and *o*-nitrosalicylic acids, are extremely unstable in a free form and therefore cannot be isolated[49]. On the other hand, isomers of *o*-nitrosalicylic acid are quite stable.

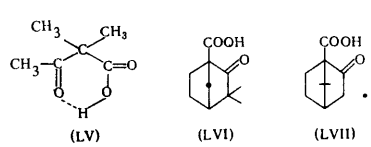
Pyridine-2-acetic[118,119] and quinoline-2-acetic[118] acids are decarboxylated very readily below 100°C. On the other hand, the isomeric 3-acetic acids are decarboxylated with considerable difficulty. This may appear strange if one remembers that the 2-isomers are weaker acids than the 3-isomers by virtue of an intramolecular hydrogen bond with the nitrogen atom[66]. One of the possible explanations of this finding is that the decarboxylation takes place in fact via the hydrogen-bonded cyclic form of the molecule. Thus the optically active methylethylpyridine-2-acetic acid is resistant to decarboxylation in acid and alkaline media and is readily decarboxylated in a neutral medium (maximum chelation) with formation of racemic 2-s-butylpyridine.

It has also been suggested[120] that the thermal decomposition of glycidic acid to carbonyl compounds is accompanied by the intermediate formation of the chelate compound (LIV):



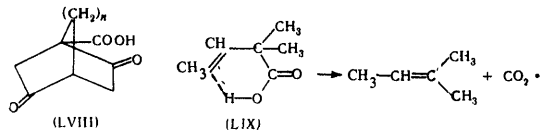
(LIV)

It has been established experimentally[121] that the noncatalysed decarboxylation of β-keto-acids, for example, dimethylacetoacetic acid (LV), is independent of the dielectric constant of the solvent. Therefore the rate-determining stage of the reaction cannot be the decomposition of strongly polar intermediate species. On this basis, and also because the primary product of the cleavage of compound (LV) is the enolic form of isopropyl methyl ketone, Westheimer and Jones[121] suggested that the reaction involves the intermediate formation of the chelate species (LV):



(LV) (LVI) (LVII)

The validity of this hypothesis is indicated by the fact that β-keto-acids incapable of enolisation (because of the considerable steric strain on formation of the enol), for example, camphenic (LVI) and ketopinic (LVII) acids, are not decarboxylated above 300°C, while derivatives of bicyclo[3,3,1]nonane (LVIII) are not decarboxylated even on vacuum sublimation at 150°C.[122] According to Arnold et al., the decarboxylation of βγ-unsaturated acids, for example 2,2-dimethylbutane-3-carboxylic acid (LIX),[123] also proceeds via a cyclic chelate formed in which the double bond behaves as a proton acceptor:



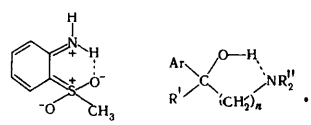
(LVIII) (LIX)

The unusual resistance to decarboxylation of styrylacetic acid and αα-dimethylstyrylacetic acid is explained by the fact that the loss of carbon dioxide with subsequent migration of the double bond leads to the breakdown of the conjugated system[123].

Similar mechanisms have been proposed for the decarboxylation of malonic acid and its half-esters and also the half-esters of 2,5-dimethylcyclopentanedicarboxylic acid[124].

8. INTRAMOLECULAR HYDROGEN BONDS AND BASICITY

Whereas fairly extensive data have accumulated on the effect of intramolecular hydrogen bonds on the acid properties of individual groups, the effect of the hydrogen bond on basicities has been investigated very much less. It may be supposed that the involvement of an atom or group of atoms with basic properties in a hydrogen bond should result in a weakening of the basic properties if the given group plays the role of a donor in the hydrogen bond. Thus *o*-aminophenyl methyl sulphone is a weaker base than the *p*-isomer although the steric effect of the methanesulphonyl group should increase and not decrease the strength of the *o*-base compared with the *p*-isomer. The reason for this is the flattening of the molecule as a result of the contribution of the resonance structure (LX) with an intramolecular hydrogen bond[125]:



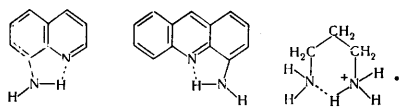
(LX) (LXI)

The less pronounced basic properties of 2-amino-4-trifluoromethylphenyl phenyl sulphone compared with the 4-amino-2-trifluoromethylphenyl isomer can be explained similarly[126].

o-Hydroxybenzylidenepentylamine (pK_a = 12.15 in acetonitrile), which, like all *o*-hydroxybenzylidenealkylamines, has a strong intramolecular hydrogen bond[127], is a weaker base than *p*-hydroxybenzylidenepentylamine (pK_a = 14.80).[128]

In a study of amino-alcohols (LXI)[129,130] it was found that there is a reciprocal relation between the strength of the intramolecular hydrogen bond (displacement of the OH band in the infrared spectrum in carbon tetrachloride solution) and the basicity of amino-alcohols (in nitrobenzene)[130]: the stronger the hydrogen bond the lower is the basicity of the amino-group and, within the limits of each series, the frequency shift is fairly well correlated with the relative basicity of the amino-alcohol.

The intramolecular hydrogen bond has a considerable influence on the basicity of the ring nitrogen atoms in 8-aminoquinoline (LXII) and 1-aminoacridine (LXIII):[131,132]



(LXII) (LXIII) (LXIV)

Among all the aminoquinolines and aminoacridines, compounds (LXII) and (LXIII) are the weakest bases. The reason for this is the presence in them of intramolecular hydrogen bonds, demonstrated by spectroscopic data[133].

The reduced basicity of the amino-group in the monocation of trimethylenediamine (LXIV) compared with other diamines has also been attributed[134] to the presence of an intramolecular hydrogen bond.

9. REDUCTION REACTIONS

a. Reduction of the Carbonyl Group

The presence of a hydroxy-group in the *ortho*-position relative to a carbonyl group considerably alters the activity of the latter. In the polarographic reduction of a series of quinones in aprotic solvents it was noted[135] that electron-donating groups displace the half-wave reduction potential towards more negative values. At the same time hydroxy-groups linked to >C=O groups via an intramolecular hydrogen bond shift the potentials towards more positive values (Table 9).

Table 9.

Quinone	Substituent	Solvent	$E_{1/2}$, V
1,4-Naphthoquinone	H	CH_3CN	−0.71
		DMF*	−0.72
	2-CH_3	CH_3CN	−0.77
	2-NH_2	CH_3CN	−0.92
	2-OH	DMF	−0.64
		CH_3CN	−0.52
	5-OH	DMF	−0.51
9,10-Anthraquinone	H		−0.98
	2-C_6H_5	DMF	−1.12
	1-OH	DMF	−0.77
	1,8-$(OH)_2$	DMF	−0.64

*DMF = dimethylformamide

An analogous effect was noted[136] also in a series of aromatic ketones: the carbonyl group in *o*-hydroxyacetophenone is reduced appreciably more readily than in the *para*-isomer. Thus the intramolecular hydrogen bond greatly increases the electron affinity of the molecule.

b. Reduction of the Nitro-group

The presence of the hydrogen bond in *o*-nitro-compounds not only increases the ease of reduction of the nitro-group but is also the reason why the reduction products are not always amines. Thus *p*-nitrophenol and nitrocresols [(3) and (4) in Table 10], which have no intramolecular hydrogen bonds, are fully reduced to the amines at any pH, while the presence of intramolecular hydrogen bonds in the *ortho*-isomers [(1), (5), (6), and (7) in Table 10] stabilises the intermediate hydroxylamine derivative and inhibits further reduction at a dropping mercury electrode[137,138]. At the same time, dihydroxynitrobenzenes [(10)–(12) and (14) in Table 10], which have weaker hydrogen bonds than *o*-nitrophenol, are reduced to the amines at any pH.[139]

Table 10.

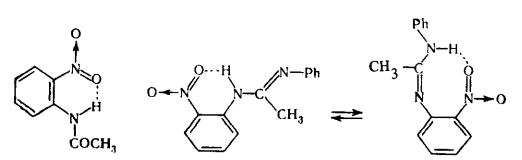
Compound	$E_{1/2}$, V		
	pH 2.2	pH 3.6	pH 6.4
(1) *o*-Nitrophenol	−0.34	−0.52*	−0.73**
(2) *p*-Nitrophenol	−0.54	−0,68*	−0.86**
(3) 6-Nitro-*m*-cresol	−0.35	−0.42	−0.58
(4) 5-Nitro-*o*-cresol	−0.30	−0.35	−0.52
(5) 3-Nitro-*p*-cresol	−0.21	−0.27	−0.42
(6) 3-Nitro-*o*-cresol	−0.20	−0.22	−0.37
(7) 4-Nitro-*m*-cresol	−0.20	−0.24	−0.42
(8) 2-Nitro-*p*-cresol	−0.28	−0.32	−0.50
(9) 4-Nitro-*o*-cresol	−0.23	−0.30	−0.48
(10) 2-Nitroresorcinol	−0.17***	−0.25	−0.36
(11) 4-Nitroresorcinol	−0.26	−0.36	−0.54
(12) 3-Nitrocatechol	−0.16	−0.24	−0.37
(13) 4-Nitrocatechol	−0.34	−0.45	−0.57
(14) 2-Nitrohydroquinone	−0.20	−0.25	−0.38

*Determination at pH 4.0
**Determination at pH 7.0
***Determination at pH 2.1.

The half-wave potentials for the reduction of *o*-nitrophenol and its substituted derivatives and also dihydroxynitrobenzenes with intramolecular hydrogen bonds [(10)–(12) and (14) in Table 10] are much more positive than for the *para*-isomers and *o*-methoxynitrobenzenes in an acid medium, but are approximately the same in alkaline solutions where there is no intramolecular hydrogen bond. This is evidently due to the fact that the hydrogen bond is formed only with one oxygen atom of the nitro-group. This makes the oxygen atoms non-equivalent and facilitates the reduction of the oxygen atom not involved in chelation. The half-wave potentials for the reduction of different nitrophenols, nitrocresols, and dihydroxynitrobenzenes are listed in Table 10.

The kinetics of the reduction of substituted nitrobenzenes with titanium trichloride in aqueous alcohol were investigated by Newton et al.[140], who showed that the *p*-hydroxy-group lowers the rate of reduction of the nitro-group by a factor of 4 compared with nitrobenzene, while the *o*-hydroxy-group increases it by a factor of 16.5. At the same time, *o*- and *p*-methoxynitrobenzenes react at almost identical rates. It is therefore clear that the enhanced reactivity of *o*-nitrophenol is a consequence of the presence of an intramolecular hydrogen bond.

Chelation can also account for the greater ease of reduction of *o*-nitroacetanilides (LXV) compared with nitrobenzene and *m*- and *p*-nitroacetanilides[141]:



(LXV) (LXVI)

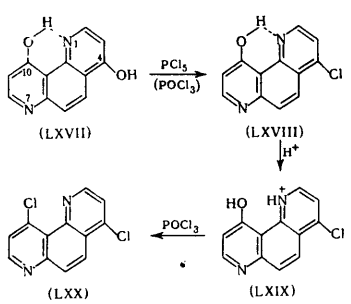
The possibility of chelation of this type is demonstrated by the fact that *o*-nitroacetanilide is more volatile than the

meta- and *para*-isomers, is less associated in naphthalene [142], and has a number of other properties typical for chelated systems [143]. At pH 8 and 12 the differences between the reduction potentials of the *ortho*- and *para*-isomers are +0.15 and +0.13 V respectively, while at pH 7 the half-wave potential for compound (LXV) is more negative by 0.04 V than for *p*-nitroacetanilide (in a highly alkaline medium there is no chelation). Similar results were obtained in a study of the polarographic and catalytic reduction of *o*-nitrophenylacetamidine (LXVI) and its isomers [144]. In the pH range between 2.2 and 7 the differences between the half-wave potentials for the reduction of the *meta*- and *para*-isomers are insignificant, while the value for (LXVI) is much less negative. The greater ease of reduction of (LXVI) compared with its isomers, due to the presence of an intramolecular hydrogen bond, was confirmed also by catalytic hydrogenation in methanol using Raney nickel as a catalyst. The times required for the complete reduction of the nitro-group in the *ortho*-, *meta*-, and *para*-isomers are in the ratios $o:m:p = 1:4:6$.

The greater ease of reduction of 4(7)-nitrobenzimidazole [145] and 4(7)-nitrobenzotriazole [146] compared with their isomeric 5(6)-nitroderivatives without intramolecular hydrogen bonds is explained by the chelation between the hydroxy- and nitro-groups in these compounds.

10. SUBSTITUTION REACTIONS

The intramolecular hydrogen bond has a considerable influence on certain substitution reactions. When 4,10-dihydroxy-1,7-phenanthroline (LXVII) is treated with phosphorus pentachloride or phosphorus oxychloride, the hydroxy-group in the 4-position is the first to be replaced by chlorine to give compound (LXVIII). Such preferential substitution of the hydroxyl can be accounted for by the "masking" of the hydroxy-group in the 10-position by the intramolecular hydrogen bond with the nitrogen atom in the 1-position [147]:



(LXVII) (LXVIII) (LXIX) (LXX)

The conversion of (LXVII) into (LXX) is achieved by prolonged heating of the former with $POCl_3$. The addition of a small amount of H_2O or HCl to the reaction mixture greatly increases the rate of reaction and the yield of the product, since under these conditions the intramolecular hydrogen bond breaks in consequence of the protonation of the ring nitrogen atoms. In a study of the reaction

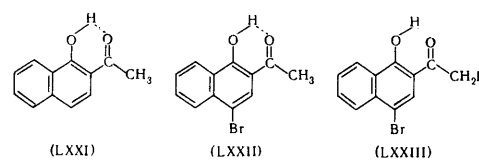
$$R{-}C_6H_4CH{=}N{-}C_6H_4R' + R''{-}C_6H_4{-}CHO \rightarrow R''{-}C_6H_4{-}CH{=}N{-}C_6H_4{-}R' + R{-}C_6H_4{-}CHO$$

it was found that among aromatic aldehydes the most reactive is salicylaldehyde [148], which may be attributed to the presence of an intramolecular bond.

It is well known that *o*-halogenonitrobenzenes react with primary and secondary amines much more rapidly than their *para*-isomers. Thus *o*-chloronitrobenzene reacts with piperidine in xylene at 102°C 80 times faster [149,150] and in benzene 47–51 times faster [150,151] than the *para*-isomer. In polar solvents, for example, alcohols or aqueous dioxan, this ratio is much less, but always greater than unity [150]. The greater reactivity of *o*-halogenonitrobenzenes compared with the *para*-isomers is explained [152] by the fact that in the transition state of these reactions there is a hydrogen bond in the case of the *ortho*-isomers, which facilitates the process. Other explanations for this phenomenon have also been proposed [149].

An important argument in favour of the hypothesis of the decisive role of the intramolecular hydrogen bond is provided by the reaction of 1,4-diazabicyclo[2,2,2]octane with *o*-chloronitrobenzene in which there is no hydrogen bond in the transition state. This compound reacts with *p*-chloronitrobenzene in benzyl alcohol at 500°C hundreds of times faster than with the *ortho*-isomer. At the same time di-n-butylamine reacts with the *ortho*-isomer 16 times faster than with the *para*-isomer. These data support the hypothesis of the formation of a hydrogen bond in the transition state. Similarly the presence of a hydrogen bond between a hydrogen atom of the amino-group and the fluorine atom accounts also for the greater reactivity of *o*-fluoronitrobenzene compared with other *o*-halogenonitrobenzenes [154,155].

The presence of intramolecular hydrogen bonds explains the characteristics of certain electrophilic substitution reactions. Chang and Yang [156] found that 2-acetyl-1-naphthol (LXXI) is readily brominated at room temperature to 2-acetyl-4-bromo-1-naphthol (LXXII) and bromination with an excess of bromine gives 4-bromo-2-bromoacetyl-1-naphthol (LXXIII). However, 2-acetyl-4-bromo-1-naphthol does not react further with bromine if it is first isolated from the reaction mixture:



(LXXI) (LXXII) (LXXIII)

This behaviour of (LXXI) becomes clear if one considers the formation of the dibromo-derivative (LXXIII): (LXXI) + $Br_2 \xrightarrow{1}$ (LXXII) + HBr $\xrightarrow{Br_2}_{2}$ (LXXIII) + HBr. It follows from this mechanism that the formation of the dibromo-derivative (LXXIII) takes place only in the presence of hydrogen bromide formed in the first stage of the reaction. Indeed (LXXII) is brominated successfully when HBr is passed through its solution in acetic acid. This antagonistic effect on bromination is shown by both 4-bromo- and 4-nitro-derivatives of 2-acetyl-1-naphthol and is common to this group of compounds. It appears logical to attribute this behaviour to the interaction between the hydroxy- and oxo-groups.

The principal stages in the acid-catalysed bromination of ketones are as follows:

$$R{-}COCH_3 \xrightarrow[1]{H^+} R{-}\overset{+OH}{\overset{\|}{C}}{-}CH_3 \xrightarrow[2]{A^-} R{-}\overset{OH}{\overset{|}{C}}{=}CH_2 + HA.$$

Chelation should interfere with the formation of the intermediate ion and should lower the rate of bromination. The addition of a proton to the carbonyl oxygen breaks the hydrogen bond and permits further bromination. The behaviour on bromination of the methyl ether and acetate derived from (LXXI), in which there are no intramolecular hydrogen bonds, confirms this. None of these compounds requires the addition of acids for the bromination of the acetyl group.

11. REACTIONS OF *o*-HYDROXY-ALDEHYDES

One of the most thoroughly investigated reactions, the kinetics of which are significantly influenced by the presence of hydrogen bonds, is the reaction of aromatic *o*-hydroxy-aldehydes with reagents for carbonyl compounds. Studies of this kind were carried out for the first time by Vavon [157]. It was found that salicylaldehyde and *o*-vanillin, which have strong intramolecular hydrogen bonds, react with hydroxylamine hydrochloride 13 and 11 times faster respectively than the isomeric *p*-hydroxybenzaldehyde and *p*-vanillin [158]. This behaviour persists also in the interaction of other *o*-hydroxy-aldehydes with the hydrochlorides of hydroxylamine, phenylhydrazine, and semicarbazide,[158], and with melamine [159]. Thus 2-hydroxy-1-naphthaldehyde reacts with hydroxylamine hydrochloride 120 times faster and with phenylhydrazine hydrochloride 53 times faster than 4-hydroxy-1-naphthaldehyde which has no intramolecular hydrogen bond. It is interesting to note than *o*-methoxybenzaldehydes react with carbonyl reagents much faster than the *p*-methoxy-derivatives. For example, *o*-methoxybenzaldehyde reacts with hydroxylamine hydrochloride 150 times faster than anisaldehyde.

Table 11.

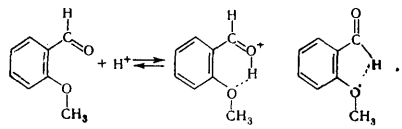
Substituent	$10^3 k_1, s^{-1}$	
	$NH_2OH \cdot HCl$	$C_6H_5NHNH_2 \cdot HCl$
o-OH	42.8	16.3
p-OH	5.9	0.8
m-OH	15.8	2

Knorre and Emanuel' [160] made a more rigorous kinetic study of this reaction. They investigated the kinetics of the interaction of hydroxy- and nitro-benzaldehydes with hydroxylamine and phenylhydrazine hydrochlorides in 95% methanol. The rate constants obtained for the reactions of hydroxybenzaldehydes are listed in Table 11, which shows that salicylaldehyde reacts with hydroxylamine hydrochloride 7.2 times faster and with phenylhydrazine hydrochloride 8.2 times faster than *p*-hydroxybenzaldehyde. On the other hand, the isomeric nitrobenzaldehydes react with these reagents for the carbonyl group at virtually identical rates (*o*-nitrobenzaldehyde even a little more slowly than the others).

The results of polarographic studies of the kinetics of the reactions of a large number of benzaldehydes with aniline in a buffer solution at pH 10.5 in 50% methanol [161] agree with those quoted above. Salicylaldehyde reacts with aniline 58 times faster than *p*-hydroxybenzaldehyde and *o*-chlorobenzaldehyde, in which there is no intramolecular hydrogen bond, reacts somewhat more slowly than *p*-chlorobenzaldehyde. It is surprising that *o*-aminophenol is very much more reactive in the reaction with benzaldehyde (by a factor of approximately 30) than *p*-aminophenol. This behaviour of *o*-aminophenol may be attributed to the greater stabilisation (by the intramolecular hydrogen bond) of benzylidine-*o*-aminophenol produced compared with the product formed by the *para*-isomer.

The data of Wolfenden and Jencks [162] on the formation of semicarbazones from aromatic aldehydes indicate a greater reactivity of *o*-aldehydes in general (*o*-Cl, *o*-OH, *o*-NO_2, *o*-CH_3) compared with the *para*-isomers. Thus the vast majority of data indicate that *o*-hydroxy- and *o*-methoxy-benzaldehydes are more reactive than their *para*-isomers, the ratio of the rate constants for the reactions of the *ortho*-isomers to those for the reactions of the *para*-isomers exceeding the analogous ratios for other substituents.

Knorre and Emanuel' [2] believe that the higher reactivity of the *o*-hydroxy- and *o*-methoxy-groups in an acid medium can be explained in the following way. The substituent in the *ortho*-position in relation to the aldehyde group affects its basicity by the stabilisation of the conjugate acid of the aldehyde as a result of the formation of a hydrogen-bonded bridge, as in compound (LXXIV):



(LXXIV) (LXXV)

Such stabilisation depends in the first place on the capacity of the substituent for the formation of hydrogen bonds. Gordy's data [163] on the shift of the OD stretching vibration frequencies on dissolution of CH_3OD in solvents with different functional groups were used to obtain quantitative characteristics of this capacity. According to these results, $\Delta\nu$ is 200 cm^{-1} for hydroxy-compounds, 70 to 110 cm^{-1} for methoxy-compounds, and 30–50 cm^{-1} for nitro-compounds (for example). Consequently the enhancement of the basic properties of the carbonyl compound will be a maximum for the hydroxy-substituent and a minimum for the nitro-substituent.

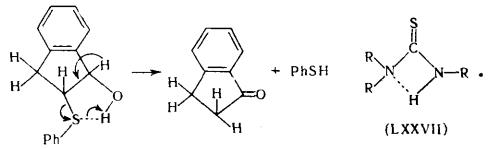
A different explanation of the greater reactivity of *o*-hydroxy- and *o*-methoxy-benzaldehyde was put forward by Vavon and Montheard [157,158,164,165], who suggested that the rate of reaction is determined by the concentration of the conformers of compound (LXXV) with exceptionally high reactivity. The possibility of the existence of hydrogen bonds of this type has been indicated by Pinchas [166,167] on the basis of infrared spectroscopic measurements for a number of benzaldehydes. However, in later studies by Forbes [168] certain characteristics of the infrared spectra of *o*-nitrobenzaldehyde and related compounds were attributed not to intramolecular hydrogen bonds but to steric interactions. In general it is difficult to believe that such weak hydrogen bonds (if they exist at all) have so great an effect on the rate of reaction. Finally, Wolfenden and Jencks [162] suggested an explanation, based on a detailed study of the kinetics on the formation of semicarbazones, for the enhanced reactivity of *o*-substituted benzaldehydes in general and not only the hydroxy- and methoxy-derivatives, namely that the transmission of electronic effects by a resonance mechanism from the *para*-position is more effective than from the *ortho*-position.

Evidently further data are required for a final choice between these hypotheses.

12. INTRAMOLECULAR HYDROGEN BONDS AND CERTAIN SPECIFIC REACTIONS

The intramolecular hydrogen bond influences also certain other types of chemical reactions, for example certain decomposition and condensation reactions. In

particular, *cis*-2-phenylthioindanol (LXXVI) undergoes spontaneous decomposition. Since the *trans*-isomer is comparatively stable, such behaviour of (LXXVI) must be attributed to its intramolecular hydrogen bond, the presence of which has been demonstrated spectroscopically [169]:



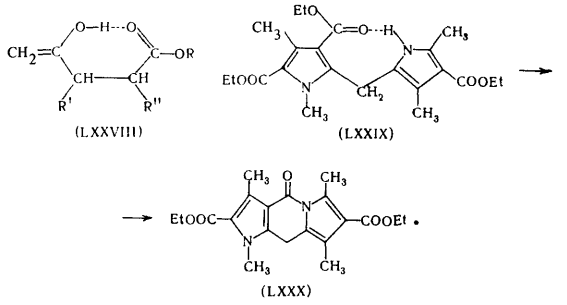
(LXXVI) (LXXVII)

The fact that the product of the addition of sodium bisulphite to salicylaldehyde decomposes much more rapidly than the products of bisulphite additions to other *o*-aldehydes can be explained by "proton transfer" from the hydroxy-group to the sulphite group being eliminated, probably via a hydrogen-bond bridge [170].

In a study of the kinetics of the decomposition of thiourea and its methyl derivatives in aqueous solution, Shaw and Walker [171,172] concluded that the reaction proceeds via a chelate cyclic species (LXXVII). This mechanism is confirmed by the finding that tetramethyl-thiourea, which is incapable of forming intramolecular hydrogen bonds, is not decomposed in aqueous solutions [173].

The effect of various types of intramolecular hydrogen bonds on the rate of cleavage of the –N=N–bond in azo-dyes under the influence of yeast has been noted [174].

Since it has been established experimentally that the reactivity of the butyl ester of levulinic acid in the Claisen condensation is higher than that of the methyl ester [175], while in the hydrolysis of the esters the ratio of the reaction rates has the usual value (the rate for the butyl ester is higher), the ionic mechanism of the Claisen condensation has been rejected [176]. The authors suggest that the active form of levulinic acid in this condensation is the seven-membered chelate ring (LXXVIII):

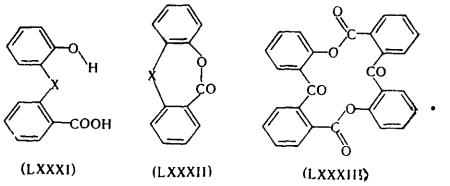


(LXXVIII) (LXXIX) (LXXX)

In consequence of the increasing $+I$ effect in the series $CH_3 < C_2H_5 < C_3H_7 < C_4H_9$, the negative charge at the carbonyl oxygen also increases, which tends to increase the stability of the intramolecular hydrogen bond and accelerates the reaction.

The ready cyclisation of dipyrrolylmethanes (LXXIX) to cyclic amides with the dipyrrolopyridine structure (LXXX) [177] is probably due to the mutual approach of the reaction centres in compound (LXXIX) caused by the intramolecular hydrogen bond, the presence of which has been demonstrated by infrared spectroscopy [178].

It is suggested that the intramolecular hydrogen bond is responsible also for the formation of various reaction products in the intramolecular cyclisation of compounds of type (LXXXI). [179,180] The dehydration of 2-carboxy-2′-hydroxybenzophenone (LXXXI, X = CO), 2-carboxy-2′-hydroxy-5′-methylbenzophenone, and 2-carboxyphenyl 2′-hydroxyphenyl ether (LXXXI, X = O) by acetic anhydride gives almost quantitative yields of the seven-membered lactones (LXXXII), while other dehydrating agents [P_4O_{10}, $POCl_3$, $(CF_3CO)_2O$] lead to the formation mainly of 14-membered lactides (LXXXIII):



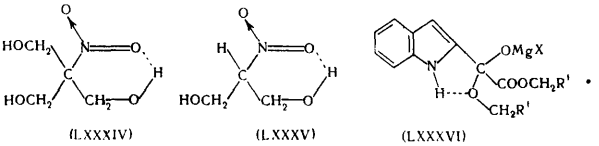
(LXXXI) (LXXXII) (LXXXIII)

This is explained by an intramolecular hydrogen bond in compound (LXXXI), which forces these molecules into a configuration which is unfavourable for lactone formation, favouring instead the formation of lactides. In fact 2-carboxy-2′-hydroxydiphenylmethane, in which an intramolecular hydrogen bond of this kind cannot exist, yields only a lactone under all conditions [180].

13. INHIBITION OF CHEMICAL REACTIONS BY INTRAMOLECULAR HYDROGEN BONDS

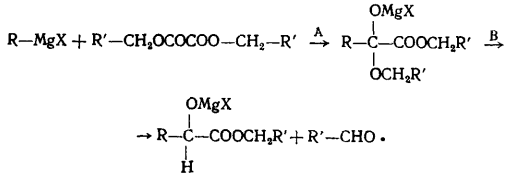
Numerous data showing that intramolecular hydrogen bonds can retard and sometimes prevent a number of chemical reactions have been published. The inhibition of alkylation and acetylation reactions by intramolecular hydrogen bonds has already been mentioned (Sections 2 and 4). In some cases the inhibition of chemical reactions by intramolecular hydrogen bonds can be explained by the fact that the latter stabilise conformations in which the reaction centres are separated and therefore the reaction cannot occur.

Thus the ability of nitro-groups to form strong hydrogen bonds is responsible for the ready formation of cyclic acetals and ketals from tri(hydroxymethyl)nitromethane (LXXXIV), which has free hydroxy-groups, while di(hydroxymethyl)nitromethane (LXXXV), where one of the hydroxy-groups is chelated, form these derivatives with great difficulty or not at all [181]:

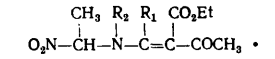


(LXXXIV) (LXXXV) (LXXXVI)

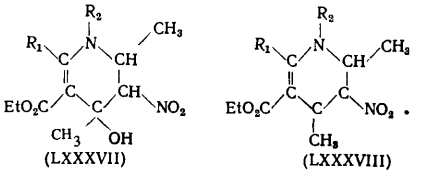
Metal alkoxide halides formed in the reactions of oxalic esters with organomagnesium compounds [reaction (A)] and containing the α-indolyl group differ sharply in their thermal stability from compounds with any other substituents. The latter break down by reaction (B) in the range 40–110°C, while (LXXXVI) remains completely unchanged at these temperatures [182]. This is explained by the stabilising effect of the intramolecular hydrogen bond on the complex formed, as shown for compound (LXXXVI). The presence of a hydrogen bond of this type in the compound is confirmed by infrared spectra:



A very interesting case of the inhibition of chemical reactions by hydrogen bonds is the cyclisation of compounds of the type [183]

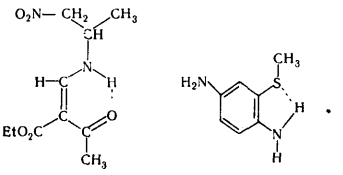


The compound with $R_1 = R_2 = H$ does not cyclise although the steric conditions should favour the formation of the cyclicaldol (LXXXVII) or its dehydration product (LXXXVIII):



(LXXXVII) (LXXXVIII)

Evidently the aldol condensation may be hindered if the initial molecule contains an intramolecular hydrogen bond, as in compound (LXXXIX):



(LXXXIX) (XC)

Indeed, when $R_1 = R_2 = H$ or $R_1 = CH_3$ and $R_2 = H$, the compounds are not cyclised under a wide variety of conditions, which suggests that their hydrogen-bond bridge is exceptionally stable, and as a result the molecule exists in the conformation unfavourable for cyclisation, since the reaction centres (the carbonyl and methylene groups) are distant from one another. This is confirmed by the behaviour of the compound with $R_1 = H$ and $R_2 = CH_3$ in which the formation of intramolecular hydrogen bonds is impossible and which therefore is instantly cyclised to 5-ethoxycarbonyl-4-hydroxy-1,2,4-trimethyl-3-nitro-1,2,3,4-tetrahydropyridine (LXXXVII).

Hydrogen bonds have a marked influence on the course and final products of condensation and substitution reactions. Thus 4-amino-3-methylthioazobenzene can be readily synthesised by the condensation of nitrosobenzene with 2-methylthio-1,4-phenylenediamine (XC). As a result of the presence of an intramolecular hydrogen bond in the initial compound, the condensation involves preferentially the free amino-group, so that the ratio of the condensation product involving the free and hydrogen-bonded amino-groups is 21 : 1. [184]

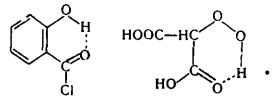
In a study of the condensation of aromatic aldehydes with benzyl carbamate [185], it was found that the reaction gives satisfactory yields with nitro- and methoxy-benzaldehydes but does not take place at all with salicylaldehyde and vanillin, owing to the presence of intramolecular hydrogen bonds in the molecule of the latter compounds. In contrast to these aldehydes, 3-nitrosalicylaldehyde, in which an analogous situation would appear to exist, gave *NN*-dibenzyloxycarbonyl-2-hydroxy-3-nitrobenzylidenediamine in high yield. However, one should not forget that in this compound the hydrogen bond is formed mainly between the hydroxy- and nitro-groups and therefore the reactive aldehyde group remains free.

The inhibiting effect of the *o*-hydroxy-group in the aldehyde component is observed also in the condensation of various aromatic aldehydes with phenylacetic acid [186].

As already mentioned, the involvement of the hydroxyl in a hydrogen bond greatly reduces its tendency to enter into other reactions. The authors believe that the presence of a strong intramolecular hydrogen bond is the reason why *o*-nitrophenol does not form compounds with 8-hydroxyquinoline [187], acetamide [188], urea [189], acetone, and dimethyl sulphoxide [190].

14. THE ROLE OF INTRAMOLECULAR HYDROGEN BONDS IN THE STABILISATION OF ORGANIC MOLECULES

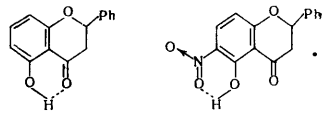
Intramolecular hydrogen bonds are known to be a factor stabilising molecules. In some cases the presence of intramolecular hydrogen bonds in molecules is the principal cause of their stability. Thus, owing to the presence in its molecule of a strong intramolecular hydrogen bond, salicyloyl chloride (XCI) can be isolated in a pure form [194,195], in contrast to its *meta*- and *para*-isomers which readily undergo polyesterification reactions. The existence of this type of hydrogen bond has been demonstrated spectroscopically [196]:



(XCI) (XCII)

The impossibility of determining (with the aid of the usual reagents) of the hydroperoxy-group in hydroperoxymalonic acid obtained in the ozonolysis of acetylenedicarboxylic acid in concentrated formic acid is probably associated with the presence of a strong intramolecular hydrogen bond in compound (XCII). [197]

Hydrogen bonds have a marked influence also on the stability of certain *o*-hydroxychalcones and their cyclisation products—flavanones. While flavanone rings are usually readily opened by alkalies, 5-hydroxyflavanone (XCIII), in which there is a strong intramolecular hydrogen bond, is fairly stable [198]:

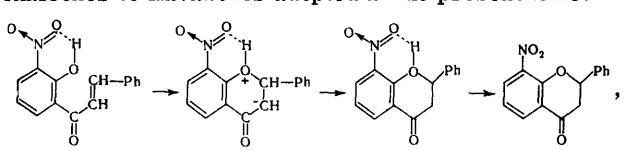


(XCIII) (XCIV)

At the same time 5-hydroxy-6-nitroflavanone (XCIV), where the hydroxy-group is hydrogen-bonded mainly on the nitro-group, readily undergoes ring opening under the action of alkalies [199].

The high stability of nitrochalcones of type (XCV) (low rate of cyclisation to flavanones) has been attributed to an intramolecular hydrogen bond between the hydroxy- and nitro-groups [199].

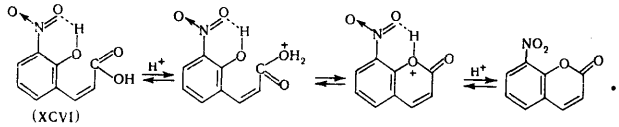
From the standpoint of the mechanism of the cyclisation of chalcones to flavanones adopted at the present time:



(XCV)

such behaviour of compound (XCV) is explained in the following way. The hydrogen bond between the nitro- and hydroxy-groups prevents the elimination of the proton in the last stage and stabilises the nitrosulphones in relation to the corresponding flavanones.

A similar stabilising effect of the nitro-group is observed with 3-nitro-*o*-coumaric acids[200]. This effect can be understood by considering the mechanism of the cyclisation of coumaric acids to coumarones:



(XCVI)

The formation of an intramolecular hydrogen bond, as in the case of hydroxynitrochalcones, prevents the loss of a proton in the last cyclisation stage. Therefore 3-nitro-*o*-coumaric acids are very stable in aqueous solutions. This explanation of the stability of compound (XCVI) is confirmed by the behaviour of 4-methyl-3-nitro-*o*-coumaric acid. The introduction of a methyl group breaks down the coplanarity of the ring and the nitro-group, as a result of which the hydrogen bond between the latter and the hydroxy-group is greatly weakened and the acid is relatively unstable in aqueous solution.

REFERENCES

1. A. E. Lutskii, Uspekhi Khim., **23**, 479 (1954).
2. D. G. Knorre and N. M. Emanuel', Uspekhi Khim., **24**, 275 (1955).
3. I. M. Hunsberger, R. Ketchan, and H. S. Gutowsky, J. Amer. Chem. Soc., **74**, 4839 (1952).
4. Y. L. Ferrari, I. M. Hunsberger, and H. S. Gutowsky, J. Amer. Chem. Soc., **87**, 1247 (1965).
5. R. Arnold and J. Sprung, J. Amer. Chem. Soc., **61**, 2475 (1939).
6. L. B. Magnusson, C. Postmus, and C. A. Craig, J. Amer. Chem. Soc., **85**, 1711 (1963).
7. C. Postmus, I. A. Kaye, C. A. Craig, and R. S. Matthews, J. Org. Chem., **29**, 2693 (1964).
8. Z. L. Ernst and F. G. Hering, Trans. Faraday Soc., **64**, 498 (1964).
9. M. de Ramaix, Ind. Chim. Belge, **18**, 587 (1963); Chem. Abs., **49**, 2390h (1955).
10. L. B. Magnusson, C. A. Craig, and C. Postmus, J. Amer. Chem. Soc., **86**, 3958 (1964).
11. D. O. D. Pascual and E. J. Gatchalian, Phillipine J. Sci., Chem. Abs., **58**, 5584g (1963).
12. D. Jannakoudakis, Chim. Chronika, **28**, 63 (1963); Chem. Abs., **60**, 1242b (1964).
13. M. Davis, J. Amer. Chem. Soc., **84**, 3623 (1962).
14. V. I. Minkin, E. A. Medyantseva, and Yu. A. Zhdanov, Dokl. Akad. Nauk SSSR, **159**, 1330 (1964).
15. H. H. Freedman, J. Amer. Chem. Soc., **83**, 2900 (1961).
16. V. I. Minkin, O. A. Osipov, and V. A. Kogan, Dokl. Akad. Nauk SSSR, **145**, 6 (1962).
17. O. A. Osipov, V. I. Minkin, and V. A. Kogan, Zhur. Fiz. Khim., **37**, 1492 (1963) [Russ. J. Phys. Chem., No. 7 (1963)].
18. A. W. Baker and A. T. Shulgin, J. Amer. Chem. Soc., **81**, 1523 (1959).
19. V. I. Minkin, Yu. A. Zhdanov, A. D. Garnovskii, and I. D. Sadekov, Dokl. Akad. Nauk SSSR, **162**, 108 (1965).
20. V. I. Minkin, Yu. A. Zhdanov, A. D. Garnovskii, and I. D. Sadekov, Zhur. Fiz. Khim., **35**, 657 (1966)[Russ. J. Phys. Chem., No. 3 (1966)].
21. L. G. Bray, J. F. J. Dippy, S. R. Hughes, and L. W. Laxton, J. Chem. Soc., 2405 (1957).
22. M. I. Gornyaev, V. S. Volkov, and G. A. Tolstikov, Zhur. Obshch. Khim., **28**, 2102 (1958).
23. O. A. Stamm, A. Zen Kalensern, and H. Zollinger, Chimia, **19**, 224 (1963); Chem. Abs., **64**, 841g (1965).
24. G. R. Sprengling and C. W. Lewis, J. Amer. Chem. Soc., **75**, 5709 (1953).
25. M. Davies, Trans. Faraday Soc., **36**, 1114 (1940).
26. A. E. Martin, Nature, **166**, 474 (1950).
27. G. R. Sprengling, J. Amer. Chem. Soc., **76**, 1190 (1954).
28. N. D. Coggeshall, J. Amer. Chem. Soc., **72**, 2836 (1950).
30. A. Albert and E. P. Serjeant, "Ionisation Constants of Acids and Bases: A Laboratory Manual" (Translated into Russian), Izd. Khimiya, Moscow–Leningrad, 1964.
31. W. F. Baitinger, Jnr. and P. von R. Schleyer, J. Amer. Chem. Soc., **87**, 3168 (1965).
32. J. G. Lombardino, J. Org. Chem., **32**, 1988 (1967).
33. V. V. Perekalin and Z. S. Segalina, Zhur. Obshch. Khim., **24**, 683 (1954).
34. J. D. Chanley and E. M. Gindler, J. Amer. Chem. Soc., **75**, 4035 (1953).
35. J. Blair and G. T. Newbold, J. Chem. Soc., 2871 (1955).
36. T. A. Geissman and E. Hinreiner, J. Amer. Chem. Soc., **73**, 782 (1951).
37. F. A. Hochstein and R. Pasternak, J. Amer. Chem. Soc., **73**, 5008 (1951).
38. V. C. Farmer, N. F. Hayes, and R. H. Thomson, J. Chem. Soc., 3600 (1956).
39. A. Schonberg and A. Mustafa, J. Chem. Soc., 746 (1946).
40. R. C. Elderfield (Editor), "Heterocyclic Compounds", Vol. 2, "Polycyclic Five- and Six-Membered Compounds Conatining One O or S Atom" (Translated into Russian), Inostr. Lit., Moscow, 1954.
41. A. Mustafa and O. H. Hishmat, J. Org. Chem., **22**, 1644 (1957).
42. C. A. Buehler, J. A. Addleberg, and D. M. Glenn, J. Org. Chem., **20**, 1350 (1955).
43. F. Cramer and W. Krum, Chem. Ber., **86**, 1586 (1953).
44. A. Shonberg and R. Moubascher, J. Chem. Soc., 366 (1944).
45. R. E. Moore, H. Singh, C. W. Chang, and P. J. Scheuer, Tetrahedron, **23**, 3271 (1967).
46. T. A. Geissman and R. O. Clinton, J. Amer. Chem. Soc., **68**, 6971 (1941).
47. N. Narasimkachari, D. Rajagopalan, and T. R. Seshadri, Proc. Indian Acad. Sci., **36A**, 1231 (1952); Chem. Abs., **48**, 2698a (1954).
48. M. K. Seikel and T. A. Geissmann, Proc. Indian Acad. Sci., **72**, 5720 (1949).
49. H. Meyer, "Analysis and Determination of Organic Compounds" (Translated into Russian), ONTI, Leningrad, 1937.
50. N. Kaneniwa, J. Pharm. Soc. Japan, **76**, 253 (1956); Chem. Abs., 50, 13793h (1956).
51. K. Hoesch, Chem. Ber., **46**, 886 (1913).
52. W. Baker and R. J. Savage, J. Chem. Soc., 1602 (1938).
53. D. B. Bruce, A. J. Sorrie, and R. H. Thomson, J. Chem. Soc., 2403 (1953).
54. G. N. Walker, J. Amer. Chem. Soc., **77**, 6699 (1955).
55. R. H. Thomson, J. Chem. Soc., 1822 (1952).
56. G. E. Branch and D. L. Jabroff, J. Amer. Chem. Soc., **56**, 2568 (1934).
57. J. Hermans, Jnr., S. J. Leach, and H. A. Scheraga, J. Amer. Chem. Soc., **85**, 1390 (1963).
58. G. E. Dunn and Fei-Lin Kung, Canad. J. Chem., **44**, 1261 (1966).

59. "Steric Effects in Organic Chemistry" (Translated into Russian), Inostr. Lit., Moscow, 1960.
60. "Spravochnik Khimika", (The Chemist's Handbook), Izd. Khimiya, Moscow–Leningrad, 1964, Vol. 3.
61. E. M. Voroshin and V. G. Vlasov, Zhur. Obshch. Khim., 30, 3004 (1960).
62. D. Chapman, D. R. Lloyd, and R. H. Prince, J. Chem. Soc., 550 (1964).
63. G. E. Dunn and T. L. Penner, Canad. J. Chem., 45, 1699 (1967).
64. M. K. Khan and K. J. Morgan, Tetrahedron, 21, 2197 (1965).
65. M. Scrocco and R. Nicolaus, Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat., 22, 311 (1957); Chem. Abs., 52, 50i (1958).
66. J. H. Blanch, J. Chem. Soc., B, 937 (1966).
67. H. H. Jaffe, L. D. Freedman, and G. O. Doak, J. Amer. Chem. Soc., 76, 1548 (1954).
68. A. W. Baker and A. T. Shulgin, J. Amer. Chem. Soc., 80, 5358 (1958).
69. W. Beckering, J. Phys. Chem., 65, 206 (1961).
70. T. M. Goldman and R. O. Crisler, J. Org. Chem., 23, 751 (1958).
71. D. S. Trifan, J. L. Weinmann, and L. P. Kuhn, J. Amer. Chem. Soc., 79, 6566 (1957).
72. M. Oki and H. Iwamura, Bull. Chem. Soc. Japan, 35, 1152 (1962).
73. M. Oki and H. Iwamura, Bull. Chem. Soc. Japan, 32, 955 (1959).
74. H. H. Jaffe, L. D. Freedmann, and G. O. Doak, J. Amer. Chem. Soc., 75, 2209 (1953).
75. D. Pressman and D. H. Brown, J. Amer. Chem. Soc., 65, 540 (1943).
76. C. A. Colman-Porter and C. B. Monk, J. Chem. Soc., 4363 (1952).
77. J. F. Norris and W. H. Strain, J. Amer. Chem. Soc., 57, 187 (1935).
78. W. F. Little and R. Eisenthal, J. Amer. Chem. Soc., 83, 4936 (1961).
79. C. K. Hancock, R. F. Gilby, and J. S. Wesmoreland, J. Amer. Chem. Soc., 79, 1917 (1957).
80. J. Pascual, J. Sistare, and A. Regas, J. Chem. Soc., 1943 (1949).
81. L. Capuani, Rev. Fac. Sci. Istanbul, 22C, 128 (1957); Chem. Abs., 51, 16437e (1957).
82. A. R. Bader, L. O. Cummings, and H. A. Vogel, J. Amer. Chem. Soc., 73, 4195 (1951).
83. A. R. Bader, J. Amer. Chem. Soc., 74, 3992 (1952).
84. R. E. Ryle, J. Org. Chem., 22, 1280 (1957).
85. J. Sawlewicz and Z. Sznigir, Acta Polon. Pharm., 18, 81 (1961); Chem. Abs., 56, 3471g (1962).
86. V. I. Minkin, Yu. A. Zhdanov, I. D. Sadekov, Yu. A. Ostroumov, N. E. Shelepin, and O. A. Raevskii, Dokl. Akad. Nauk SSSR, 169, 1095 (1966).
87. M. C. Clark, J. Chem. Soc., C., 2081 (1966).
88. S. G. Kuznetsov and E. V. Roginskaya, Zhur. Obshch. Khim., 31, 3360 (1961).
89. S. G. Kuznetsov, Zhur. Obshch. Khim., 31, 3353 (1961).
90. K. W. Buck, A. B. Foster, A. R. Perry, and J. M. Webber, J. Chem. Soc., 417 (1963).
91. R. U. Lemieux and A. G. McInnes, Canad. J. Chem., 38, 136 (1960).
92. D. H. R. Barton, Experientia, 6, 316 (1950).
93. H. B. Henbest and B. J. Lovell, Chem. Ind., 278 (1956).
94. H. B. Henbest and B. J. Lovell, J. Chem. Soc., 1965 (1957).
95. R. West, J. J. Korst, and W. S. Johnson, J. Org. Chem., 25, 1976 (1960).
96. S. M. Kupchan and C. R. Narayanan, J. Amer. Chem. Soc., 81, 1913 (1959).
97. S. M. Kupchan and W. S. Johnson, J. Amer. Chem. Soc., 78, 3864 (1956).
98. S. M. Kupchan, P. Slade, and R. J. Young, Tetrahedron Letters, 221 (1960).
99. S. M. Kupchan, P. Slade, R. J. Young, and G. W. A. Milne, Tetrahedron, 18, 499 (1962).
100. H. G. Zachau and W. Karau, Chem. Ber., 93, 1830 (1960).
101. M. J. Allen, J. Chem. Soc., 4904 (1960).
102. M. J. Allen, J. Chem. Soc., 4252 (1961).
103. T. C. Bruice and T. H. Fife, J. Amer. Chem. Soc., 84, 1973 (1962).
104. B. Hansen, Acta Chem. Scand., 17, 1375 (1963).
105. B. Capon, Tetrahedron Letters, 911 (1963).
106. E. A. Goodhue and H. L. Dunlop, J. Amer. Chem. Soc., 50, 1920 (1928).
107. B. Hansen, Acta Chem. Scand., 12, 324 (1958).
108. A. Agren, U. Hedsten, and B. Johnson, Acta Chem. Scand., 15, 1532 (1961).
109. B. Hansen, Acta Chem. Scand., 16, 1927 (1962).
110. A. Agren, Acta Pharm. Suecica, 2, 387 (1965); Chem. Abs., 64, 4887e (1965).
111. O. Bloch-Chaude, Compt. rend., 239, 804 (1954).
112. A. R. Surrey, G. Y. Lesher, and J. R. Mayer, J. Amer. Chem. Soc., 81, 2887 (1959).
113. F. C. Nachod, A. R. Surrey, G. Y. Lesher, C. W. Martin, J. R. Mayer, M. Priznar, and W. G. Webb, J. Amer. Chem. Soc., 81, 2897 (1959).
114. F. H. Vernoek, J. Amer. Chem. Soc., 56, 571 (1934).
115. G. A. Hall Jnr. and F. H. Vernoek, J. Amer. Chem. Soc., 69, 613 (1947).
116. G. A. Hall Jnr., J. Amer. Chem. Soc., 71, 2691 (1949).
117. B. A. Zadorozhnyi and I. K. Ishchenko, Optika i Spektrosk., 19, 551 (1965).
118. W. E. Doering and V. Z. Pasternak, J. Amer. Chem. Soc., 72, 143 (1950).
119. H. E. Smith and R. H. Eastman, J. Amer. Chem. Soc., 79, 5500 (1957).
120. R. T. Arnold, "Abstracts of the 10th National Organic Symposium of the American Chemical Society, June, 1947, Boston, Mass.
121. F. H. Westheimer and W. A. Jones, J. Amer. Chem. Soc., 63, 3283 (1941).
122. F. S. Fawcett, Chem. Rev., 47, 219 (1950).
123. R. T. Arnold, O. C. Elmer, and R. M. Dodson, J. Amer. Chem. Soc., 72, 4359 (1950).
124. T. L. Jacobs and W. H. Florsheim, J. Amer. Chem. Soc., 72, 256 (1950).
125. E. A. Fehnel and M. Carmack, J. Amer. Chem. Soc., 72, 1292 (1950).
126. G. W. Stacy and C. R. Bresson, J. Org. Chem., 24, 1893 (1959).
127. L. A. Kazitsina and V. Mishchenko, Vestnik Moskov. Gos. Univ., Ser. Khim., No. 3, 22 (1964).
128. V. I. Minkin, V. A. Bren', and E. A. Malysheva, "Reaktsionnaya Sposobnost' Organicheskikh Soedinenii", 5, 565 (1969).
129. M. T. Zaitseva, S. V. Bogatkov, and E. M. Cherkasova, Zhur. Obshch. Khim., 35, 2066 (1965).
130. S. V. Bogatkov, E. Ya. Skobeleva, and E. M. Cherkasova, Zhur. Obshch. Khim., 36, 134 (1966).
131. A. Albert and R. Goldacre, J. Chem. Soc., 453 (1943).

132. A. Albert, R. Goldacre, and J. Phillips, J. Chem. Soc., 2240 (1948).
133. L. N. Short, J. Chem. Soc., 4584 (1952).
134. A. Gero, J. Amer. Chem. Soc., **76**, 5159 (1954).
135. M. E. Peover, J. Chem. Soc., 4540 (1962).
136. N. A. Valyashko and Yu. S. Rozum, Zhur. Obshch. Khim., **18**, 710 (1948).
137. M. J. Astle and W. V. McConnel, J. Amer. Chem. Soc., **65**, 351 (1943).
138. M. J. Astle and W. P. Cropper, J. Amer. Chem. Soc., **65**, 2395 (1943).
139. M. J. Astle and S. P. Stephenson, J. Amer. Chem. Soc., **65**, 3299 (1943).
140. S. A. Newton, E. J. Stubbs, and C. C. Hinshelwood, J. Chem. Soc., 3384 (1953).
141. M. E. Runner and E. C. Wagner, J. Amer. Chem. Soc., **74**, 2529 (1952).
142. H. O. Chaplin and L. Hunter, J. Chem. Soc., 375 (1938).
143. W. Baker, J. Chem. Soc., 1687 (1934).
144. M. E. Runner, M. L. Kilpatrick, and E. C. Wagner, J. Amer. Chem. Soc., **69**, 1406 (1947).
145. J. L. Rabinowitz and E. C. Wagner, J. Amer. Chem. Soc., **73**, 3030 (1951).
146. N. L. Miller and E. C. Wagner, J. Amer. Chem. Soc., **76**, 1847 (1954).
147. A. R. Surrey and R. A. Culter, J. Amer. Chem. Soc., **76**, 1109 (1954).
148. P. Nagy, Szegedi Pedagog, Foiskola Evkonyne, Masodik Pesz., 205 (1960); Chem. Abs., **55**, 24611i (1961).
149. M. F. Hawthorne, J. Amer. Chem. Soc., **76**, 6358 (1954).
150. J. F. Bunnet and R. J. Morath, J. Amer. Chem. Soc., **77**, 5051 (1955).
151. W. Greizerstein and J. A. Brieux, J. Amer. Chem. Soc., **84**, 1032 (1962).
152. R. R. Bishop, E. A. S. Cavele, and N. B. Chapman, J. Chem. Soc., 437 (1952).
153. "Modern Problems in Physical Organic Chemistry", (Translated into Russian), Izd. Mir, Moscow, 1967.
154. T. O. Bamkole, C. W. L. Bevan, and J. Hiest, Chem. Ind., 119 (1963).
155. R. E. Parker and T. O. Read, J. Chem. Soc., 9 (1962).
156. F. C. Chang and Yen-shang Yang, J. Amer. Chem. Soc., **76**, 464 (1954).
157. G. Vavon and P. Anziani, Bull. Soc. chim. France, **4**, 2026 (1937).
158. G. Vavon and P. Montheard, Bull. Soc. chim. France, **7**, 551 (1940).
159. G. Vavon and P. Montheard, Bull. Soc. chim. France, **7**, 560 (1940).
160. D. G. Knorre and N. M. Emanuel', Dokl. Akad. Nauk SSSR, **153**, 1163 (1953).
161. V. N. Dmitrieva, A. V. Kononenko, and V. D. Bezuglyi, Symposium, "Azometiny" (Azomethines), Izd. Rostov. Gos. Univ., 1967.
162. R. Wolfenden and W. P. Jencks, J. Amer. Chem. Soc., **83**, 2763 (1961).
163. W. Gordy and S. C. Stanford, J. Chem. Phys., **9**, 204 (1941).
164. G. Vavon and I. Scandel, Compt. rend., **223**, 1144 (1946).
165. S. Ambrose and O. L. Brady, J. Chem. Soc., 1243 (1950).
166. S. Pinchas, Analyt. Chem., **27**, 21 (1955).
167. S. Pinchas, Chem. Ind., 1451 (1959).
168. W. F. Forbes, Canad. J. Chem., **40**, 189 (1962).
169. H. H. Szmant and J. J. Rigau, J. Org. Chem., **31**, 2288 (1966).
170. D. A. Blackadder and C. C. Hinshelwood, J. Chem. Soc., 2720 (1958).
171. W. H. R. Shaw and D. G. Walker, J. Amer. Chem. Soc., **78**, 5769 (1956).
172. W. H. R. Shaw and D. G. Walker, J. Amer. Chem. Soc., **79**, 3683 (1957).
173. W. H. R. Shaw and D. G. Walker, J. Amer. Chem. Soc., **79**, 4329 (1957).
174. M. Reinhard and S. Dietrich, Naturwiss, **42**, 153 (1955).
175. I. V. Zotchin, L. D. Miroshnichenko, R. P. Evstigneeva, and N. A. Preobrazhenskaya, Zhur. Obshch. Khim., **32**, 2823 (1962).
176. R. P. Evstigneeva, I. V. Zotchin, R. B. Teplinskaya, G. N. Kol'tsova, and S. D. L'vova, Zhur. Org. Khim., **3**, 1770 (1967).
177. A. H. Corwin and R. C. Ellington, J. Amer. Chem. Soc., **66**, 1146 (1944).
178. L. P. Kuhn and G. G. Kleinspehn, J. Org. Chem., **28**, 721 (1963).
179. W. D. Ollis and D. E. Clark, Chem. Ind., 337 (1952).
180. W. Baker, D. Clark, W. D. Ollis, and T. S. Zealley, J. Chem. Soc., 1452 (1952).
181. T. Urbanski, in "Hydrogen Bonding" (Edited by D. Hadzi), Pergamon Press, London, 1959.
182. I. I. Lapshin and Yu. P. Dormidontov, Khim. Geterotsikl. Soed., **5**, 857 (1967).
183. C. A. Grob and K. Gameniski, Helv. Chim. Acta, **36**, 3748 (1953).
184. J. D. Scribner and J. A. Miller, J. Org. Chem., **32**, 2348 (1967).
185. R. J. Lewis, F. R. Butler, and A. E. Martell, J. Org. Chem., **10**, 145 (1945).
186. R. N. Singh, V. Chand, and N. Chojer, Agra Univ. J. Res. (Sci), **1**, 153 (1952); Chem. Abs., **48**, 2654b (1954).
187. D. E. Dionis'ev and Z. K. Dzholemanova, Uch. Zap. Rostov. Gos. Univ., **25**, 125 (1955).
188. Z. K. Dzholemanova, N. Z. Rudenko, and D. E. Dionis'ev, Zhur. Obshch. Khim., **26**, 1866 (1956).
189. N. Z. Rudenko and D. E. Dionis'ev, Zhur. Obshch. Khim., **24**, 1327 (1954).
190. V. F. Chesnokov, I. M. Bolovkin, A. P. Orlova, and E. G. Veselkova, Zhur. Obshch. Khim., **38**, 12 (1968).
191. K. Kunz, Angew. Chem., **52**, 436 (1939).
192. T. Tanaka, J. Chem. Soc. Japan, **79**, 942 (1958); Chem. Abs., **54**, 4456b (1960).
193. V. I. Kharitonova, Izv. Akad. Nauk Kirgiz. SSR, **2**, 39 (1960).
194. E. H. Merris, US P. 289458 (1959); quoted after Bull. Chem. Soc. Japan, **40**, 1428 (1967).
195. T. Amakasu, Bull. Chem. Soc. Japan, **40**, 1428 (1967).
196. R. A. Nyquist, Spectrochim. Acta, **19**, 1655 (1963).
197. E. Bernatek, T. Ledael, and A. Asen, Acta Chem. Scand., **18**, 1317 (1964).
198. T. A. Geissman, J. Amer. Chem. Soc., **64**, 1704 (1942).
199. S. Seshadri and P. L. Trivedi, J. Org. Chem., **22**, 1633 (1957).
200. M. Crawford and J. M. Rasburn, J. Chem. Soc., 2155 (1956).

Rostov-on-Don State University
Lenin Kharkov Polytechnic Institute