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Some new views on the tautomerisation mechanism

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Abstract. Published data on the prototropic tautomerism of some carbonyl and nitrogen-containing acyclic and heterocyclic compounds are systematised. Mechanisms of intramolecular and intermolecular proton transfer in tautomerisation reactions are considered. On the basis of the results of semiempirical and *ab initio* quantum-chemical calculations, preference is given to an intermolecular collective (dimeric, trimeric, tetrameric or oligomeric) mechanism. A new approach to the description of the solvent effect on the prototropic tautomeric equilibrium is proposed. The bibliography includes 107 references.

I. Introduction

Since the discovery of prototropic tautomerism, its nature and essence have attracted much attention. Studies performed for more than a hundred years led to the general conclusion that many processes typical of chemical reactions involve the tautomeric interconversion. Hence, the latter serves as a convenient model for studying the reaction mechanisms. In this connection, it is pertinent to mention the appropriate statement by Bilobrov [1] that tautomeric interconversions of molecules are one of the reasons for a striking diversity of the world of chemical reactions.

It is known that the more polar keto form dominates in the keto – enol equilibrium and the mobile hydrogen atom is transferred as the ion. However, in the case of acetylacetone and benzoylacetone, the equilibrium is almost completely shifted to the enol form. It is still unclear whether this fact is an exception from the general situation with the keto – enol tautomeric equilibrium or there are no general regularities at all. When discussing this problem, one might reason that there is no need to reveal the general regularities of this phenomenon. It is only necessary to establish the character of a particular process reliably and unambiguously by chromatographic and spectroscopic methods and quantum-chemical calculations. The tautomeric equilibria can be quantitatively described with the advantageous use, for example, of intensities of stretching vibrations of the carbonyl (ν_{CO}) and hydroxy (ν_{OH}) groups in the IR spectra [2] and chemical shifts of the protons and carbon nuclei of the corresponding functional groups in the ^1H and ^{13}C NMR spectra.[3] Of theoretical methods, semiempirical [4, 5] and *ab initio* [6] quantum-chemical methods find wide application. These methods allow one to calculate the energy, electronic and structural characteristics of individual tautomeric forms and estimate the tautomeric equilibrium constants (K_T). It should be noted that a necessary condition for the quantitative description of the tautomeric equilibrium is the existence of two rather deep minima in the plot of the proton-transfer energy *vs.* the reaction coordinate.

Investigations on tautomeric processes were surveyed in the reviews [7 – 10] and considered in more recent detailed studies cited below.

The present review considers new views in the theory of prototropic tautomerism, in particular, the intermolecular mechanism of proton transfer, and a new approach to the determination of tautomeric equilibrium constants and quantitative description of the influence of the solvent on the equilibrium. The results of quantum-chemical calculations of prototropic tautomeric equilibria and their examination by spectroscopic methods are discussed in particular sections.

II. Keto – enol tautomerism

The keto – enol tautomerism is the most well-studied type of prototropic rearrangements. Since individual tautomeric forms can be readily detected by different methods, measurements of the equilibrium constants of this process present no difficulties. Due to the high affinity of the carbonyl oxygen atom for the proton, keto – enol tautomerism is observed in many compounds. The tautomeric equilibrium constants for various β-dicarbonyl compounds were estimated by Meyer [11] back in the early 20th century with the use of bromometric titration. These results are still scientifically useful. The constants K_T determined by Meyer correlate with the polarities of the solvents, which were determined by spectroscopic methods many decades later.

Modern studies of the keto – enol equilibrium confirmed the earlier views that the keto form is thermodynamically more stable than the enol form. This is evidenced, for example, by calculations

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of the relative stabilities of the keto and enol forms and energy barriers to enolisation of ketones MeCOR (R = Me, H, F, CN).[12]

With the aim of studying the effect of substituents on the keto–enol tautomerism, the reaction coordinates and activation energies for enolisation of aldehydes XCH_2CHO (X = H, BH_2, NH_2, OH, F, CN, NC, Cl) were calculated by *ab initio* methods. The results of calculations at different levels of theory showed that the keto forms of the compounds under study are thermodynamically more stable than the corresponding enol forms.[13]

The *ab initio* calculations of the ethenethiol–thioacetaldehyde tautomeric interconversion demonstrated that ethenethiol in the gas phase is 2.6 kcal mol^{-1} less stable than thioacetaldehyde.[14]

The position of the keto–enol equilibrium depends, among other factors, on the polarity of the solvent. Thus, the molecular modelling of the photoinduced transformation of the excited enol tautomeric form of 7-hydroxy-8-morpholinomethylquinoline into the keto form demonstrated that an intramolecular hydrogen bond between the protonated morpholine nitrogen atom and the deprotonated hydroxy group in cyclohexane hinders the proton transfer. By contrast, an intermolecular hydrogen bond is formed in 1,4-dioxane, and the morpholine nitrogen atom serves as a proton carrier.[15]

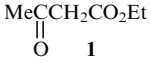
The tautomeric equilibrium in methyl esters of para-substituted benzoylacetic acids was studied by ^1H NMR spectroscopy [16] and the dependences of the equilibrium constants K_T on the solvent and the nature of the substituent were found.

The third-order terms were measured for the concerted acid-base catalysis of enolisation of simple aldehydes and ketones to form substituted acetic acids. It was concluded that aldehydes undergo enolisation under the conditions of base catalysis. The isotopic effect of the solvent in enolisation of aldehydes under the conditions of concerted acid-base catalysis shows that the transition state with proton transfer to the carbonyl group is formed more readily than that in the case of ketones.[17]

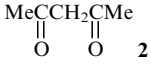
Until recently, the dielectric permeability of the medium has been used as the main parameter describing the influence of the solvent on the tautomeric equilibrium.[18–20] However, Prezhdo *et al.*[21] reasonably noted that the dielectric permeability of the solvent cannot be considered as a universal characteristic of interactions between molecules and the medium. To obtain a more adequate estimate of the polarity of the solvent, the dipole moment, polarisability, molar volume and specific and non-specific interactions should also be taken into account.[22, 23]

In 1963, Dimrot *et al.*[23] proposed the empirical polarity parameters (E_T) for organic solvents. These parameters are estimated on the basis of the energy of electron transfer corresponding to long-wavelength absorption bands in the UV-vis spectra of *N*-phenoxypyrimidine dyes exhibiting negative solvatochromism.

The experimental constants K_T for acetoacetic ester in different solvents, which were determined by spectroscopic, kinetic, refractometric and bromometric methods, were published in the study.[21] The plot of the constants K_T *vs.* E_T for 12 solvents, including acetoacetic ester (**1**), exhibits a hyperbolic character (Fig. 1). Analogous qualitative and quantitative characteristics were found for acetoacetic ester (**1**) and acetylacetone (**2**) by titrimetry, liquid chromatography and NMR spectroscopy.[3, 24]



1



2

The experimental curves also indicate that the constants K_T are inversely proportional to E_T.

The proton transfer in keto–enol tautomerism can occur along the intermolecular hydrogen bond between the oxygen atom of the carbonyl group and the proton at the α position in the cyclic dimer of carboxylic acid.[25] This is somewhat contradictory to the concept according to which the involvement of the hydrogen atom in hydrogen bonding requires high electronegativity of the atom to which this hydrogen atom is bound. The IR

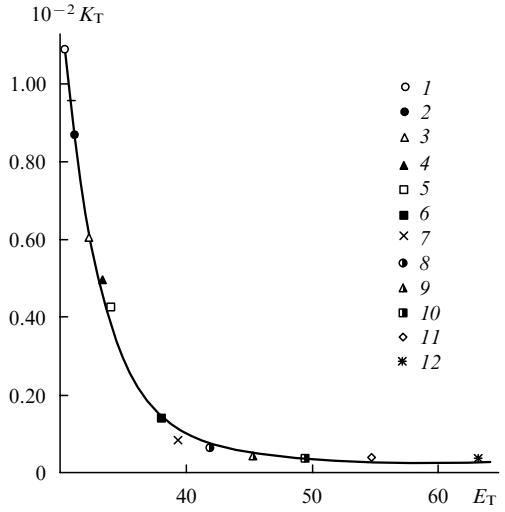
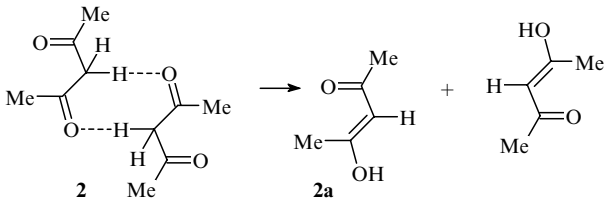


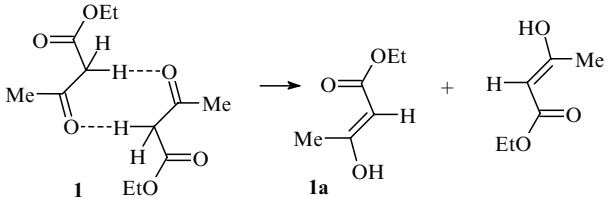
Figure 1. Tautomeric equilibrium constant K_T of acetoacetic ester *vs.* the polarity parameter of the solvent E_T.
(*1*) cyclo-C_6H_{12}; (*2*) n-C_6H_{14}; (*3*) CCl_4; (*4*) CS_2; (*5*) Et_2O; (*6*) $MeCO_2Et$; (*7*) $CHCl_3$; (*8*) Me_2CO; (*9*) MeCN; (*10*) acetoacetic ester (**1**); (*11*) MeOH; (*12*) H_2O.[21]

spectroscopic study [26] performed by one of the authors of the present review showed that a proton of the methyl group can be involved in intermolecular hydrogen bonding in acetophenone. In the studies,[27, 28] preference was given to the mechanism of proton transfer through intramolecular hydrogen bonding, although the activation barrier for this process is rather high. In some early studies [25, 29] and in more recent investigations,[30–37] evidence was reported for the formation of dimeric associates through two-proton transfer in the case of carbonyl and nitrogen-containing acyclic and heterocyclic compounds in which intramolecular hydrogen bonding is energetically and geometrically unfavourable.

We proposed that the mechanism of tautomerisation involving dimers be used to obtain quantitative estimates of the energy of proton transfer and constants K_T for acetoacetic ester (**1**) and acetylacetone (**2**) upon transformations into the corresponding enol forms **1a** and **2a**.



2 **2a**



1 **1a**

We carried out calculations to establish the dependence of the enthalpy on the reaction coordinate (R_{CH}), which allowed us to construct the energy diagram for the two-proton transfer in the dimer of acetoacetic ester (**1**), *i.e.*, the dependence of ΔH on R_{CH} for the C···H···O triad corresponding to an intermolecular hydrogen bond (for R_{CHO}, the value of 2.60 Å was assumed). From this diagram, we determined the activation enthalpies of the two-proton transfer $\Delta\Delta H^{\#} = 91.1$ kJ mol^{-1} and heats of reaction $\Delta\Delta H = 32.2$ kJ mol^{-1}, which have reasonable values for this

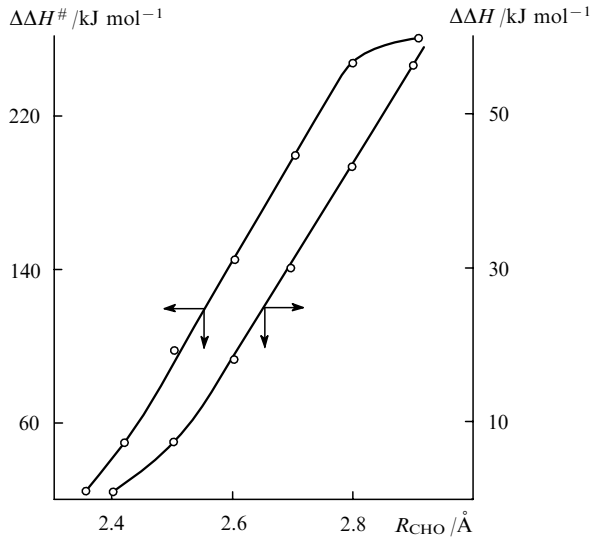


Figure 2. Activation enthalpy $\Delta\Delta H^{\#}$ and heat of reaction $\Delta\Delta H$ for the proton transfer *vs.* the length of the CHO triad corresponding to an intermolecular hydrogen bond (R_{CHO}) in acetoacetic ester (**1**) (our data).

process. The $\Delta\Delta H^{\#}$ and $\Delta\Delta H$ values depend on R_{CHO}. As can be seen from Fig. 2, $\Delta\Delta H^{\#}$ and $\Delta\Delta H$ can be considered as average values based on the reference points in the middle of the linear region, although the linearity of the plot is disrupted in the vicinity of the boundaries. Analogous results were obtained for acetylacetone (**2**) (Fig. 3). In particular, at R_{CHO} = 2.60 Å, the activation enthalpy $\Delta\Delta H^{\#}$ = 103.7 kJ mol^{-1} and the heat of reaction $\Delta\Delta H$ = 23.7 kJ mol^{-1}.

The choice of the calculation method for estimating the constant K_T is of great importance. Since the thermodynamic equation $\ln K_T = -\Delta\Delta H/RT$ is independent of the reaction mechanism (in the case under consideration, on the mechanism of proton transfer), it is of little use for the adequate estimation of K_T. Besides, this equation describes the overall process of two-proton transfer, although if tautomeric interconversions of different nature take place (for example, in nucleic bases), the constants

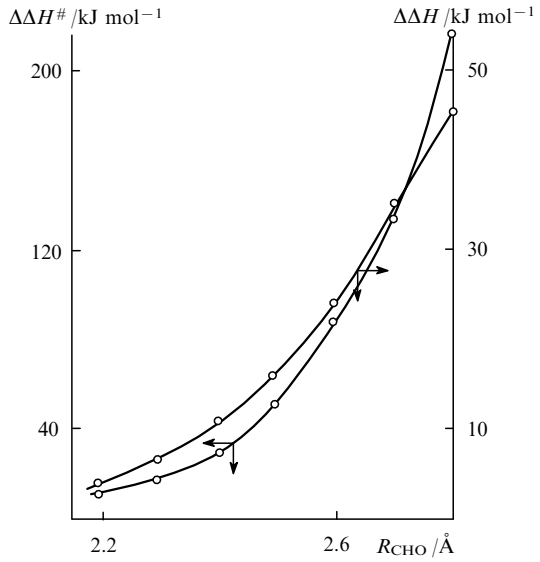


Figure 3. Activation enthalpy $\Delta\Delta H^{\#}$ and heat of reaction $\Delta\Delta H$ for the proton transfer *vs.* the length of the CHO triad corresponding to an intermolecular hydrogen bond (R_{CHO}) in acetylacetone (**2**) (our data).

K_T for each proton depend differently on the structural changes. We propose a new approach to estimating the tautomeric equilibrium constants according to which the constant K_T can be represented as a function of the orders of the bonds that are cleaved and formed in the course of proton transfer.[38] In the case of the keto–enol tautomerism proceeding through a cyclic dimer, the proton transfer is accompanied by an increase in the O–H (P_{OH}) bond order to the maximum value ($\sim$ 0.900) and a decrease in the C–H (P_{CH}) bond order to zero, *i.e.*, the latter bond is cleaved. Simultaneously, the order of the C=O double bond (P_{CO}) decreases to the single-bond order ($\sim$ 1.000), while the order of the C–C (P_{CC}) single bond increases to the order of the C=C double bond ($\sim$ 1.600). Hence, the double bond is shifted from the carbonyl group to the adjacent C–C bond giving rise to the enol tautomeric form. The bond orders under consideration (P_{CH}, P_{OH}, P_{CO}, and P_{CC}) would change in parallel with changes in the percentage of the keto and enol forms in the course of proton transfer. On going from the first to the second energy term, the percentages of the keto and enol forms can be described by Eqn (1):

$$\frac{P^1_{OH}}{P^1_{CH}}E_n + \frac{P^1_{CO}}{P^1_{CC}}Kt = \frac{P^2_{OH}}{P^2_{CH}}En + \frac{P^2_{CO}}{P^2_{CC}}Kt, \qquad (1)$$

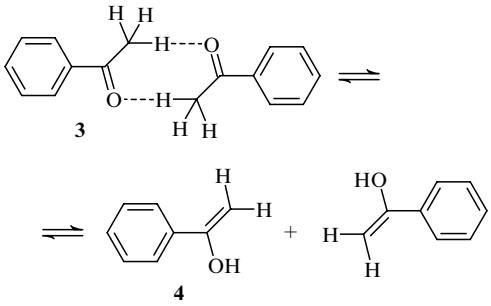
where *En* and *Kt* are the initial contributions (in %) of the enol and keto forms, and P^1_{ij} and P^2_{ij} are the orders of the corresponding bonds in the first and second terms.

After dividing both sides of Eqn (1) by *Kt* taking into account that $K_T = En/Kt$ followed by simple algebraic transformation, we get Eqn (2) for the constant of the keto–enol tautomeric equilibrium.

$$K_T = \frac{P^1_{CH}P^2_{CH}(P^1_{CO}P^2_{CC} - P^2_{CO}P^1_{CC})}{P^1_{CC}P^2_{CC}(P^1_{CH}P^2_{OH} - P^2_{CH}P^1_{OH})}. \qquad (2)$$

The value of K_T calculated according to Eqn (2) is independent of the external factors and depends only on the electronic structures of the molecules involved in tautomeric interconversions.

An analogous approach was applied to the quantitative description of the tautomerisation of acetophenone (**3**) to the enol form **4**.



The dependences of $\Delta\Delta H^{\#}$ and K_T on R_{CHO} thus obtained are consistent with those for acetoacetic ester (**1**) and acetylacetone (**2**). A decrease in the length of the triad to R_{CHO} = 2.60 Å in the dimer of acetophenone leads to a decrease in $\Delta\Delta H^{\#}$ from 405.0 to 120.4 kJ mol^{-1} and a decrease in $\Delta\Delta H$ from 110.8 to 41.0 kJ mol^{-1}, the constant K_T being increased from 0.024 to 0.107.

A model was constructed for the quantitative description of the effect of the solvent on K_T. The plots of K_T *vs.* R_{CHO} for acetoacetic ester (**1**) (Fig. 4) and acetylacetone (**2**) calculated by Eqn (2) (Fig. 5) are hyperbolic curves, *i.e.*, the constants K_T are inversely proportional to R_{CHO}. For compounds **1** and **2**, the constant K_T is also inversely proportional to the polarity parameter of the solvent E_T (Figs 6 and 7, respectively). A comparison of these dependences shows that the dimers are extended in more polar solvents and compressed in less polar solvents. Actually, the plots of R_{CHO} *vs.* E_T for compounds **1** and **2** (Figs 8 and 9,

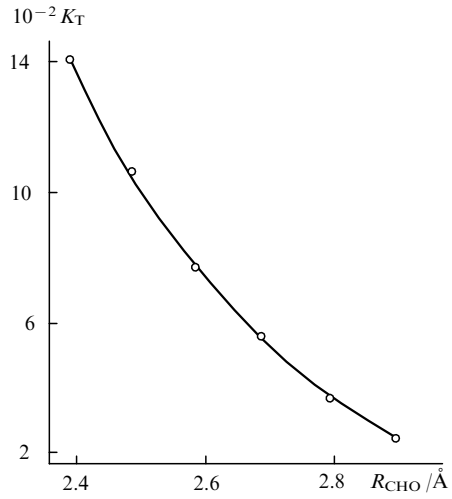


Figure 4. Plot of the constant K_T of acetoacetic ester (**1**) *vs.* the length of the CHO triad corresponding to an intermolecular hydrogen bond (R_{CHO}) (our data).

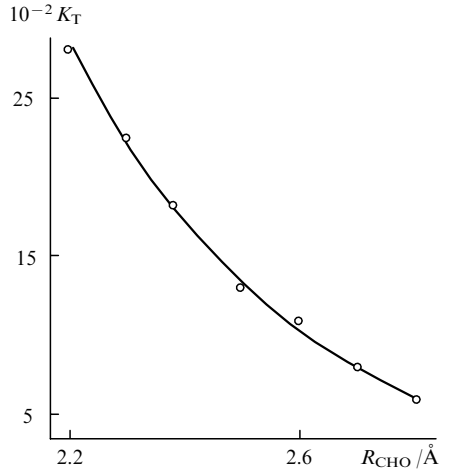


Figure 5. Plot of the constant K_T of acetylacetone (**2**) *vs.* the length of the CHO triad corresponding to an intermolecular hydrogen bond (R_{CHO}) (our data).

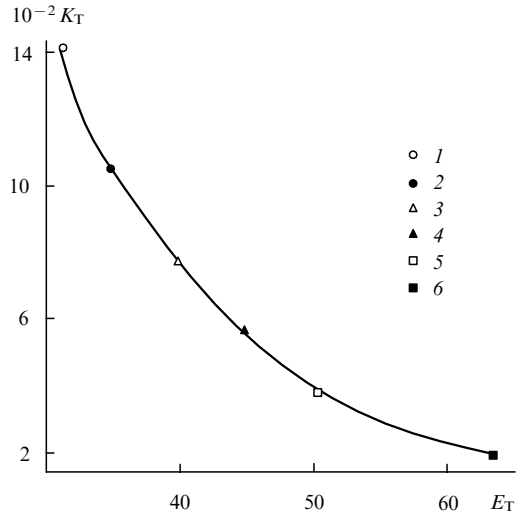


Figure 6. Plot of the tautomeric equilibrium constant of acetoacetic ester (**1**) *vs.* the polarity parameter of the solvent E_T.
(*1*) n-C_6H_{14}; (*2*) Et_2O; (*3*) $CHCl_3$; (*4*) MeOH; (*5*) EtOH; (*6*) H_2O (our data).

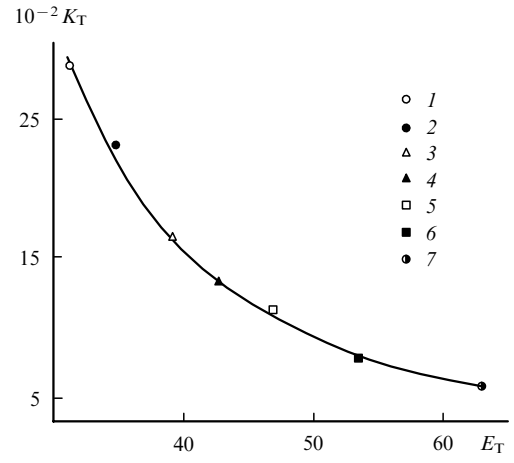


Figure 7. Plot of the tautomeric equilibrium constant of acetylacetone (**2**) *vs.* the polarity parameter of the solvent E_T.
(*1*) n-C_6H_{14}; (*2*) Et_2O; (*3*) $CHCl_3$; (*4*) Me_2CO; (*5*) MeCN; (*6*) EtOH; (*7*) H_2O (our data).

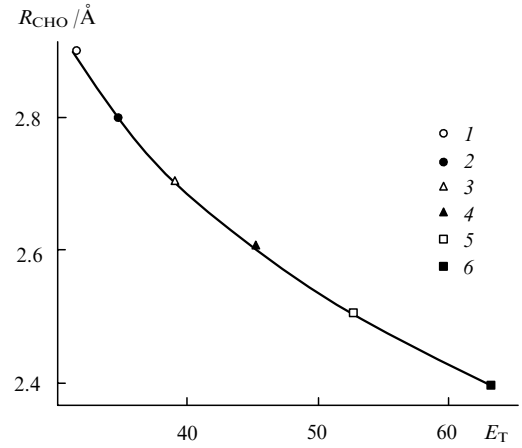


Figure 8. Length of the CHO triad of an intermolecular hydrogen bond (R_{CHO}) in the dimer of acetoacetic ester (**1**) *vs.* the polarity parameter of the solvent E_T.
(*1*) n-C_6H_{14}; (*2*) Et_2O; (*3*) $CHCl_3$; (*4*) Me_2CO; (*5*) MeCN; (*6*) EtOH; (*7*) H_2O (our data).

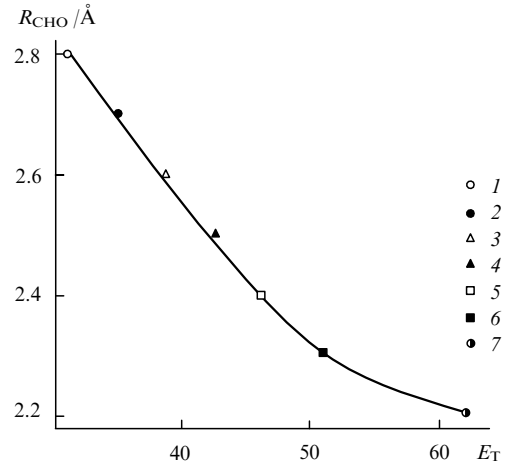
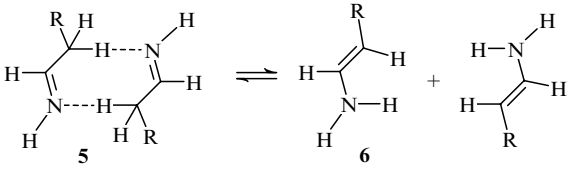


Figure 9. Length of the CHO triad of an intermolecular hydrogen bond (R_{CHO}) in the dimer of acetylacetone (**2**) *vs.* the polarity parameter of the solvent E_T.
(*1*) n-C_6H_{14}; (*2*) Et_2O; (*3*) $CHCl_3$; (*4*) Me_2CO; (*5*) MeCN; (*6*) EtOH; (*7*) H_2O (our data).

respectively) indicate that the length of the triad corresponding to an intermolecular hydrogen bond is inversely proportional to the polarity of the solvent. This model can be used to advantage for the quantitative description of the effects of external factors on some biologically important processes (see below).

III. Imine – enamine tautomerism

Tautomerisation involving the proton bound to the nitrogen atom is a key step in reactions of heterocyclic compounds. The possibility of the transformation of imines into the corresponding enamines was first studied by Lawer.[39] This classical reaction can be represented as the intermolecular proton transfer in the dimer of imine **5** to form enamine **6**.



5 **6**

The influence of the α- and β-substituents on the position of the imine – enamine tautomeric equilibrium was estimated quantitatively. In particular, the percentage of the enamine form in α-substituted derivatives of the $R^1CH=C(Me)NHR^2$ type changes from 50% to 70%,[40] whereas this percentage in β-substituted analogues is in the range of 30% – 100%.[41]

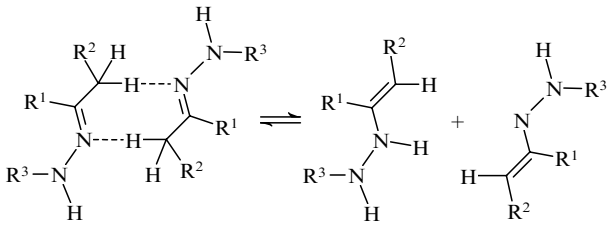
The investigation of the tautomerism in analogous *N*-substituted imines showed that an increase of the charge on the nitrogen atom [42] as well as an increase in the volume of the substituent at the same atom [42, 43] led to a decrease in the percentage of imine in the equilibrium mixture. An attempt was made to find the dependence of the percentage of enamine on its pK_a [44] assuming that the mobility of the proton of the amino group should facilitate an increase in the percentage of enamine. However, no correlation was revealed.

The study of the effect of the solvent on the imine – enamine equilibrium [45] demonstrated that the percentage of enamine increases in the series of the solvents $CHCl_3 < PhH < MeNO_2 < MeCN < MeCOMe < C_5H_5N < MeSOMe$. This series does not correlate with a change in the polarity parameter E_T of the solvent,[23] which accounts for all types of interactions. Apparently, this inconsistency results from experimental errors.

In 1971, using *N*-methylphenylhydrazone of ethyl pyruvate as an example, Ahlbrecht[46] discovered the hydrazone – enehydrazine interconversion as a special case of the imine – enamine tautomerism. The examination of the characteristic features of the transformation of hydrazone into enehydrazine is of great importance for the target synthesis of indole derivatives.[47] It was assumed that the hydrazone – enehydrazine tautomerisation is the rate-determining step of Fischer indolisation,[48] although we do not share this opinion.[36]

The results of qualitative and quantitative studies of the imine – enamine tautomerism and, in particular, the hydrazone – enehydrazine tautomerism, were comprehensively discussed in the review.[49] Shainyan and Mirskova [49] believed that the proton transfer in these processes occurs through an intermolecular mechanism. It was also noted that the hydrazone form is more stable in the absence of conjugation with an electron-withdrawing substituent.[50] In the presence of an electron-withdrawing substituent in any position, conjugation with this substituent stabilises enehydrazine (due to the predominance of the negative mesomeric effect), which was confirmed by quantum-chemical calculations of the tautomerisation of acetophenone hydrazone to the corresponding enehydrazine.[51]

In our opinion, the tautomerisation of phenylhydrazones of some carbonyl compounds **7a**–**j** into the corresponding enehydrazines **8a**–**j** proceeds through the formation of cyclic dimers.



7a–**j** **8a**–**j**

To confirm this assumption, the activation enthalpies ($\Delta\Delta H^{\#}$), heats of reaction ($\Delta\Delta H$) and tautomeric equilibrium constants (K_T) for the above-considered reaction were calculated (Table 1).[38]

Table 1. Activation enthalpies ($\Delta\Delta H^{\#}$ /kJ mol^{-1}) and heats of reaction ($\Delta\Delta H$ /kJ mol^{-1}) for the hydrazone – enehydrazine tautomerism in phenylhydrazones **7a**–**j**.

Compound	R^1	R^2	R^3	K_T	$\Delta\Delta H^{\#}$	$\Delta\Delta H$
a	H	H	Ph	0.05	185.2	171.3
b	Me	H	Ph	0.04	150.0	130.4
c	Et	H	Ph	0.04	124.1	92.0
d	CO_2Et	H	Ph	0.05	145.5	128.4
e	Ph	H	Ph	0.05	134.2	98.2
f	4-MeC_6H_4	H	Ph	0.05	133.3	97.0
g	4-$NO_2C_6H_4$	H	Ph	0.05	140.0	107.8
h	Ph	H	4-MeC_6H_4	0.04	133.8	98.0
i	Ph	H	4-$NO_3C_6H_4$	0.05	134.8	98.0
j	$(CH_2)_4$		Ph	0.09	83.2	46.0

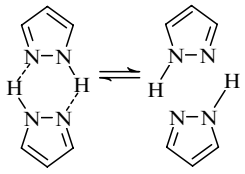
The constants K_T were calculated by Eqn (3).

$$K_T = \frac{P^1_{CH}P^2_{CH}(P^1_{NC}P^2_{CC} - P^2_{NC}P^1_{CC})}{P^1_{CC}P^2_{CC}(P^1_{CH}P^2_{NH} - P^2_{CH}P^1_{NH})}. \quad (3)$$

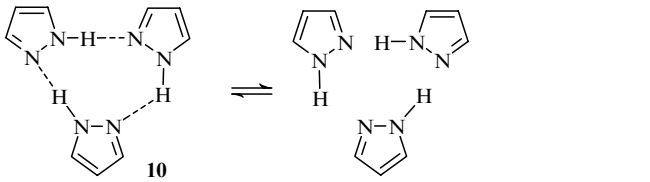
As can be seen from Table 1, the constants K_T for phenylhydrazones **7a**–**i** have virtually equal values, whereas the constant for cyclohexanone phenylhydrazone **7j** is twice as large as these values. The electron-withdrawing (NO_2) and electron-donating (Me) substituents in the para position of the benzene ring of both the hydrazine and carbonyl fragments (compounds **7f**–**i**) exert only a slight effect on K_T and $\Delta\Delta H^{\#}$, although it is known [52] that these substituents have a substantial effect on the kinetics of indolisation. In our opinion, this is evidence that the hydrazone – enehydrazine tautomerisation is not a rate-determining step of Fischer indolisation of arylhydrazones.

IV. Tautomerism in diazoles

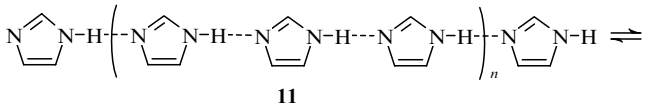
Tautomerism in the series of azoles is associated with the mobility of the hydrogen atom of the amino group.[53] In the study,[54] it was demonstrated that the tunnelling proton transfer can occur through an intermolecular hydrogen bond between the NH group of one pyrazole molecule and the lone electron pair of the nitrogen atom of the second molecule. Collective mechanisms involving dimers (**9**) and trimers (**10**) of pyrazole and oligomers of imidazole **11** were proposed.[54]



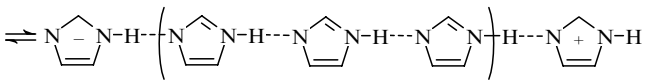
9



10



11

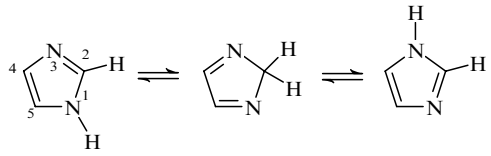


12

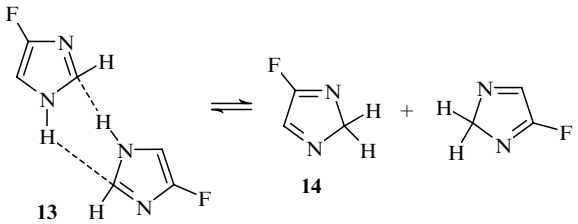
However, the existence of an oligomeric structure of imidazole **12** seems to be unlikely because the IR spectra have no absorption bands of the N^+H group, which must be present in the structure of **12**.[55] Based on the ^1H NMR spectroscopic data,[56] it was suggested that solutions of N-derivatives of imidazole contain associates as stacks, which are stabilised by interplanar interactions due to overlapping of the π-electron clouds of the adjacent molecules. Later on, the possibility of the intermolecular proton transfer in imidazole and pyrazole proceeding through the tunnelling mechanism was demonstrated by Nesmeyanov *et al.*[57] by ^1H and ^{13}C NMR spectroscopy. However, an intermolecular structure was not described. In investigations of the proton transfer in imidazole, preference is given to an intermolecular mechanism. An intramolecular mechanism is energetically unfavourable, which was demonstrated by quantum-chemical calculations[58] and ^{13}C NMR spectroscopy.[59] Recently, the proton conductivity in crystalline imidazole was studied by ^{14}N NMR spectroscopy and the so-called migration and reorientation mechanisms were proposed for processes occurring in oligomeric chains.[60] This conclusion about the formation of oligomeric chains is in contradiction with the results of another study.[55] It is difficult to give preference to a particular investigation. However, it can be assumed that oligomeric chains can exist in the excited states, due, among other factors, to the difference in the potentials in measurements of the proton conductivities of the imidazole systems. It should be noted that the equilibrium constants depend substantially on the basis set used in *ab initio* quantum-chemical calculations.[61]

The ability of imidazole derivatives to occur in a particular tautomeric form depends on many factors. Thus, both the NH and 3-OH tautomeric forms of 2,4,5-triphenylimidazole 3-oxide were observed in aqueous solutions, whereas only the latter form was found in non-polar solvents.[62] Quantum-chemical calculations[63] demonstrated that 4- and 5-nitroimidazoles are equally stable in the gas phase, whereas the 4-nitro isomer prevails in solutions. The self-associations of imidazole and 1-, 2-, 4-, and 5-methylimidazoles in aqueous solutions were studied by UV spectroscopy and it was demonstrated that these compounds are prone to dimerisation and polymerisation.[64]

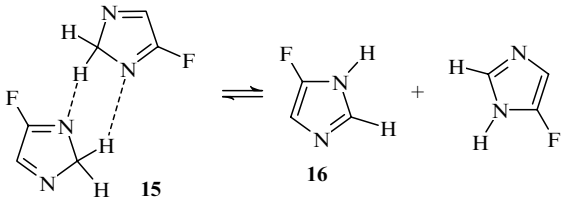
As mentioned above, the intramolecular proton transfer in imidazole is energetically unfavourable. The intermolecular H^1-H^3 proton transfer in the dimer is sterically hindered.[65] Hence, it was proposed that the tautomerisations of imidazole might proceed through a two-step mechanism involving the H^1-H^3 proton transfer.[66]



This complex process can occur in two steps through the proton transfer in dimer **13** from position 1 to position 2 to give H^2-tautomer **14** followed by the proton transfer in dimer **15** from positions 2 to position 3 to form 3H-tautomer **16**.



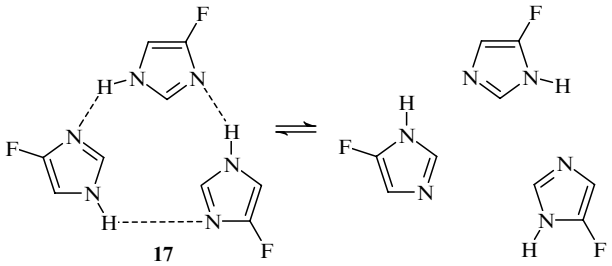
13 **14**



15 **16**

We calculated the activation enthalpies of these steps and the heat of reaction for 4-fluoroimidazole **13**. The activation enthalpies of the first and second steps are 170.5 and 116.6 kJ mol^{-1}, respectively. The heat of the overall reaction ($\Delta\Delta H$) is -50.6 kJ mol^{-1}, *i.e.*, the H^1-H^3 tautomeric transformation in 4-fluoroimidazole is an exothermic process. The equilibrium constants for the first and second steps calculated by Eqn (3) are 2.87×10^{-2} and 3.96×10^{-2}, respectively.

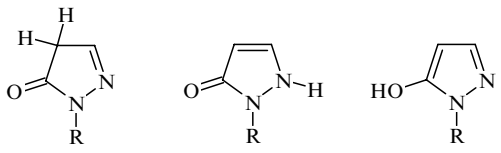
The one-step H^1-H^3 proton transfer in 4-fluoroimidazole can also occur in trimer **17**.



17

To obtain a quantitative description of the simultaneous transfer of three protons, we calculated the energy, electronic and structural characteristics of these processes in the reaction coordinate mode (R_{NH}).[65] The high activation enthalpy ($\Delta\Delta H^{\#} = 454.4$ kJ mol^{-1}) and low heat of reaction ($\Delta\Delta H = 3.8$ kJ mol^{-1}) provide evidence that the tunnelling proton transfer in the trimer of imidazole can occur. The tautomeric equilibrium constant ($K_T = 10^{-2}$) was calculated.

The tautomeric equilibrium for pyrazoles was systematically studied by Elguero and co-workers.[66–68] Spectroscopic studies demonstrated that 1-substituted 5-hydroxypyrazoles in non-polar solvents exist predominantly in 4H form **18** with a small admixture of NH form **19**. In aqueous solutions, these compounds exist predominantly in NH form **18** with an admixture of OH form **20**.



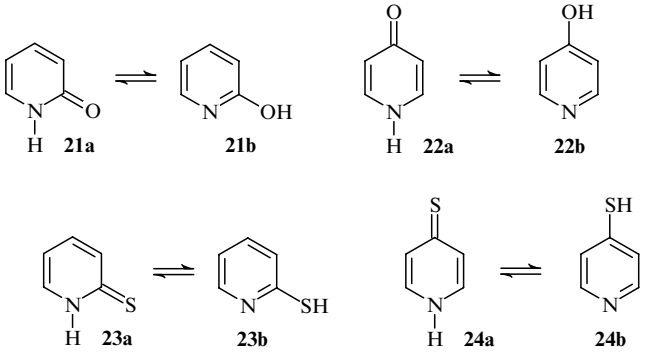
18 **19** **20**

In early studies, it was assumed that the long-range proton transfer takes place in pyrazole.[66,69] Later on, the dynamics of the intermolecular tautomerisation of pyrazole derivatives in the solid state was studied by NMR spectroscopy and X-ray diffraction analysis.[67–69] It was concluded that these compounds can exist as cyclic trimers. In the recent review by Japan researchers,[34] the results of subsequent studies performed by Elguero and co-

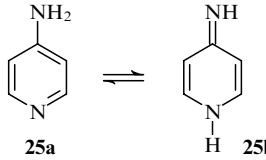
workers were discussed. In these studies, the dimeric,[70] trimeric [71–73] and tetrameric [74,75] mechanisms of proton transfer in pyrazoles through intermolecular hydrogen bonds were examined. Based on the results of NMR spectroscopy and X-ray diffraction analysis, it was concluded that the proton transfer in the compounds under study can proceed through so-called collective mechanisms.

V. Tautomerism in pyridines

In the reviews,[9,76] it was reported that 2- (**21a**) and 4-pyridones (**22a**) as well as 2- (**23a**) and 4-thiopyridones (**24a**) in aqueous and polar solvents occur predominantly in the oxo and thioxo forms.



However, the amino rather than imino form is typical of 4-aminopyridine (**25a**).



Katritzky attributed this difference in the behaviour of these compounds to stabilisation of ionic intermediates.[76]

It was demonstrated [77] that stability of tautomeric forms is associated with low enthalpies. Studies of the effect of the solvent on the tautomeric equilibrium led to the conclusion that the ratio between the hydroxy and oxo forms increases linearly as the polarity of the solvent increases.

In the review,[78] the influence of the structural and external factors, including the possible formation of intra- and intermolecular hydrogen bonds, on the tautomeric equilibrium in pyridine derivatives was examined by spectroscopic and quantum-chemical methods and by investigating individual tautomers.

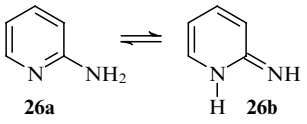
The position of the tautomeric equilibrium in pyridine derivatives often depends on the concentration of the solutions used. In particular, the constant K_T for 2-pyridone (**21a**) decreases by a factor of 7 upon a 100-fold dilution of a solution in cyclohexane.[29] This is attributable to self-association of the molecules. Hence, it was suggested that 2-pyridone (**21a**) might occur as a dimer and 4-pyridone (**22a**) might exist as a chain associate.

With the aim of studying the effect of the nature of substituents on the tautomeric equilibrium in α-substituted 4-pyridones, the constants K_T were determined by UV spectroscopy. It was demonstrated that K_T depends linearly on the Hammett σ-constant of the substituent.[79] It was also found that the electron-donating and electron-withdrawing substituents led to increases and decreases in $\log K_T$, respectively.

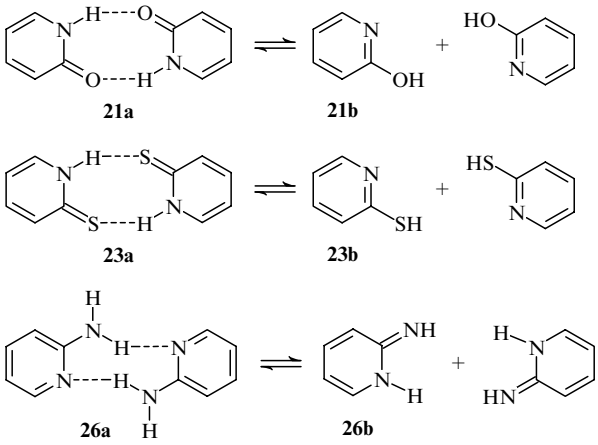
An intramolecular mechanism of proton transfer was proposed for the lactam–lactim tautomerism in 2-pyridone (**21a**).[80] The activation barrier calculated by the CNDO/2 quantum-chemical method is 145 kJ mol^{-1}. It should be noted that this method is of little use for the estimation of the energy indices. The value calculated by this method is substantially overestimated. Actually, the activation energy determined in the study on the tautomeric equilibrium in 6-methoxy-2-pyridone [81] (46 kJ mol^{-1}) is three times lower, which casts some doubt on the energetically unfavourable intramolecular mechanism of proton transfer proposed in the study.[80]

Quantum-chemical methods find wide use for studying the tautomeric equilibria in pyridine derivatives. Thus, the relative stabilities of tautomers of monosubstituted (OH, SH, NH_2) pyridines were studied by the MNDO method.[82] It was noted that the lactam form is energetically more favourable in all cases, which is in good agreement with the experimental data. Schlegel *et al.*[83] calculated the energies of tautomerisation of 2- and 4-pyridones by semiempirical and *ab initio* quantum-chemical methods. The calculations by the semiempirical CNDO/2 and MINDO/3 methods gave unreasonable results, whereas the results of *ab initio* calculations depend substantially on the basis set used. However, in some cases, the calculated values are close to the experimental data. Noteworthy is the study [84] in which the proton transfer in the lactim–lactam tautomerism in 2-pyridone (**21a**) was examined by *ab initio* methods. Three types of proton transfer were considered, *viz.*, those proceeding by intramolecular and self-association mechanisms and the proton transfer due to the addition of a water molecule. The authors of the cited study believed that the mechanisms, in which the proton transfer occurs either in a dimer or through the addition of a water molecule, are the most reasonable. The enthalpies (ΔH) of tautomerism in 2-, 3- and 4-pyridones were calculated by the semiempirical AM1, MNDO and PM3 methods.[85] The results obtained by different methods differ substantially from each other and from the experimental data. A good agreement with experiment was achieved only with the use of the AM1 method (ΔH = 32.5 and 30.1 kJ mol^{-1}). The influence of the solvents on the tautomeric equilibrium in 2- and 4-pyridones was studied by the AM1 method, [86] for which purpose the dielectric permeability of the solvent was introduced into the equation for the total energy. The constant K_T thus calculated is in good agreement with experiment. It should be noted that the calculated and experimental constants K_T depend linearly on the Onsager parameter $\varepsilon - 1/2\,\varepsilon + 1$, where ε is the dielectric permeability of the solvent.

To obtain a quantitative desciption of the tautomerism **21a** → **21b**, **22a** → **22b**, the enthalpies (ΔH) and orders of the bonds that are changed (P_{ij}) were calculated by the AM1 and MNDO quantum-chemical methods.

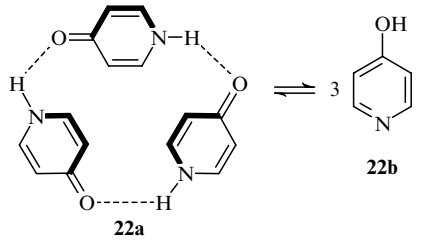


For 2-substituted pyridines **21a**, **23a** and **26a**, the proton transfer was calculated with the use of a dimeric mechanism in the reaction coordinate mode (R_{NH}).[87]

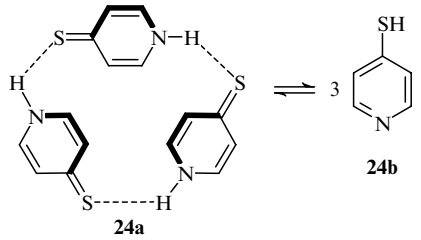


For the tautomersation of 4-substituted pyridines **22a** and pyridinethiones **24a**, the proton transfer through a dimeric mech-

anism is sterically hindered. In this connection, we proposed a trimeric mechanism for the proton transfer in compounds **22a** and **24a**. In the trimeric forms, the pyridine rings are located perpendicular to the plane of the figure, which excludes repulsions between the hydrogen atoms at positions 2, 3, 5 and 6.



22a **22b**



24a **24b**

We calculated the equilibrium constants for all types of proton transfer occurring in the course of this process by Eqn (4). (For pyridinethiones, the oxygen atom is replaced by the sulfur atom.)

$$K_T = \frac{P^1_{NH}P^2_{NH}(P^1_{CO}P^2_{CN} - P^2_{CO}P^1_{CN})}{P^1_{CN}P^2_{CN}(P^1_{NH}P^2_{OH} - P^2_{NH}P^1_{OH})}. \quad (4)$$

The activation enthalpies ($\Delta\Delta H^{\#}$), heats of reaction ($\Delta\Delta H$) and equilibrium constants (K_T) for the tautomerisation reactions under study are given in Table 2. It can be seen that the 4-pyridone–4-hydroxypyridine tautomerisation (**22a** → **22b**) with proton transfer through a trimeric mechanism is characterised by a rather high activation enthalpy (446.5 kJ mol^{-1}) and low heat of reaction (9.2 kJ mol^{-1}). This indicates that the proton transfer in this process can proceed through a tunnelling mechanism. The 4-pyridinethione–4-thiopyridine transformation (**24a** → **24b**) is an exothermic process characterised by a substantial heat evolution and a large equilibrium constant. The largest constant K_T was found for the 2-pyridinethione–2-thiopyridine equilibrium (**23a** → **23b**) characterised by small energy indices $\Delta\Delta H^{\#}$ and $\Delta\Delta H$. It can also be seen from Table 2 that the tautomeric equilibrium constant is inversely proportional to the activation enthalpy. The fact that the known dependence persists in this case provides evidence that the approach used is suitable for the quantitative description of prototropic tautomerism.

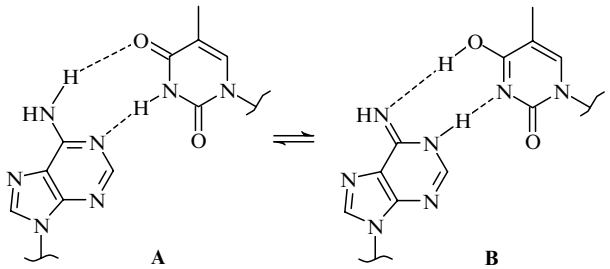
Table 2. Activation enthalpies, heats of reactions and equilibrium constants for tautomerisation of substituted pyridines.

Tautomerisation	$\Delta\Delta H^{\#}$ /kJ mol^{-1}	$\Delta\Delta H$ /kJ mol^{-1}	$10^{-2}\,K_T$
23a → 23b	44.3	23.4	13.0
24a → 24b	102.0	−99.1	5.2
21a → 21b	195.5	29.7	3.8
26a → 26b	196.6	106.6	4.4
22a → 22b	446.5	9.2	1.8

In conclusion, let us mention the study [88] in which the vibrational spectrum of 2-hydroxypyridine in an argon matrix was studied by Fourier IR spectroscopy and the constant for the 2-pyridone–2-hydroxypyridine tautomeric equilibrium **21a** → **21b** was estimated. This value (0.4) differs substantially from all known constants K_T, which were determined both by theoretical and experimental methods.

VI. Tautomerism in nucleotide bases

From the very beginning of molecular genetics, it has been discussed that mutations in DNA replication arise from the ability of nucleic acid bases to occur in rare tautomeric forms involved in mutagenesis.[89] The keto–amine tautomers **A** are the dominant forms of base pairs (for example, of the adenine–thymine pair) in DNA duplexes. However, each base pair can be transformed into its minor, while still quite stable, enolimine tautomer **B**.[90] Löwdin [91] attributed the formation of rare tautomeric forms of nucleic acid bases to the concerted transfer of two protons within the base pair linked by a hydrogen bond.



A **B**

If the ratio between the tautomer **B** and canonical tautomer **A** is larger than 10^{-4}–10^{-5} and the rare tautomer remains stable over time necessary for DNA replication, the double proton transfer may play an important role in spontaneous mutations.[92–94] Rapid proton transfer between bases can make a contribution to the physical properties of DNA, such as duplex flexibility, protein recognition or stability in DNA replication, *etc*.[90] The accuracy of the *in vitro* replication per base pair is 10^8–10^{10} (Ref. 95). A possible reason for mismatches in DNA replication is the formation of hypothetical structures including thermodynamically unfavourable tautomers of natural bases in mismatched pairs, such as AC or GT.[96] The typical frequency of mismatches upon the insertion of mismatching bases was estimated at 10^{-4}–10^{-6} (see Ref. 96), which is in good agreement with the experimental values (10^{-6}– 10^{-10}, see Ref. 85).

In spite of importance of tautomerisation in nucleic acid bases, this process is not characterised experimentally, because studies of the superfast and reversible proton transfer between specific base pairs present difficulties.[97]

The parameters of the tautomeric equilibrium in nucleic acid bases and dynamics of proton transfer are estimated by numerous calculation methods.[98–101]

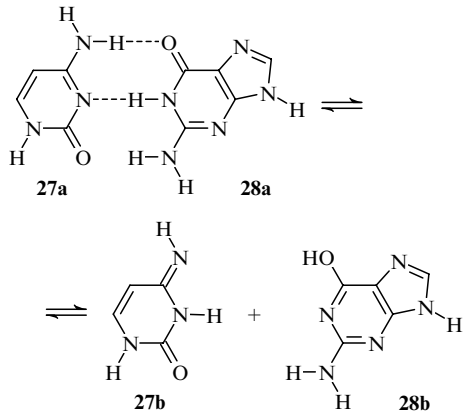
For example, the internal energies of isolated tautomeric forms of guanine and cytosine were calculated by an *ab initio* quantum-chemical method [102] (ΔE = 84.6 kJ mol^{-1}). The authors of the cited study proposed also the equation for calculations of the corresponding equilibrium constants. This equation includes the ratio of the standard state functions of individual tautomeric forms as the preexponential factor.

$$K_{aa'} = \frac{f_a}{f_{a'}} \exp\left(-\frac{\Delta E_{aa'}}{RT}\right),$$

where $K_{aa'}$ is the equilibrium constant of the tautomeric conversion $a \rightarrow a'$; f_a, $f_{a'}$ are the standard state functions of the tautomeric forms a and a', respectively, and $\Delta E_{aa'}$ is the activation energy of the tautomeric conversion.

Calculations of isolated tautomeric forms of nucleic acids as applied to the quantitative description of the proton transfer in complementary base pairs of DNA do not necessarily provide adequate results. For example, one can calculate the activation enthalpy ($\Delta\Delta H^{\#}$) of the simultaneous transfer of two protons in the cytosine (**27a**)–guanine (**28a**) complementary pair to form tautomers **27b** and **28b** (equilibrium processes are better described

by the enthalpy difference than by the total energy difference, which is a standard practice in *ab initio* calculations).



However, in this case, two tautomeric conversions, *viz*., amine–imine (**27a** → **27b**) and lactam–lactim (**28a** → **28b**), take place and their equilibrium constants can have different values and depend on structural changes in DNA. Consequently, these constants K_T cannot be determined with the use of one thermodynamic equation, which is, in addition, invariant with respect to the mechanism of proton transfer.

An intermolecular mechanism was proposes for proton transfer in isolated mono- and dihydrated guanine complexes on the basis of the results of *ab initio* quantum-chemical calculations.[103] By contrast, an intramolecular mechanism of proton transfer from the amido group with the activation energy of 150 kJ mol^{-1} was suggested in another study[104] also on the basis of *ab initio* quantum-chemical calculations. In our opinion, the formation of such an intramolecular hydrogen bond is impossible from the viewpoint of geometry, although the energy barrier is rather low.

We calculated the activation enthalpies, heats of reaction and constants of the amine–imine (K_T^{AI}) and lactam–lactim (K_T^{LL}) tautomeric equilibria in the cytosine–guanine pair for different lengths of the triad group corresponding to the intermolecular hydrogen bond (R_{NHN} or R_{NHO}) by the semiempirical AM1 method in the reaction coordinate mode R_{NH}. The equilibrium constants were calculated by Eqns (5) and (6).

$$K_T^{AI} = \frac{P_{NH}^1 P_{NH}^2 (P_{CN}^1 P_{CN}^2 - P_{CN}^2 P_{CN}^1)}{P_{CN}^1 P_{CN}^2 (P_{HN}^2 P_{NH}^1 - P_{HN}^1 P_{NH}^2)}, \quad (5)$$

$$K_T^{LL} = \frac{P_{NH}1 P_{NH}^2 (P_{CO}^1 P_{CN}^2 - P_{CO}^2 P_{CN}^1)}{P_{CN}^1 P_{CN}^2 (P_{NH}^1 P_{OH}^2 - P_{NH}^2 P_{OH}^1)}. \quad (6)$$

Based on the calculated data, we construct the plot of ΔH *vs*. R_{NH} for R_{NHN} = 2.8 Å, which is an energy curve with two minima. The first minimum or term corresponds to the amine and lactam tautomeric forms, and the second term corresponds to the imine and lactim tautomeric forms. The results of complete calculations are given in Table 3. It can be seen that $\Delta\Delta H^{\#}$ decreases linearly with decreasing R_{NHN} (R_{NHO}). An excellent correlation (r = 0.99) achieved in this case indicates that this approach is adequate for the quantitative description of proton exchange between the nucleotides under study. The dependence of K_T^{AI} (K_T^{LL}) on R_{NHN} is a hyperbolic curve, which indicates that the equilibrium constant is inversely proportional to the length of the triad describing an intermolecular hydrogen bond.

According to the opinion that the mutation frequency N_m can be determined from the product of the concentrations of rare tautomeric forms of nucleotides,[90,92] this parameter can be calculated by Eqn (7)

$$N_m = K_T^{AI} K_T^{LL}, \quad (7)$$

Table 3. Activation enthalpies ($\Delta\Delta H^{\#}$/kJ mol^{-1}), heats of reaction ($\Delta\Delta H$/kJ mol^{-1}), amine–imine (K_T^{AI}) and lactam–lactim (K_T^{LL}) equilibium constants and mutation frequencies (N_m) depending on R_{NHN} (R_{NHO}) of the proton exchange in the cytosine–guanine pair.

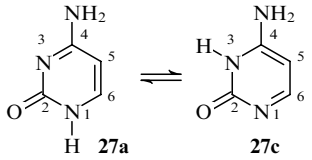
R_{NHN} (R_{NHO})	$\Delta\Delta H^{\#}$	$\Delta\Delta H$	K_T^{AI}	K_T^{LL}	N_m
3.00	282.6	65.6	1.51	2.16	0.33
2.95	274.6	75.2	1.90	3.00	0.57
2.90	238.7	75.2	2.19	3.38	0.74
2.85	211.5	64.2	2.34	4.28	1.00
2.80	183.1	66.9	3.15	4.83	1.52
2.75	157.6	58.5	3.35	5.50	1.84
2.70	140.9	66.0	4.17	6.70	2.79

because the constants K_T^{AI} and K_T^{LL} give the ratios between the imine and amine or lactim and lactam forms, respectively.

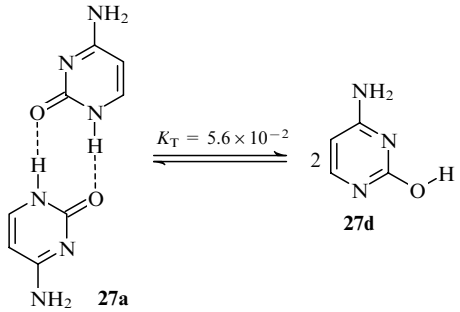
For some R, the mutation frequencies calculated by this equation (see Table 3) are substantially higher than the experimental values reported in the study.[96] However, it is known that experimental data obtained in studies of rapid processes proceeding at low concentrations of the compounds are sometimes of low accuracy.

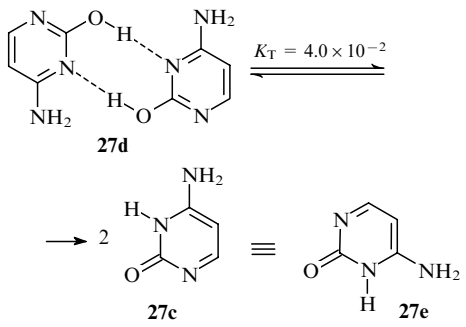
The influence of the solvent on the tautomeric equilibrium of nucleotide bases can be manifested in a deformation of the solvation cavity of the cytosine–guanine dimer, in particular, in a change in the length of the triad corresponding to an intermolecular hydrogen bond [R_{NHN} (R_{NHO})]. As can be seen from Table 3, a decrease in the length of the triad group in the dimer leads to a decrease in $\Delta\Delta H^{\#}$ resulting in an increase in K_T^{AI} and K_T^{LL} and, consequently, in an increase in N_m. However, the tautomeric equilibrium constant is inversely proportional to the polarity parameter E_T. Consequently, a nucleotide dimer is extended along the intermolecular hydrogen bond in a more polar solvent, whereas this dimer might be contracted in a less polar solvent. Hence, it can be concluded that more polar solvents decrease the spontaneous mutation frequency, whereas this frequency increases in less polar solvents. Since water serves as the solvent in mutation processes in DNA, this approach to modelling the influence of the solvent on the tautomeric equilibrium (see Section II) cannot be applied in the case under consideration. However, this approach may be useful for the qualitative description of scientifically created conditions.

In addition to prototropic tautomerism in DNA, prototropic rearrangements proceeding directly in nucleic acid bases deserve notice. Thus, the amine–imine equilibrium (**27a** → **27c**) in cytosine was considered.[105,106]



It is not difficult to understand that the $H^1 \rightarrow H^3$ proton transfer can proceed only through an intermolecular mechanism. In our opinion, this process involves two steps.





The first step represents the keto–enol (lactam–lactim) tautomerisation in compound **27a** with the proton transfer from the amino group to the carbonyl group through a dimeric mechanism. The second step involves the enol–ketone (lactim–lactam) tautomerisation in tautomer **27d** with the proton transfer from the hydroxy group to the imine N(3) atom. The activation enthalpies ($\Delta\Delta H^{\#}$) of the first and second steps are 157.8 and 107.8 kJ mol^{-1}, respectively. The total enthalpy of the overall process ($\Delta\Delta H^{\#}$) is 168 kJ mol^{-1}. The heat of reaction ($\Delta\Delta H$) is -5.0 kJ mol^{-1}. Consequently, the 1H → 3H proton transfer is an exothermic process. The rotation of tautomer **27c** about the C(2)–C(5) axis by 180° gives rise to an isomer of cytosine, *viz.*, 2-oxo-6-aminopyrimidine (**27e**). Hence, this transformation can be formally considered as the 1,3-shift of the amino group and a new type of a molecular rearrangement.

VII. Conclusion

It is often assumed that the proton transfer as well as other molecular rearrangements involved in prototropic tautomerisation proceed through an intramolecular mechanism. The results of modern studies show that this mechanism of proton transfer is sometimes both energetically and geometrically unfavourable. From this viewpoint, the so-called collective (dimeric, trimeric, tetrameric or oligomeric) mechanism seems to be more reasonable. The mechanism involving dimers works well in the case of the proton transfer to the *ortho* position. For the proton transfer to the *para* position, trimeric models are more adequate from the viewpoint of geometry. By contrast, a two-step proton transfer is more suitable for the description of tautomerism in compounds containing functional groups in the *meta* positions (as was accepted, for example, for imidazole).

The quantitative description of the prototropic equilibrium by purely chemical methods presents certain difficulties,[107] because the experimental parameters, which are necessary for calculating the equilibrium constants, are sometimes impossible to determine with a high degree of accuracy for compounds present at low concentrations. In this connection, the representation of K_T as a function of the orders of the bonds, which are cleaved and formed in the course of proton transfer, can be used for estimating the reliability of experimental data.

It should be noted that the approach proposed to modelling the influence of the solvent on the prototropic equilibrium is, to a certain extent, formal. However, the K_T–E_T correlation taking into account the polarity parameter of the solvent may be of practical use.

References

1. V M Bilobrov *Vodorodnaya Svyaz'. Vnutrimolekulyarnye Vzaimodeistviya* (Hydrogen Bond. Intramolecular Interactions) (Kiev: Naukova Dumka, 1991)
2. S F Tayyari, Th Zeegers-Huyskens, J L Wood *Spectrochim. Acta, Part A* **35** 1289 (1979)
3. S G Mills, P Beak *J. Org. Chem.* **50** 1216 (1985)
4. M S Gordon, R D Koob *J. Am. Chem. Soc.* **95** 5863 (1973)
5. M L Morris, D E Tallman, M S Gordon *J. Mol. Struct.* **34** 263 (1976)
6. W E Noack *Theor. Chim. Acta* **53** 101 (1979)
7. A I Kol'tsov, G M Kheifets *Usp. Khim.* **40** 1646 (1971) [*Russ. Chem. Rev.* **40** 773 (1971)]
8. G Klopman, P Andreozzi *Bull. Soc. Chim. Belg.* **86** 481 (1977)
9. A R Katritzky, A J Boulton (Eds) *Advances in Heterocyclic Chemistry. Suppl. 1* (New York: Academic Press, 1976)
10. J Toullec *Adv. Phys. Org. Chem.* **18** 1 (1982)
11. K H Meyer, P Kappelmeier *Berichte* **44** 2718 (1911)
12. D Lee, C K Kim, B-S Lee, I Lee, B C Lee *J. Comput. Chem.* **18** 56 (1997)
13. C-C Su, C-K Lin, C C Wu, M-H Lien *J. Phys. Chem. A* **103** 3289 (1999)
14. K Suenobu, M Nagaoka, T Yamabe *J. Mol. Struct. (THEOCHEM)* **461** 581 (1999)
15. J D Geerlings, C A Varma, M C van Hemert *J. Phys. Chem. A* **104** 7409 (2000)
16. S Masuda, K Minagawa, H Osoka, M Tanaka *Nippon Kagaku Kaishi* (8) 585 (2000); *Chem. Abstr.* **133** 237 545 (2000)
17. A F Hegarty, J P Dowling, S J Eustase, M Mc Garraghy *J. Am. Chem. Soc.* **120** 2290 (1998)
18. Yu Ya Fialkov, V L Gumak *Zh. Fiz. Khim.* **53** 885 (1979) [a]
19. G A Chalabiev, M M Guseinov, I R Akhverdiev *Zh. Fiz. Khim.* **54** 2101 (1980) [a]
20. J N Spenser, E S Holmboe, M R Kirshenbaum, D W Firth, P B Pinto *Can. J. Chem.* **60** 1178 (1982)
21. V V Prezhdo, N L Khimenko, Yu N Surov *Ukr. Khim. Zh.* **52** 57 (1986)
22. C Reichardt *Solvents and Solvent Effects in Organic Chemistry* (Weinheim: VCH, 1988)
23. K Dimrot, C Reichardt, T Stepmann, F Bollman *Liebigs Ann. Chem.* **661** 1 (1963)
24. M Moriyasu, A Kato, Y Hashimoto *J. Chem. Soc., Perkin Trans. 2* 515 (1986)
25. I I Kukhtenko, B V Chizhov, V K Pogorelyi *Teor. Eksp. Khim.* **10** 403 (1974) [b]
26. J A Kereselidze *Zh. Fiz. Khim.* **72** 144 (1998) [a]
27. W J Bouma, D Poppinger, L Radom *J. Am. Chem. Soc.* **99** 6443 (1977)
28. J Andres, L R Domingo, M T Picher, V S Safont *Int. J. Quant. Chem.* **66** 9 (1998)
29. P Beak, J B Covington, S G Smith *J. Am. Chem. Soc.* **98** 8284 (1976)
30. R Nakamura, K Masuda, S Hayashi *J. Mol. Struct.* **146** 101 (1986)
31. T M Ivanova, K Ya Burshtein, L I Mizrakh, A M Vasil'ev, A N Gvozdetskii *Khim. Geterotsikl. Soedin.* 981 (1989) [c]
32. B J Smith, M Th Nguye, W J Bouma, L Radom *J. Am. Chem. Soc.* **113** 6452 (1991)
33. C-C Wu, M-H Lien *J. Phys. Chem.* **100** 594 (1996)
34. T Sugawara, I Takasu *Adv. Phys. Org. Chem.* **32** 219 (1999)
35. R Gawinecki, E D Raczynska, D Rasala, S Styrcz *Tetrahedron* **53** 17 211 (1997)
36. J A Kereselidze, Sh A Samsoniya, M A Tsikoliya *Khim. Geterotsikl. Soedin.* **8** 1092 (1995) [c]
37. J A Kereselidze *Izv. Akad. Nauk Gruzii, Ser. Khim.* **19** 317 (1993)
38. J A Kereselidze *Khim. Geterotsikl. Soedin.* 752 (1999) [c]
39. R W Lawer *Chem. Rev.* **63** 489 (1963)
40. P Bourbon, P Dorbes, A Lattes, Ph Puig *Bull. Soc. Pharm. (Marseille)* **15** 289 (1967)
41. M Ahlbrecht, S Fischer *Tetrahedron* **26** 4777 (1970)
42. A Savignac, A Lattes *C. R. Hebd. Seances Acad. Sci, Ser. C* **272** 1623 (1971)
43. L Duhamel, P Duhamel, J-C Legal *Bull. Soc. Chim. Fr.* 3230 (1972)
44. A Savignas, M Bon, A Lattes *Bull. Soc. Chim. Fr.* 3167 (1972)
45. H Ahlbrecht *Tetrahedron Lett.* 4421 (1968)
46. H Ahlbrecht *Tetrahedron Lett.* 545 (1971)
47. N M Przheval'skii, M E Kletskii, I I Grandberg, L Yu Kostromina *Khim. Geterotsikl. Soedin.* 779 (1985) [c]
48. J A Kereselidze, N I Raevskii, Yu A Borisov *Izv. Akad. Nauk, Ser. Khim.* 202 (1993) [d]
49. B A Shainyan, A N Mirskova *Usp. Khim.* **48** 201 (1979) [*Russ. Chem. Rev.* **48** 107 (1979)]

50. I I Grandberg, T I Zuyanova, N M Przheval'skii, V I Minkin *Khim. Geterotsikl. Soedin.* 750 (1970) [c]
51. N C Baird, M J S Dewar *J. Chem. Phys.* **50** 1262 (1969)
52. J A Kereselidze, M A Tsikoliya, Sh A Samsoniya *Soobshch. Akad. Nauk Gruzii* **147** 408 (1993)
53. M R Grimmett, in *Comprehensive Organic Chemistry* Vol. 4 (Eds D Barton, W D Ollis) (Oxford: Pergamon Press, 1979)
54. H Zimmermann *Z. Electrochim.* **65** 821 (1961)
55. G Zundel, J Muehlinghaus *Z. Naturforsch., B: Chem. Sci.* **26** 546 (1971)
56. Yu A Teterin, L N Nikolenko *Dokl. Akad. Nauk SSSR* **210** 1382 (1973) [e]
57. A N Nesmeyanov, E B Zavelovich, V N Babin, N S Kochetkova, E I Fedin *Tetrahedron* **31** 1461 (1975)
58. Yu A Borisov, N P Vorob'eva, I A Abronin, A F Kolomiets *Izv. Akad. Nauk SSSR, Ser. Khim.* 2779 (1988) [d]
59. L A Fedorov, P Savarino, G Viskardi, A I Rebrov, E Borni *Izv. Akad. Nauk, Ser. Khim.* 299 (1992) [d]
60. B S Hickman, M Mascal, J J Titman, I G Wood *J. Am. Chem. Soc.* **121**11486 (1999)
61. G-S Li, M F Ruiz-Lopez, M-S Zhang, B Maigret *J. Mol. Struct. (THEOCHEM)* **422** 197 (1998)
62. S O Chua, M J Cook, A R Katritzky *J. Chem. Soc. B* 2350 (1971)
63. P Jimenez, J Laynez, R M Claramunt, D Sanz, J P Fayet, M C Vertut, J Catalan, J L G De Paz, G Pfister-Guillouzo *New J. Chem.* **13** 151 (1989)
64. F Peral, E Gallego *J. Mol. Struct.* **415** 187 (1997)
65. T J Kikalishvili, J A Kereselidze *Khim. Geterotsikl. Soedin.* 1225 (2002) [c]
66. J Berthou, J Elguero, C Rérat *Acta Crystallogr., Sect. B* **26** 1880 (1970)
67. A Baldy, J Elguero, R Faure, M Pierrot, E-J Vincent *J. Am. Chem. Soc.* **107** 5290 (1985)
68. J A S Smith, B Wehrle, F Aguilar-Parrilla, H-H Limbach C Foces-Foces, F H Cano, J Elguero, A Baldy, M Pierrot, M M T Khurshid, J-B Larcombe-McDouall *J. Am. Chem. Soc.* **111** 7304 (1989)
69. F Aguilar-Parrilla, C Cativiela, M D D de Villegas, J Elguero, C Foces-Foces, J I G Laureiro, F H Cano, H-H Limbach, J A S Smith, C Toiron *J. Chem. Soc., Perkin Trans. 2* 1737 (1992)
70. F Aguilar-Parrilla, G Scherer, H-H Limbach, C Foces-Foces, F H Cano, J A S Smith, C Toiron, J Elguero *J. Am. Chem. Soc.* **114** 9657 (1992)
71. A L Llamas- Saiz, C Foces-Foces, F H Cano, P Jimenez, J Laynez, W Meutermans, J Elguero, H-H Limbach, F Aguilar-Parrilla *Acta Crystallogr., Sect. B* **50** 746 (1994)
72. C Foces-Foces, L Llamas- Saiz, R M Claramunt, C Lopez, J Elguero *J. Chem. Soc., Chem. Commun.* 1143 (1994)
73. F Aguilar-Parrilla, H-H Limbach, C Foces-Foces, F H Cano, N Jagerovic, J Elguero *J. Org. Chem.* **60** 1965 (1995)
74. A L Llamas- Saiz, C Foces-Foces, I Sobrados, J Elguero, W Meutermans *Acta Crystallogr., Sect. C* **49** 724 (1993)
75. B Beagley, K J Farnworth, E T Moss, R G Pritchard, S Tajammal, A E Topping *Acta Crystallogr., Sect. C* **50** 1130 (1994)
76. A R Katritzky *Chimia* **24** 134 (1970)
77. J Frank, A R Katritzky *J. Chem. Soc., Perkin Trans. 2* 1428 (1976)
78. Yu N Sheinker *Izv. Sib. Otd. Akad. Nauk, Ser. Khim. Nauk* (2) 37 (1980)
79. H Besso, K Iamafuku, H Matsumura *Bull. Chem. Soc. Jpn.* **50** 710 (1977)
80. A Lledós, J Bertrán *Tetrahedron Lett.* **22** 775 (1981)
81. M Chevrier, J Giellerez, J-E Dubois *J. Chem. Soc., Perkin Trans. 2* 979 (1983)
82. J Merek, A Sugua *J. Mol. Struct. (THEOCHEM)* **86** 85 (1981)
83. H B Schlegel, P Gund, E M Fluder *J. Am. Chem. Soc.* **104** 5347 (1982)
84. M J Field, I H Hillier *J. Chem. Soc., Perkin Trans. 2* 617 (1987)
85. W H Fabian *J. Comput. Chem.* **12** 17 (1991)
86. M Szafran, M M Karelson, A R Katritzky, J Koput, M C Zerner *J. Comput. Chem.* **14** 371(1993)
87. J A Kereselidze, T Sh Zarqua *Khim. Geterotsikl. Soedin.* 1342 (2000) [c]
88. J Smets, G Maes *Chem. Phys. Lett.* **187** 532 (1991)
89. M D Topal, J R Fresko *Nature (London)* **263** 285 (1976)
90. O K Abou-Zied, R Jimenez, F E Romesberg *J. Am. Chem. Soc.* **123** 4613 (2001)
91. P Löwdin *Adv. Quant. Chem.* **2** 213 (1976)
92. W Seanger *Principles of Nucleic Acid Structure* (New York, Berlin: Springer, 1983)
93. J Florian, V Hrouda, P Hobza *J. Am. Chem. Soc.* **116** 1457 (1994)
94. E A Grebneva *Ukr. Fiz. Zh.* **37** 1636 (1992)
95. J W Drake, in *The Molecular Basis of Mutation* (San Francisco: Holden-Dey, 1970) p. 59
96. M F Goodman *Nature (London)* **378** 237 (1995)
97. P Strazewski, C Tamm *Angew. Chem., Int. Ed. Engl.* **29** 36 (1990)
98. J P Lewis, O F Sankey *Biophys. J.* **69** 1068 (1995)
99. M Hutter, T Clark *J. Am. Chem. Soc.* **118** 7574 (1996)
100. M Meyer, J Suhnel *J. Biomol. Struct. Dyn.* **15** 619 (1997)
101. J Bertran, A Oliva, L Rodriguez-Santiago, M Sodupe *J. Am. Chem. Soc.* **120** 8159 (1998)
102. R Czerminski, J S Kwiatkowski, W B Person, K Szczepaniak *J. Mol. Struct.* **198** 297 (1989)
103. L Gorb, J Leszczynski *J. Am. Chem. Soc.* **120** 5024 (1998)
104. J Leszczynski *J. Phys. Chem. A* **102** 2357 (1998)
105. T K Ha, H-J Keller, R Gunde *J. Phys. Chem. A* **103** 6612 (1999)
106. P U Civcir *J. Mol. Struct. (THEOCHEM)* **532** 157 (2000)
107. A R Katritzky, M Karelson, Ph A Harris *Heterocycles* **32** 329 (1991)

[a] — *Russ. J. Chem. Phys. (Engl. Transl.)*
[b] — *Theor. Exp. Chem. (Engl. Transl.)*
[c] — *Chem. Heterocycl. Compd. (Engl. Transl.)*
[d] — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*
[e] — *Chem. Dokl. (Engl. Transl.)*