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Review Commentary

Intramolecular hydrogen bonding in *o*-hydroxyaryl Schiff bases†

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ABSTRACT: This review deals with selected aspects of research on *o*-hydroxyaryl Schiff bases. Special attention is given to results obtained by x-ray, IR, UV and NMR spectroscopic methods and quantum-mechanical calculations that allow a better understanding of the nature of *o*-hydroxyaryl Schiff bases. The paper reports on studies of sterically modified *o*-hydroxyaryl Schiff bases with an intramolecular hydrogen bond made short owing to steric repulsion. The following points are focused upon: structural and energetic analysis of the steric effect and its influence on the hydrogen bond length; proton localization and the proton transfer process; the impact of proton transfer on the chelate and phenol rings in the intramolecular hydrogen bond; a generalized scheme of tautomer equilibrium and its study with the use of experimental and theoretical methods; some discrepancies found in standard parameters for a particular tautomeric form; calculations of the potential energy curve for basic tautomer forms; influence of the steric effect on the potential curve shape; and a review of semi-empirical and quantum-mechanical calculations of molecular structures in the ground state. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: intramolecular hydrogen bonding; proton transfer; *o*-hydroxyaryl Schiff base; ketimine; steric effect; aromaticity

INTRODUCTION

Steric effect research has seen major advances in the last decade, with important contributions from Exner's group.[1–12] This paper focuses on several aspects of the *o*-hydroxyaryl Schiff bases research. The paper focuses on the intramolecular hydrogen bond of the O—H···N type which forms between the hydroxyl group of the phenol ring (the proton donor) and the nitrogen atom of the imine (the proton acceptor) (Scheme 1). In the literature,[13–20] a wide range of applications of Schiff bases has been revealed both by theoretical and experimental investigations. The following nomenclature is used in this paper: aldimines refer to compounds where R_1 is hydrogen; ketimines refer to compounds where R_1 is an alkyl or aryl group (Scheme 1). Both aldimines and ketimines refer to Schiff bases. To simplify the text, '*o*-hydroxyaryl' is omitted in further discussion.

The imine formation mechanism that actively participates in physiological tempering of the human immune system has attracted conciderable attention from immunologists in the last decade.[21–29] The series of *N*-hydroxy-N^1-aminoguanidines can serve as an example of aldimines with antitumor and antiviral properties[30–35] and those fighting or slowing leukaemia cell growth.[36,37] Also, ketimines with a bulky naphthyl or phenyl substituent at the imine group influence the central nervous system, regulating its activity in a special way.[38,39] Two main functions are considered to describe the bulky substituent. The outside function is to defend the acid–base centre (e.g. propyl or butyl moieties, leading to weakening of hydrogen bonding[40]) from the environment and the inside function (inductive and mesomeric effects) is to change the acid–base characteristics of the hydrogen bridge. An elaborate study was conducted of the biologically active series of 2-(α-alkoxyimino)benzylpyridine and its *N*-oxide derivatives as K^+ channel openers, which are very promising in treating serious diseases, e.g. hypertension, angina pectoris, urinary incontinence and asthma. The greatest potential activity of the series of compounds was found to be triggered by a bulky *tert*-butoxy group attached to the nitrogen atom.[41] Substitution by this group enhances the steric repulsion between the *tert*-butoxy group and the pyridine ring substituted in the imine group of Schiff bases. Such an interaction indirectly corroborates the importance of the above-mentioned functions' participation in biological processes.

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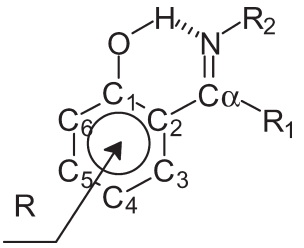


Scheme 1. Structure of *o*-hydroxyaryl Schiff bases

STERIC ASPECT

Schiff bases are of a great interest to crystallographers' as demonstrated by the presence of >300 solved crystallographic structures in the Cambridge Structural Database (CSD).[42] Crystal structure research is a very important aspect of predicting the photo- and thermochromic properties of Schiff bases. Since the pioneering work of the groups of Schmidt[43] and Pfluger[44] over 40 years ago, the discussion of the dependences between structural parameters of the molecules and the packing of the molecule in a unit cell is still in progress.

Our group[45] presented a correlation of the *d*(OH) and *d*(HN) distances with the hydrogen bond length for Schiff bases in a way typical for systems revealing proton transfer equilibrium.[46–49] Two curves of the above-mentioned correlation were obtained (Fig. 1), one for aldimines and the other for ketimines. The curve lying below 2.5 Å refers to a special class of Schiff bases where the hydrogen bridge is extremely shortened owing to the steric effect. Hence the existence of two types of Schiff bases was postulated, being conditioned by a certain type of hydrogen bonding. We further scrutinized the influence of the steric effect on regulation of the hydrogen bridge length.[45,50–54]

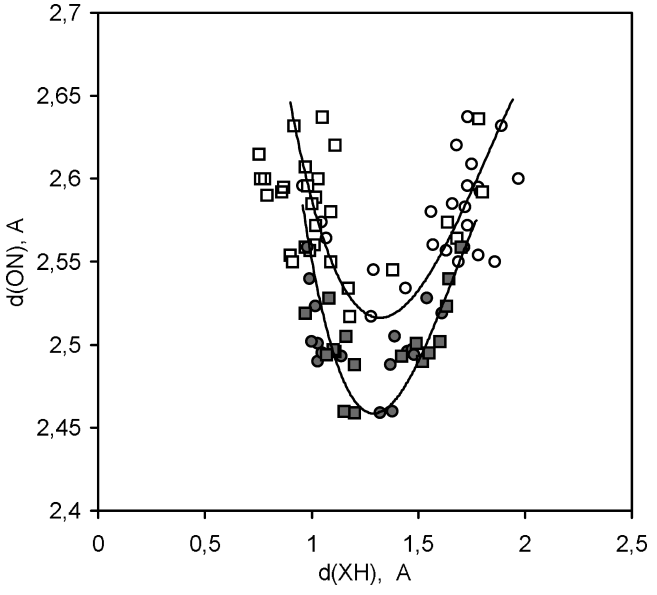
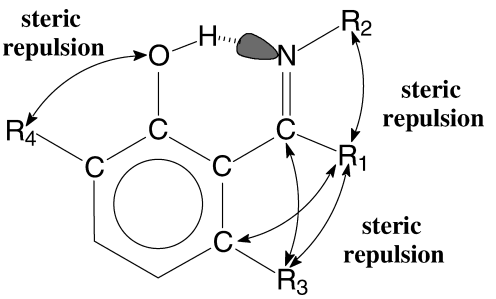


Figure 1. Scatter plot in the [*d*(OH), *d*(ON)] (□) and [*d*(HN), *d*(ON)] (○) space for crystallographic data for Schiff bases.[42] Shaded symbols concern the results with steric substitution. Reprinted with permission from Ref. 45. Copyright 2002 The Royal Society of Chemistry

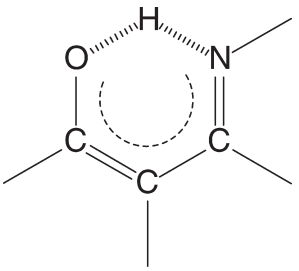
The specific difference between the ketimine and aldimine structures is the localization of the proton at two equally possible positions, at the nitrogen atom and the oxygen atom,[55–57] for aldimines, whereas such alternative locations of the proton have not been discovered in ketimines so far. In ketimines, the proton is preferably localized in the centre of the hydrogen bridge.[45,50,51]

The impact of the steric effect on the hydrogen bond strength has been referred to in a few papers.[58–60] Applying NMR spectroscopy, Hansen *et al.*[58] observed a low-field shift of the OH resonance in *o*-hydroxyacylaromatics caused by a deutero substitution in the methyl group. This experimental phenomenon was explained by weakening of the steric compression of the deuteromethyl group (CD_3) with respect to the protiomethyl group (CH_3). Therefore, the reduction of the twist angle of the methyl group brings about both strengthening of the hydrogen bond and prevailing of the negative isotopic effect, $\Delta\delta(^1H)$. In investigations of the *cis*- and *trans*-isomers of urocanic acid, Cloninger and Frey[59] confirmed the supposition that steric strain in the bromo- and chloro-substituted derivatives affects the basicity of the imidazole ring in the *cis*-isomers with the intramolecular hydrogen bond. One of the most convincing explanations of this fact is the shortening and, consequently, reinforcement of the intramolecular hydrogen bond caused by steric repulsion, which hinders the removal of a proton from the hydrogen bond and, therefore, enhances the pK_a value.[59] However, the opposite conclusion was drawn by Schmiedekamp-Schneeweis and Payne,[60] where quantum-mechanical calculations suggested hydrogen bond attenuation by means of steric compression of either a methoxy, methyl, naphthyl, nitro or *tert*-butyl group on the proton-acceptor part (the methoxy group).

It is important to keep in mind that in ketimines two counteracting steric processes take place, one between the R_1 and R_2 groups and the phenol ring (Scheme 2) and the other between the donor and acceptor groups. It is obvious that the opposition between the two steric



Scheme 2. Directions of steric repulsion between particular fragments in Schiff bases



Scheme 3. Structure of pseudo-aromatic ring in *o*-hydroxyaryl Schiff bases

repulsions should result in the nitrogen atom being forced out from the plane of the phenol ring. However, this deflection does not occur between the imine and phenol moieties owing to strong conjugation, thereby forming a six-membered pseudo-aromatic ring (Scheme 3). The steric effect in ketimines is likely to shorten the hydrogen bridge or lead to breaking of the intramolecular hydrogen bond by the extremely strong repulsion (e.g. $R_1 = CF_3$).[61] However, Mannich bases, structurally resembling Schiff bases, are characterized by rather weak conjugation between the nitrogen atom and the phenol ring owing to 'isolation' of the methylene bridge.[62] Thus, in Mannich bases the steric effect can be expressed unpredictably in defferent ways. First, it can shift the nitrogen atom in the direction of the oxygen atom, thus shortening the hydrogen bridge.[63] Second, it induces a stronger declination of the nitrogen atom from the plane of the phenol ring, weakening the intramolecular hydrogen bond.

However, in 2-(*N*-R_2-α-iminoalkyl)phenols the steric effect is combined with the inductivity effect of the electron-donor alkyl group that brings about both an increase in the electron density on the proton acceptor and strengthening of the hydrogen bond. To corroborate the decisive role of the steric effect in hydrogen bond shortening, we replaced the alkyl group with an electron-acceptor aryl group ($R_1 = C_6H_5$) able to diminish electron density of the nitrogen atom and, thus, to attenuate the hydrogen bond strength.[64] It should be emphasized that crystallographic studies of *o*-hydroxybenzophenone derivatives provide evidence of shortening of the hydrogen bridge length [e.g. d(ON) = 2.496, 2.488 Å;[64] d(ON) = 2.497, 2.465, 2.487 Å[65]) with respect to the analogous aldimines. X-ray crystallographic studies[16,66] of charge-transfer complexes of aldimines with 7,7,8,8-tetracyanoquinodimethane, 2,3,5,6-tetrafluoro-7,7,8,8-tetracyanoquinodimethane revealed a pronounced correlation between charge-transfer interactions and hydrogen bonding, i.e. an increase in intermolecular overlapping of π-orbitals and, consequently, alteration of the net charge on the pseudo-aromatic ring brings about shortening of the hydrogen bond to give an extremely short bond for aldimines [d(ON) = 2.496 Å].

The most convincing argument in favour of the impact of the steric effect on the hydrogen bridge length is analysis based on comparison of crystallographic structures, where one of the structures possesses a definitely pronounced steric effect. The particular examples presented in Scheme 4 show the impact of steric substitution on shortening of the hydrogen bridge length in the sequence H (2.587 Å), C_6H_5 (2.528 Å), CH_3 (2.497 Å), C_2H_5 (2.494 Å), and also linearization of the hydrogen bridge (the OHN angle increased by 10°). The same tendency is found for both the OH and NH forms.

Structural–energetic analysis of the steric effect

A structural–energetic analysis method can be applied for a quantitative estimation of the impact of steric interactions on the hydrogen bond. According to this method, the energy of tensions in a molecule can be estimated as a sum of the energies of non-valence interactions and angle deformations [Eqn (1)]: the energy of interaction between the nitrogen atom and the oxygen atom ($E^{st}_{O\cdots N}$), the energy of interaction in the fragment $C_6H_4(R_3)$—$C(R_1)$═NR_2 ($E^{st}_{R_i,R_j}$), the energy of angle deformation (E^{def}_{α}) and the energy of torsional angle deformation (E^{twist}_{θ}):

$$E^{st} = E^{st}_{R_i,R_j} + E^{def}_{\alpha} + E^{st}_{O\cdots N} - E^{twist}_{\theta} \qquad (1)$$

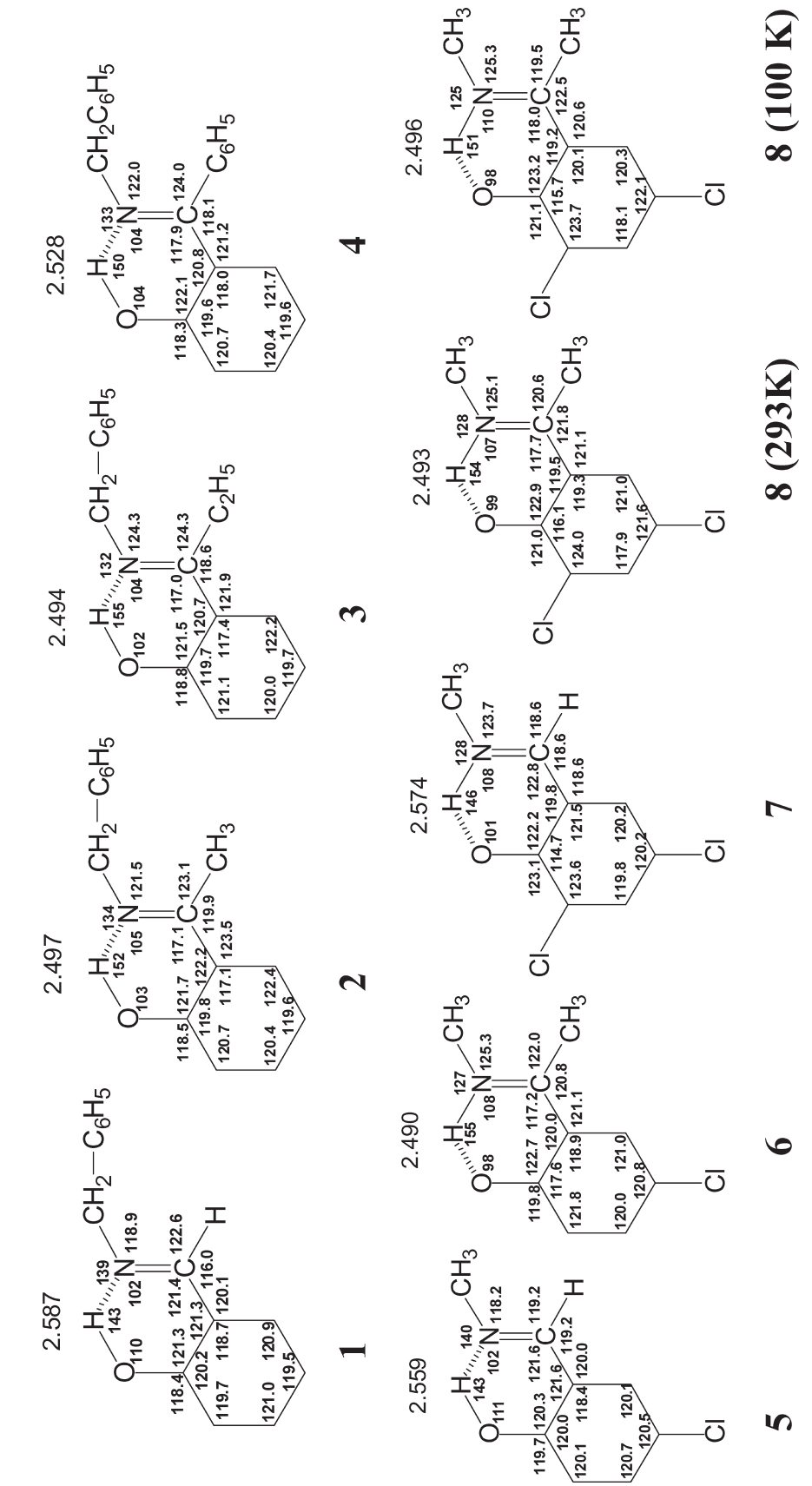
The meaning of the steric repulsion energy in the fragment —$C(R_1)$═NR_2 can be obtained with the help of the modified Buckingham potential of van der Waals:

$$E^{st}_{R_iR_j} = \sum_{i,j=1}^{N} \varepsilon_{ij} \times \left[A_{ij} \times \exp\left(-B_{ij} \times \frac{r_{ij}}{r_v} \right) - \frac{C_{ij}}{\left(\frac{r_v}{r_{ij}}\right)^6} \right] \qquad (2)$$

where r_{ij} is the interatomic distance between the two interacting atoms, r_v is the sum of the van der Waals radii of the adjacent atoms,[69] A_{ij}, B_{ij} and C_{ij} are adjustable parameters and ε_{ij} is the energy scale factor for each atom pair.[70,71] Counteractions of the O···N type require one to take into account their ionic character and to apply an additional component, $q_O\ q_N/r_{ON}$ (where q_O, q_N and r_{ON} are charges and distance of the interacting atoms, respectively),[72] in Eqn (2). The energy of the angle deformation is estimated according to the equation.

$$E^{def}_{\alpha} = \frac{1}{2}\sum_{i=1}^{N} C_i(\alpha_0 - \alpha_i)^2 \qquad (3)$$

where C_i is the elasticity constant[73] and $\Delta\alpha_i = \alpha_0 - \alpha_i$ is the deviation from the valence angle α_0. In 2-(methyliminophenylmethyl)phenols,[64] the phenyl ring is involved in steric tensions owing to rotation around the C_α—C_{ipso}



Scheme 4. Examples of structural data obtained by x-ray method[45,50,54,67,68]

Table 1. Energy of steric repulsion, E^{st} (kcal mol^{-1}), in steric squeezing fragment (Fig. 3) for selected compounds[45]

Substitution	$E^{st}_{R_i,R_j}$ non-bonded interactions		E^{st}_{α} deformation of angles	E^{st} total	
	MM3	MM2		MM3	MM2
$R_1 = R_2 = CH_3$; $R_3 = H$	3.98	4.65	3.80	7.78	8.45
$R_1 = CH_3$; $R_2 = CH_2C_6H_5$; $R_3 = H$	4.15	4.31	2.94	7.09	7.25
$R_1 = R_2 = CH_3$; $R_3 = p$-Cl	3.85	3.48	2.74	6.59	6.22
$R_1 = CH_3$; $R_2 = C_3H_7$; $R_3 = p$-Cl	3.90	3.50	3.14	7.04	6.64
$R_1 = CH_3$; $R_2 = C_2H_5$; $R_3 = m$-CH_3, p-Cl	3.82	3.49	2.94	6.76	6.43
$R_1 = CH_3$; $R_2 = C_3H_7$; $R_3 = m$-CH_3; p-Cl	3.91	3.09	4.04	7.95	7.13
$R_1 = C_2H_5$; $R_2 = CH_2C_6H_5$; $R_3 = H$	4.82	5.93	3.14	7.96	9.07
$R_1 = H$; $R_2 = CH_3$; $R_3 = p$-Cl	1.99	2.29	—	1.99	2.29
$R_1 = H$; $R_2 = CH_3$; $R_3 = o$, p-di-Cl	1.40	1.39	—	1.40	1.39
$R_1 = H$; $R_2 = CH_2C_6H_5$; $R_3 = H$	1.48	1.54	—	1.48	1.54

axis. The energy spent on the steric rotation is estimated according to the equation

$$E_{\theta}^{twist} = \sum_i \frac{E_0^{twist}}{2}(1 - \cos 2\theta_i) \qquad (4)$$

where E_0^{twist} is a stable constant for the phenyl ring rotation in a conjugated system and θ_i is the angle of rotation.

As stated earlier,[74] the definition of the energy of a thermodynamically stable intramolecular hydrogen bond is unlikely to be obtained by experiment. As a consequence, the definition of the energy needed to be spent on shortening the hydrogen bond length is very difficult. The steric repulsion energy between the nitrogen atom and the oxygen atom ($E^{st}_{O\cdots N}$) can be estimated with the application of the calculation method suggested by Lipkowski *et al.*[75] The values of the steric repulsion energy for the selected compounds are presented in Table 1.

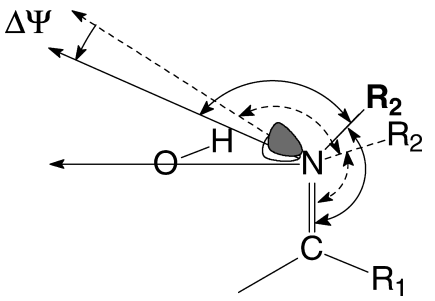
The strain between the oxygen atom and the R_4 fragment should also be taken into consideration, especially if the R_4 substituent is electronegative (e.g. chlorine, bromine, nitro group). For example, the strong tension in 2-(*N*-methyl-α-iminoethyl)-4-chloro-6-nitrophenol is the reason for the disruption of conjugation between the phenol moiety and the nitro group, and displacement of this group by 30° from the phenol ring plane. Two-sided steric pressure in the given compound results in linearization of the hydrogen bridge [α(OHN) = 167°] and keeps it fairly short [d(ON) = 2.501 Å], despite the expected elongation of the hydrogen bond length owing to the ionic character of this bond ($\Delta pK_a \approx 3$–4[76,77]). In similar aldimines the evidently ionic character of the hydrogen bond (according to the ΔpK_a value[78,79]) led to visible elongation of the ON distance [d(ON) = 2.638, 2.667 Å].[80] A short hydrogen bridge [d(ON) = 2.512 Å] in *N*-tetrachlorosalicylideneaniline was also explained as a result of steric repulsion of the chlorine atom (R_4 fragment) towards the oxygen atom.[81] In order to analyze the steric effect more completely, it is crucial to keep in mind also the influence of crystal packing[82] on the orientation of the interacting fragments.

The direction of a lone electron pair plays an essential role in the hydrogen bond and a linear hydrogen bridge[83–86] is optimal where a lone electron pair is placed on the OHN line. This type of location is mainly observed in strong complexes; however, these characteristics are hardly found in the intramolecular hydrogen bond systems under discussion. The important factor affecting the lone electron pair direction is the configuration of the $C_6H_4(R_3)$—$C(R_1)$=NR_2 fragment. Therefore, an increase in steric repulsion leads to the decrease in the angle formed by oxygen, nitrogen and the lone electron pair, thereby arranging a more optimal linear configuration of the hydrogen bridge (Scheme 5).

The OHN angle dependence on the O···N length can serve as a verification of the above-described phenomenon; this dependence shows that shortening of the hydrogen bond bridge goes along with its linearization (Fig. 2).

AROMATICITY AND PROTON TRANSFER

The proton transfer process in Schiff bases leads to alteration of the bond lengths in the whole molecule



Scheme 5. Diagram of direction change of a lone electron pair on alteration of the imine fragment geometry caused by steric repulsion. Reprinted with permission from Ref. 51. Copyright 2002 Elsevier

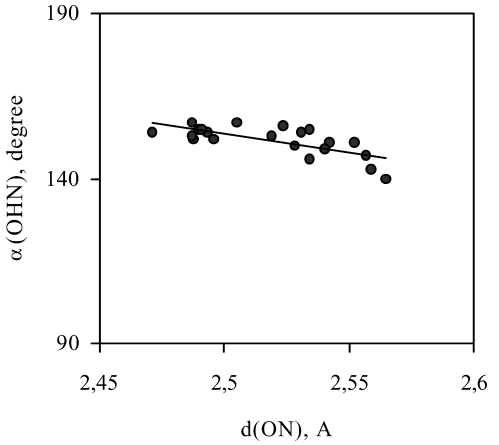


Figure 2. Correlation of the OHN angle on the *d*(ON) distance for crystallographic data for ketimines[42]

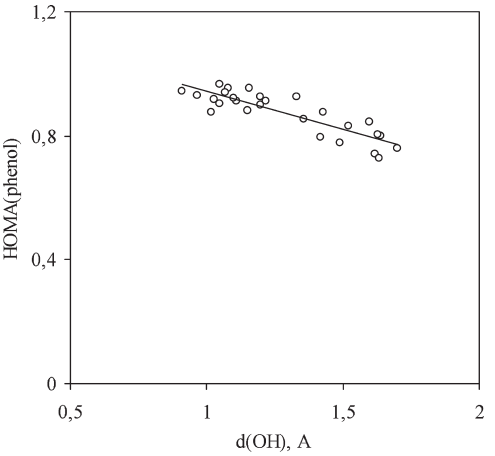


Figure 3. The HOMA(phenol) aromaticity index versus the *d*(OH) bond length for crystallographic data for ketimines.[42] Reprinted with permission from Ref. 94. Copyright 2005 John Wiley & Sons, Ltd

and, as a consequence, to a change in tautomeric equilibrium. Recently, this phenomenon has been accurately reinvestigated over a wide range of temperatures with an x-ray method.[87] The impact of the proton transfer process on aromatic and pseudo-aromatic rings of a molecule is an attractive topic of investigation with respect to photo- and thermochromic properties. The most appropriate way to demonstrate the influence of the proton transfer process on the aromaticity of the phenol ring and pseudo-aromaticity of the donor—C═C—C═ acceptor chain is the application of the HOMA (harmonic oscillator measure of aromaticity) aromatic index [Eqn (5)[88]] describing the impact of substitution on distortion of aromaticity,[89–91] and the HOSE (harmonic oscillator stabilization energy) index [Eqn (6)[92]] corresponding to the stabilization energy of the pseudo-aromatic moiety:

$$\mathrm{HOMA} = 1 - \frac{\alpha}{n}\sum \left(R_{\mathrm{opt}} - R_i\right)^2 = 1 - \left[\alpha\left(R_{\mathrm{opt}} - R_{\mathrm{av}}\right)^2 + \frac{\alpha}{n}\sum \left(R_{\mathrm{av}} - R_i\right)^2\right] \quad (5)$$

$$\mathrm{HOSE} = 301.15 \times \left[\sum \left(R_i' - R_0^{\mathrm{s}}\right)^2 \left(a + bR_i'\right) + \sum \left(R_i' - R_0^{\mathrm{d}}\right)^2 \left(a + bR_i''\right)\right] \quad (6)$$

where R_{av} is an averaged bond length, n is the number of bonds, α is an empirical constant, R_i is an individual bond length and R_{opt} is an optimal bond length.[93]

To scrutinize the character of this impact, two correlations, HOMA(phenol) = *f*[*d*(OH)] (Fig. 3) and HOMA(phenol) = *f*(HOSE) (Fig. 4) are considered.[94] The first correlation illustrates that the proton transfer process (OH bond elongation) causes dearomatization of the phenol ring (decrease in the HOMA index). The second exhibits the linear connection of the dearomatization of the phenol ring with the energy required for stabilization of the pseudo-aromatic moiety. What rests on the aforesaid facts is the inference that the proton transfer process induces the simultaneous dearomatization of the phenol ring and the destabilization of the pseudo-aromatic moiety.

The most elaborate analysis of the structural parameters for ketimines[51] and aldimines[56] reveals that the most reliable parameter appears to be the CO bond length, which also reflects the proton transfer process {HOMA(phenol) = *f*[*d*(CO)]} (Fig. 5). Therefore, the structural–aromatic analysis manifests relations between the phenol and chelate moieties, these relations being described by the state of the proton transfer equilibrium.

The *Q* parameter[95] could also be made use of to describe the pseudo-aromatic ring state; this parameter is the sum of differences of the chelate ring bonds and depends on the proton localization. Therefore, the *Q* parameter can be applied to determine the tautomeric

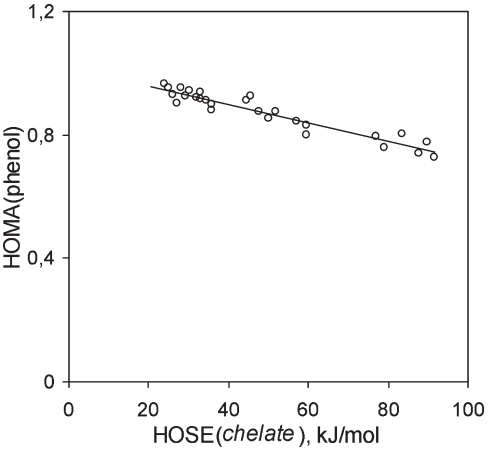


Figure 4. The HOMA(phenol) aromaticity index versus the HOSE(chelate) destabilization index for crystallographic data for ketimines.[42] Reprinted with permission from Ref. 94. Copyright 2005 John Wiley & Sons, Ltd

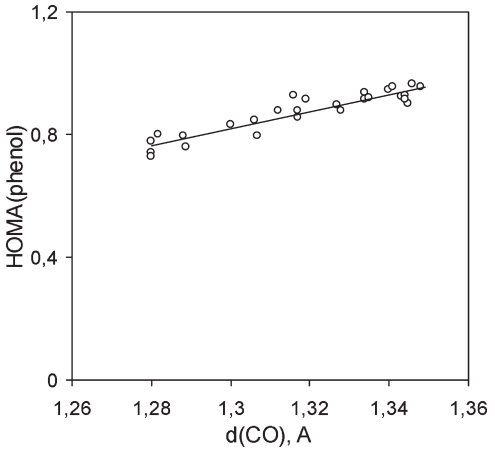


Figure 5. The HOMA(phenol) aromaticity index versus the *d*(CO) bond length for crystallographic data for ketimines.[42] Reprinted with permission from Ref. 94. Copyright 2005 John Wiley & Sons, Ltd

form in compounds with a resonance-assisted hydrogen bond (RAHB). The values of this parameter for the enol and keto forms were obtained by means of a set of standard bond lengths[96] for each particular tautomeric form.[68]

QUANTUM-MECHANICAL CALCULATION OF SCHIFF BASES

To identify clearly the nature of physicochemical processes occurring in the intramolecular hydrogen bond of Schiff base, the results of semi-empirical and *ab initio* calculations were considered.[97–101] In these studies, the following parameters were assumed as a basis for inspection of the proton transfer process: adiabatic and non-adiabatic potentials and the change in dipole moment and point charge on extension of the hydroxyl bond length. Important discrepancies between the intra- and intermolecular hydrogen bridges (complexes of phenols with *N*,*N*-dimethylbenzylamine or *N*-methylidenebezylamine, Mannich bases and aldimines) were examined.[97] One of the differences is in the hydrogen bond geometry, namely the intermolecular hydrogen bond appears to be more linear than the intramolecular hydrogen bridges in the aldimines and Mannich bases, as established experimentally[62,86] and from quantum-mechanical calculations.[97] The second phenomenon is a distinction of the intramolecular hydrogen bridges a with lack of conjugation between acid and base centres (e.g. Mannich bases) from those with a pseudo-aromatic ring (e.g. Schiff bases) (Fig. 6). Whereas the experimental data confirm a similarity of both phenomena for the aldimine and ketimine analogues [points that characterize both ketimines and aldimines lie on one line (Fig. 7)], spectroscopic data reveal stronger hydrogen bonds in the ketimines, confirmed by the adiabatic potentials for both Schiff bases (Fig. 8).[45]

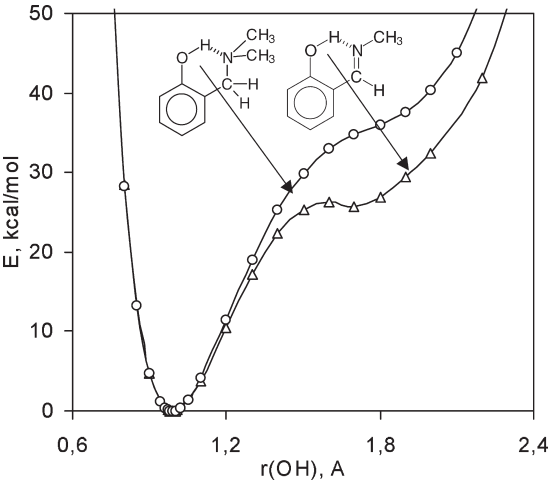


Figure 6. Adiabatic potential curves for the proton movement for 2-(*N*-dimethylaminomethyl)phenol (○) (Mannich base) and 2-(*N*-methyliminomethyl)phenol (Δ) (aldimine) at the MP2/6–31G(d,p) level[97]

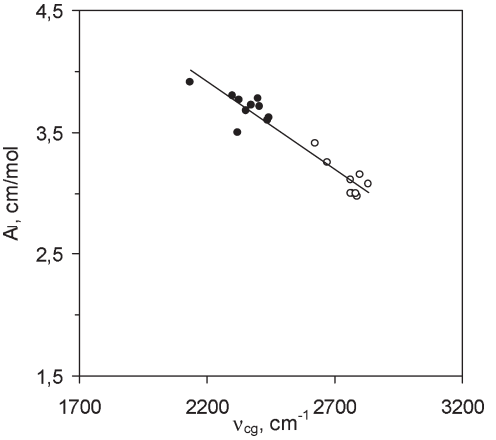


Figure 7. Integrated intensities (A_I) of stretching OH vibration versus the positions of gravity centres of the ν(OH) band. Closed and open circles correspond to ketimines and aldimines,[86] respectively

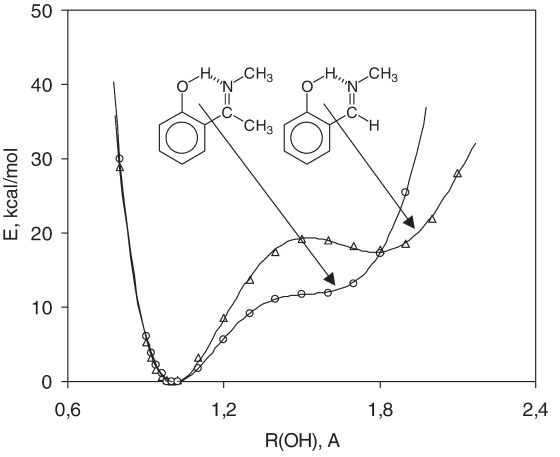


Figure 8. Adiabatic potential curves for proton movement for 2-(*N*-methyl-α-iminoethyl)phenol (○) (ketimine) and 2-(*N*-methyliminomethyl)phenol (Δ) (aldimine) at the B3LYP/6–31G(d,p) level.[45] Reprinted with permission from Ref. 45. Copyright 2002 The Royal Society of Chemistry

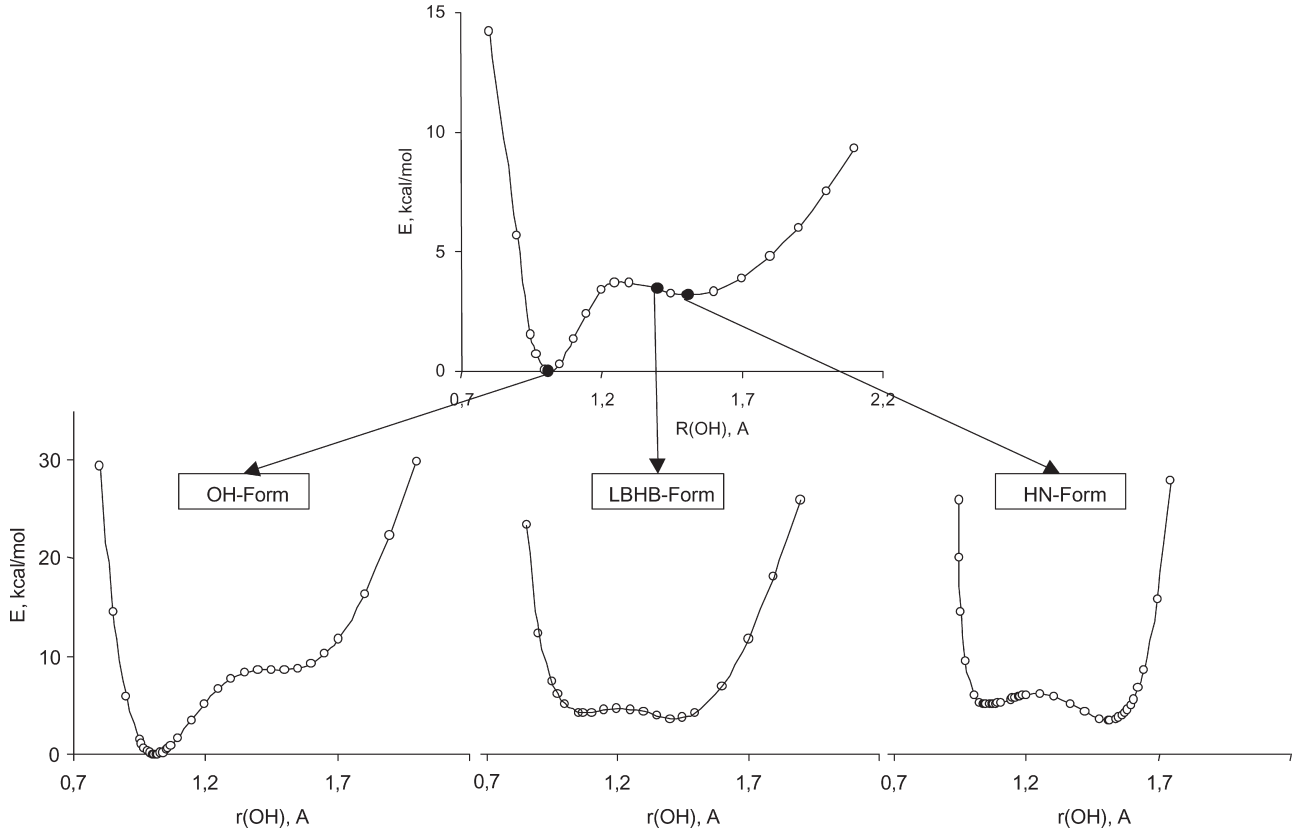


Figure 9. Adiabatic (bottom) and non-adiabatic (top) potential functions for proton displacement [B3LYP/6–31G(d,p) calculation] for 2-(*N*-methyl-α-iminoethyl)phenol. Reprinted with permission from Ref. 100. Copyright 2005 American Chemical Society

The difference between the potentials (the potential for ketimine is more symmetrical owing to a decrease in the energy minimum for the $^{-}O\cdots H—N^{+}$ state and its gradual approach to the global energy minimum for the O—H$\cdots$N state) undoubtedly corroborates the fact of the modification of the intramolecular hydrogen bond with steric effects involved.

One of the most noteworthy aspects of the hydrogen bond is the localization of the proton in the centre of the hydrogen bridge. The proton being a rather mobile particle, it possesses two most stationary states: the global one, close to the proton donor, and the local one, close to the proton acceptor. Further, the transition state seems to be particularly interesting, with the proton located in the centre of the hydrogen bond. The special interest in this type of hydrogen bond is due to the importance of its participation in biological processes[102–105] (it should be noted that opposing arguments have also been presented[106,107]). The necessary requirement for the existence of the transition state is that the main energy level is located in the vicinity of the potential barrier maximum between two stationary states or this barrier fails to occur. This phenomenon is called the low barrier of the hydrogen bond (LBHB) or Speackmann–Hadžy hydrogen bond. Experimental criteria for verification of this type of hydrogen bond have been elucidated.[108–110] A series of theoretical papers[111–113] and also studies of ketimines[100] (Fig. 9) deal with this aspect.

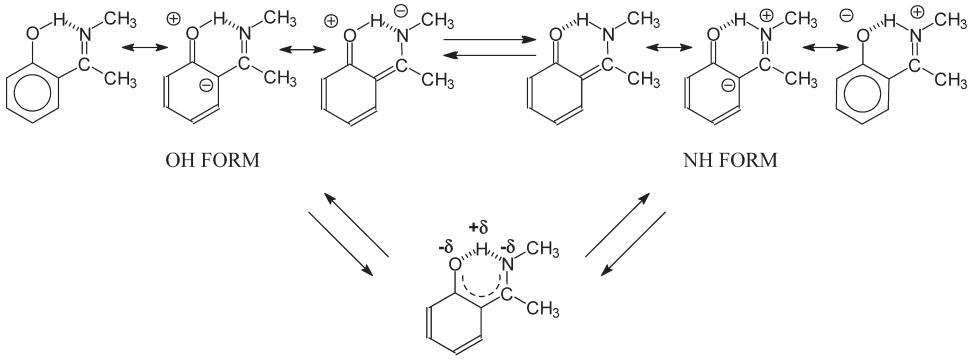
Quantum-mechanical calculations [B3LYP/6–311++G(d,p)] proved the height of the energy barrier for the proton transfer to be comparatively small (Table 2), and this supports the existence of LBHB in the ketimines.

NMR AND UV INVESTIGATIONS OF TAUTOMERIC EQUILIBRIUM

The proton transfer equilibrium (Scheme 6) in Schiff bases has been investigated by NMR spectroscopy.[114–130] The description of the NH tautomer by only a keto structure is not adequate, and therefore the procedure for description of the NH form needs the application of at least two resonance structures (keto and zwitterionic). To

Table 2. Calculated energy gap (kcal mol^{-1}) between proton transfer and molecular forms with variation of electric permittivity (ϵ)[100]

Method and basis set	$\varepsilon = 1.0$	$\varepsilon = 2.3$	$\varepsilon = 35.0$	$\varepsilon = 47.0$
B3LYP/6–311++G(d,p)	2.80	2.23	1.45	1.43



Scheme 6. Tautomeric equilibrium in Schiff bases

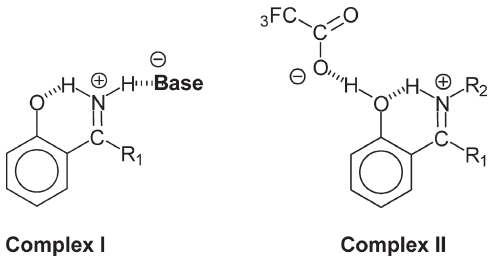
demonstrate the existence of the 'pure' zwitterionic structure, the proton transfer tautomeric equilibrium should be shifted in the direction of the boundary structure. It turned out that obtaining solely the zwitterionic structure was possible only in an additional complex with an active environment.[114,116]

Two different approaches to obtaining a complex of a Schiff base with an active environment have been presented.[114,116] The first approach is based on obtaining intermolecular hydrogen bonding between the imine group and an additional base (complex **I** in Scheme 7), which strongly enhances the nitrogen basicity, thus creating a zwitterionic structure. The second approach is based on creating intermolecular hydrogen bonding, but alternatively the oxygen atom interacts with an additional strong acid (complex **II** in Scheme 7). In both cases the cooperative effect results in a 'pure' zwitterionic structure. The application of these two approaches led to fairly concordant results.[114,116]

The calculation of values for two selected 'boarding' forms (e.g. enol–imine and zwitterionic) facilitates the estimation of the value of the equilibrium constant K_{PT}:

$$K_{PT} = \frac{A(X)_{obs} - A(X)_{OH}}{A(X)_{HN} - A(X)_{obs}} \qquad (7)$$

where $A(X)_{OH}$ and $A(X)_{HN}$ are boundary values for the enol and proton transfer forms, respectively, and $A(X)_{obs}$ is the magnitude observed. The dependence on temperature of the equilibrium constant K_{PT} provides an aid to defining thermodynamic parameters of the intramolecular hydrogen bond (ΔH°, ΔS°).[18,20,131–133]



Scheme 7. Structures of inter- and intra molecular complexes

The most accurate magnitude of $A(X)$ in terms of measurements and physical evidence is the coupling constant $^1J(^{15}N,H)$ between the bridge proton and the nitrogen atom that depicts the degree of residence of the bridge proton on the nitrogen atom. Consequently, the application of the aforesaid method allowed one to obtain the following values of the coupling constant $^1J(^{15}N,H)$ for salicylideneimines [$^1J(^{15}N,H)_{HN} = 92.5$ Hz for zwitterionic form and 2 Hz for enol–imine form[116,117]], for naphthalideneaniline [$^1J(^{15}N,H)_{HN} = 95$ Hz] and for acetonaphthones [$^1J(^{15}N,H)_{HN} = 87$–91 Hz[114]]. The most suitable method for the determination of the degree of proton transfer is to measure the coupling constant between the bridge proton and the imine proton, $^3J(NH,C_\alpha H)$ [e.g. for *N*-(2-hydroxy-1-naphthylidene)-*tert*-butylamine $^3J(NH,C_\alpha H)_{HN} = 12.6$ Hz[118] and for aldimines $^3J(NH,C_\alpha H)_{HN} = 16$ Hz[116,122]]. Unfortunately, a failure to detect this coupling constant does not speak in favour of the existence of the enol form alone. Hence it is reasonable to add the chemical shift value as a further parameter $A(X)$. Chemical shifts $\delta(^{13}C1)$ have been reported[125] for boarding tautomers [$\delta(^{13}C1)_{OH} = 166.89$ ppm), $\delta(^{13}C1)_{HN} = 180.41$ ppm[126]]. A similar approach in the determination of the keto form was employed by Zhuo,[129] where the chemical shift $\delta(^{17}O)$ was used as the defining parameter $A(X)$. The above-mentioned coupling constants and the linear dependence $\delta(N) = -1.93\ ^1J(^{15}N,H) - 83.23$[130] enable one to evaluate limited conditions for the chemical shift of nitrogen, $\delta(N)$ [$\delta(N)_{OH} \approx -85$ ppm, $\delta(N)_{HN} \approx -245$ ppm].

However, it would be illogical to confirm the existence of solely intra-resonance equilibrium in the presence of the directed intermolecular acid–base interaction that leads to competitive tautomer equilibrium (Scheme 7). This interaction causes of alteration the bond lengths of the hydrogen bridge of the phenol and pseudo-aromatic rings and, as a consequence, a change in the superposition of the resonance structures. Moreover, the existence of a

'pure' intramolecular zwitterionic form may be called into question, in view of the separation of the negative and positive charges due to the adjacent intermolecular hydrogen bond (see Scheme 7). The consequences of the interaction described are clearly observed in electron spectra of Schiff bases.[134,135] The result is that a bathochromic band, recognized as a feature of the HN resonance tautomeric form, keeps shifting hypsochromically owing to the ever stronger intermolecular interaction. This observation suggests that the 'contradictions' revealed when NMR and UV spectroscopic methods are applied are the result of two different NH tautomeric equilibria: intramolecular and competitive. The standard $J(^{15}N,H)$[114,116,117] determines the degree of the competitive tautomeric HN form, whereas the bathochromic band in the electron spectra turns to be the standard of the intramolecular HN form.

CONFORMERS IN GROUND STATE

Determination of the energy of the intramolecular hydrogen bond is a difficult task experimentally, so to settle this problem *ab initio* and semi-empirical methods of calculations were used[136–147] for Schiff bases.[141–147] However, there the question arises of how to define a reference state, the most stable one among the states deprived of a hydrogen bond. Both experimental and theoretical viewpoints verify that the *trans*-OH conformer of *o*-halophenols is a suitable reference state (see Ref. 137 and references cited therein). Scheiner and co-workers[138,139] put forward the suggestion of employing a conformer with the hydroxyl group turned by 180° around the carbonyl bond in *ortho*-substituted phenols. A similar suggestion was made for *N*-methylsalicylaldimine ($R_1 = H$, $R_2 = CH_3$, $R_3 = H$) on the basis of semi-empirical CNDO/2 calculations[142] (conformer **6** in Scheme 8). Even so, having applied *ab initio* calculations (HF/STO-3G level), the same group[143] calculated the dependence of the energy of 2-hydroxybenzylideneamine ($R_1 = R_2 = R_3 = H$) on the turning angle around the C2—C_α axis and obtained the most stable non-hydrogen-bonded conformer **3** (the hydrogen bonding energy was estimated as $5.8\,kcal\,mol^{-1}$; $1\,kcal = 4.184\,kJ$).

However, this suggestion was called in to question in several studies[75,139,140,144] where a series of conformers of aldimines and Mannich bases were calculated with application of semi-empirical (AM1, PM3) and *ab initio* [HF/3–21G, B3LYP/6–31(d,p), MP2/6–31(d,p), B3LYP/d–95(d,p)] methods. The results obtained indicate that the most stable non-hydrogen-bonded conformer is that with both groups turned by 180° (conformer **3**). The generalized conformer analysis carried out for the ketimine[100] does not provide clear evidence of the *trans*-CO and *trans*-C═N 'open' conformer being more stable at the expense of steric repulsion of the C—CH_3 group (Scheme 8). On account of this repulsion, the ketimine group is strongly deflected from the phenol ring plane (33.3° for conformer **3**), whereas the aldimine molecule is flat.

The results of both semi-empirical AM1 calculations and x-ray experiments make possible to complete a worthwhile comparison of salicylaldehyde-2-methylthiosemicarbazone [Scheme 9(a)] and 5-methylacetophenonethiosemicarbazone [Scheme 9(b)].[145] AM1 calculations on the first compound revealed conformer **3** to be the most stable ($\Delta E_{\mathbf{1}-\mathbf{3}} = -0.79\,kcal\,mol^{-1}$) with a rotational barrier height of $5\,kcal\,mol^{-1}$. The second compound is distinctive for its more stable conformer **1** ($\Delta E_{\mathbf{1}-\mathbf{2}} = 0.82\,kcal\,mol^{-1}$), where the rotational barrier height is $24\,kcal\,mol^{-1}$. Despite some weak points in the AM1 calculations, a conclusion can be drawn of greater stability of the intramolecular hydrogen bond in the second compound, this being supported by crystallographic studies. The studies show that in the case of the first compound an additional molecule of water causes disruption of the intramolecular O—H···N bond, thus creating an intermolecular O—H···O bond, whereas the intramolecular hydrogen bond of the second compound remains even if a water molecule is added.[145]

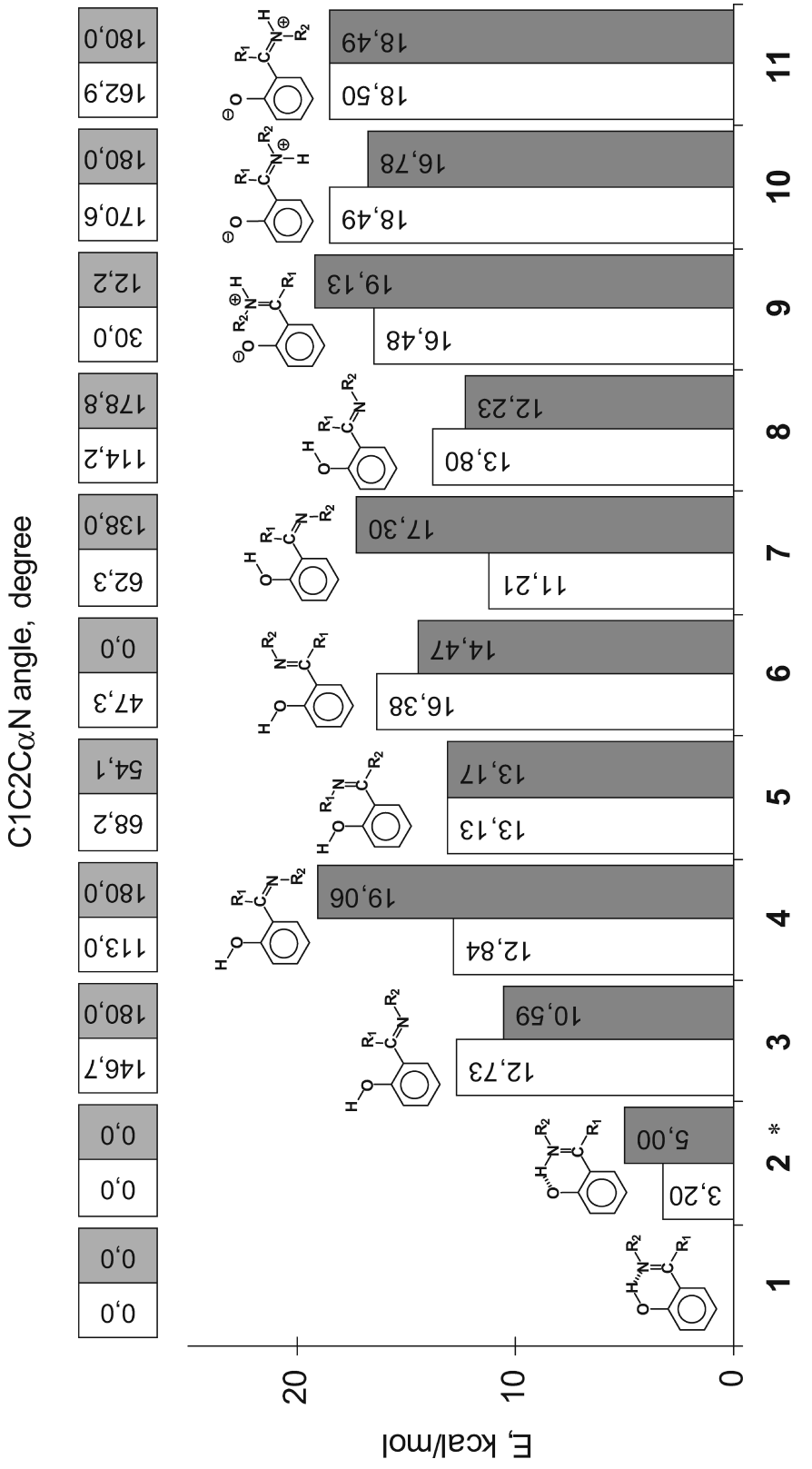
Quantum-mechanical calculations [HF/6–31G(d,p) level] for the aldimine and its conformer **3** have been reported,[146] where the energy difference between conformers **1** and **3** was estimated to be $41.8\,kJ\,mol^{-1}$. However, the energy of hydrogen formation was also evaluated as the energy of the isodesmic reaction[147] and estimated to be -28.8 and $-36.8\,kJ\,mol^{-1}$ at the HF/6–31G(d) and MP2(FC)/6–31G(d) levels, respectevely.

It should be emphasized that Elguero *et al.*[148] studied the liquid crystal properties of benzalazines (including α,α'-dimethylbenzalazines in that number) by semi-empirical methods (MNDO, CNDO/2) and, despite disputable results, they succeeded in predicting the hydrogen bond reduction caused by steric effects.

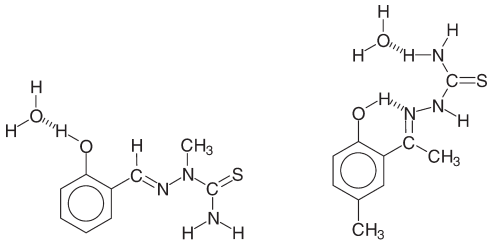
The literature presents a controversial discussion on research on coloured species,[43,149–154] and only recently was a photoinduced coloured crystal structure of *N*-3,5-di-*tert*-butylsalicylidene-3-nitroaniline defined,[155] which turned out to be a *trans*-keto form. This form can be considered as an argument in favour of the possible existence of open conformers of types **3** and **7**.

The most popular and widely used method is the theoretical analysis of the proton transfer energy (ΔE_{PT}), which is the difference between the OH and HN tautomers ($\Delta E_{PT} = E_{OH} - E_{HN}$). The energy calculated in this way correlates well with the proton chemical shifts δ(OH) for aldimine bases, $\Delta E_{PT} = (-1.476 \pm 0.266) \times \delta(OH) + (24.643 \pm 3.823)$.[144]

All things considered, overall conformer analysis is a theoretical tool helpful in estimating both the hydrogen bond energy and the energy of proton transfer, and this procedure can serve for designing hydrogen bond systems.



Scheme 8. Scheme of the energy obtained with B3LYP/6–31G(d,p) for ketimine (white: $R_1 = CH_3$; $R_2 = CH_3$) and aldimine (grey: $R_1 = CH_3$; $R_2 = H$). *Structure 2 presents a tautomer. Reprinted with permission from Ref. 100. Copyright 2005 American Chemical Society



a **b**

Scheme 9. Structures of (a) salicylaldehyde-2-methylthiosemicarbasone and (b) 5-methylacetophenonethiosemicarbazone

Acknowledgement

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