

Invited Review

***Mannich* Bases as Model Compounds for Intramolecular Hydrogen Bonding II [1]. Structure and Properties in Solution**

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Summary. Studies on hydrogen bond properties and on the structure of *ortho*-alkylaminomethylphenols and -naphthols in solution are presented. The main advantages of these systems are their stability and the defined stoichiometry of the molecules in comparison to intermolecularly hydrogen bonded complexes. Some specific properties of intramolecular hydrogen bonds are additionally discussed.

Keywords. *Mannich* bases; Alkylaminomethylphenol; Alkylaminomethylnaphthol; Intramolecular hydrogen bond; Proton transfer.

***Mannich*-Basen als Modellverbindungen für intramolekulare Wasserstoffbrückenbindungen, 2. Mitt. [1]. Struktur und Eigenschaften in Lösung**

Zusammenfassung. Eigenschaften und Strukturen der Wasserstoffbrücken von *ortho*-Alkylaminomethylphenolen und -naphtholen in Lösung werden präsentiert. Der große Vorteil dieser Verbindungen als Modelle für Wasserstoffbrückensysteme ist ihre große Stabilität und die Stöchiometrie dieser Verbindungsklasse in Vergleich mit intermolekularen Wasserstoffbrückenkomplexen. Einige spezielle Eigenschaften von intramolekularen Wasserstoffbrücken werden zusätzlich beschrieben und diskutiert.

Introduction

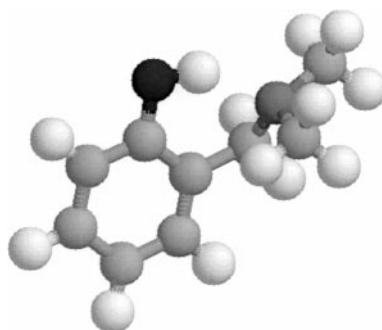
Hydrogen bonding between phenols and amines is of general interest because such systems are very convenient models for the investigation of the influence of various factors on hydrogen bond properties and proton transfer reactions in biomolecules. As in intermolecularly bonded complexes the stoichiometry may be uncertain and additional association steps can render the interpretation difficult, alternative model systems were selected. In particular, *ortho-Mannich* bases, the condensation

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products of phenols or naphthols with aldehydes and secondary amines, seem to be very useful. The main advantage of these systems is the pronounced thermodynamic stability of the intramolecular hydrogen bonds. They permit the investigation of species characterized by the same stoichiometry and very similar structure in wide range of temperature and different surroundings without the need to determine equilibrium constants of a set of additional association steps and their variation under varying conditions as it is the case with intermolecular hydrogen bonding.

A large number of such intramolecularly hydrogen bonded compounds of the *Mannich* base type were studied in dependence of a variety of different parameters, like the properties of proton donor and acceptor components, temperature, environment, concentration, or phase. In the present paper we shall discuss the problems of structure and properties of *Mannich* bases upon variation of these parameters.

A specific feature of *ortho-Mannich* bases like that shown below is the bent hydrogen bond caused by steric circumstances, leading also to a nonplanar geometry of such molecules [1].



Discussion

Stoichiometry and stability of the intramolecular hydrogen bond in solution

One of the principal topics in hydrogen bond investigations is the stoichiometry of the considered complexes. In intramolecular hydrogen bonds, the situation seems to be simpler, because the stoichiometry is known. The limits of the stability of intramolecular hydrogen bonds as a function of concentration, solvents, and temperature has been of interest from the beginning of investigations on *Mannich* bases. It has been shown that in nonpolar and medium polar solvents (up to a permittivity of 37) the free $\nu_s(\text{OH})$ bands do not appear in the IR spectra [2–6]. Moreover, strong dilution up to conditions under which analogous complexes of phenols with amines do not exist any more does not evoke appearance of such bands.

The results of IR absorption studies in the gas phase demonstrate the stability of the intramolecular hydrogen bond in *ortho-Mannich* bases even up to +150°C and a partial pressure of about 1 torr [7] (Fig. 1). Similar conclusions based on the results of dielectric measurements in solutions are presented in Refs. [8–11].

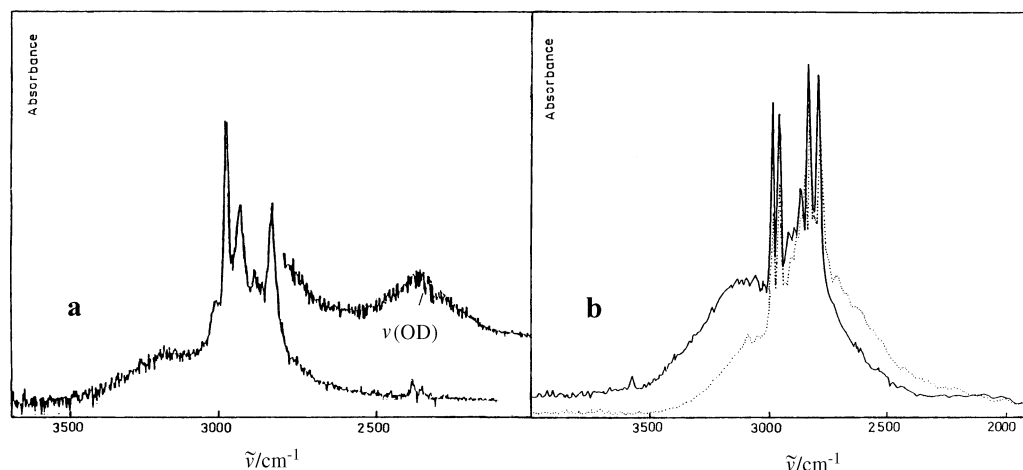


Fig. 1. IR spectra of a) 2-(N,N-diethylaminomethyl)-4,6-dimethylphenol in the gas phase (150°C, partial pressure 1 torr) and b) 2-(N,N-dimethylaminomethyl)-4,6-dichlorophenol in the gas phase (full line) and in CCl_4 solution (broken line, $c = 0.005 \text{ mol} \cdot \text{dm}^{-3}$, $d = 2 \text{ cm}$); Specord M-30 (Carl Zeiss Jena), resolution: 1.5 cm^{-1}

Structure of *Mannich* bases in solution

In the solid state, intramolecularly hydrogen bonded molecules or zwitterions forming cyclic dimers or chains were observed [1], depending on the difference of the acidity constants of the free proton donor and the protonated secondary amine (ΔpK_a), a parameter commonly used to characterize hydrogen bonds [12, 13]. Therefore, the question arises to what extent inter- and intramolecularly bonded species exist in solution in dependence on solvent polarity and temperature. It can be expected that nonionic structures with intramolecular hydrogen bonds as found in the solid state for *Mannich* bases with $\Delta pK_a < 2.5$ [1] should predominate in nonpolar solutions. Indirect support of such a suggestion is the similarity of the IR spectra of these compounds in CCl_4 solutions and in the solid state [3]. It was found, however, that for compounds with ΔpK_a above 2.5 the spectra may be pronouncedly different in both phases. The solution spectra in these cases resemble the spectra of molecular forms of hydrogen bonds in the solid state. This suggests that some *Mannich* bases which are of zwitterionic type in the solid state form intramolecular hydrogen bonds of molecular type in low polar solvents (Fig. 2) [14].

Systematic studies on a wide class of 75 different *Mannich* bases have shown that in CCl_4 solutions a drastic change of the IR spectra in the $\nu(\text{OH})$ band region occurs for systems with $\Delta pK_a \approx 3.5$ [3]. At this value zwitterionic forms begin to appear. The position of the maximum of the absorption shifts in the direction characteristic for the ionic forms of hydrogen bonds (see Fig. 2). Intermediate frequencies are observed for systems exhibiting equilibria of molecular and ionic forms. Both OH and NH^+ bands of hydrogen bonded species are too broad to allow the discrimination of separate bands of particular forms.

Some direct information about the structure of intramolecular hydrogen bonds in solution of these compounds can be gained from dipole moment studies. For

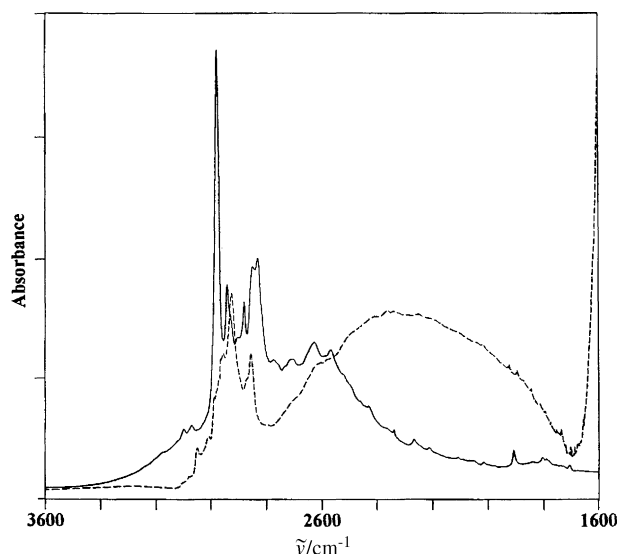


Fig. 2. Comparison of IR spectra in the $\nu(\text{OH})$ absorption region of 2-(N,N-diethylaminomethyl)-4-nitrophenol in the solid state (KBr pellets, broken line) and in CCl_4 solution (full line, $c = 0.005 \text{ mol} \cdot \text{dm}^{-3}$, $d = 9.55 \text{ mm}$); Nicolet 205, resolution: 2 cm^{-1}

intermolecular complexes, a sigmoidal dependence of the polarity of the hydrogen bond ($\Delta\mu$) on ΔpK_a (Fig. 3) was observed [15–18]. Calculated values for *Mannich* bases assuming nonplanar geometries (found for molecular hydrogen bonded structures in the solid state) show a very good coincidence with this dependence which was interpreted in terms of proton transfer equilibria [12, 15]. A small increase of μ in the order of 0.5–1.0 D is a consequence of mutual polarization of the complex components. A stronger increase of μ , as observed for *Mannich* bases, indicates the existence of some amounts of ionic forms in solution [19].

Formation of cyclic dimers, as observed for some solid states structures [1], would lead to a decrease of the dipole moment; the increase stated in Ref [19]

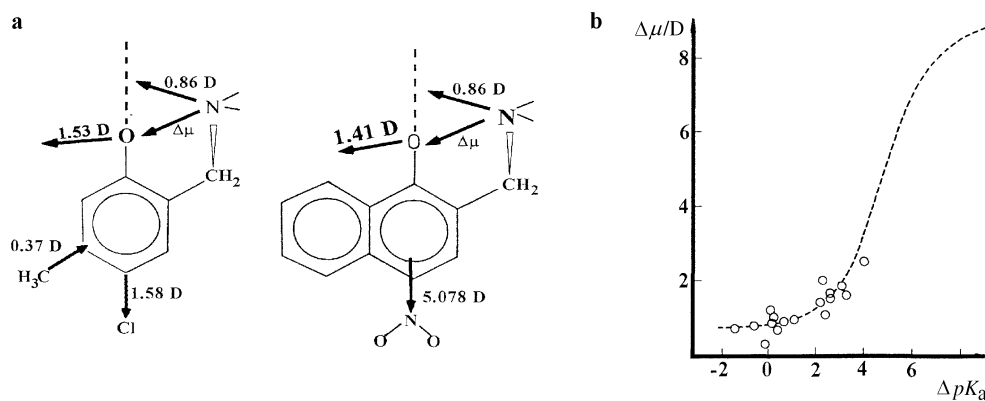


Fig. 3. a: Scheme of vector addition for some representative *Mannich* bases; b: Dependence of the hydrogen bond polarity ($\Delta\mu$) on ΔpK_a in benzene; open circles: data for *Mannich* bases [19], dotted line: intermolecular complexes [15]

suggests that intramolecular zwitterionic forms or chains are formed. The complexes with ΔpK_a below 4 do not show a concentration dependence of experimental dipole moments. From that it follows that in solutions of such *Mannich* bases no aggregation of the zwitterionic structures occurs. The influence of the solvents electric permittivity increase on dipole moments has been studied as well [20]. For a compound with a ΔpK_a of 2.72, no such dependence was found up to a permittivity of 10. Compounds with $\Delta pK_a = 3.04$ and 3.72 show an increase of experimental dipole moments with permittivity, thus demonstrating that the formed ionic species are not associated to cyclic dimers.

A model of proton transfer equilibria was verified by measurements of the temperature dependence of dipole moments in solutions [21], and full agreement of the obtained results with the model was found. A specific feature of these studies should be mentioned: due to the large stability of intramolecular hydrogen bonds, $\Delta\mu$ changes were caused by permittivity and temperature variation over a broad range for the particular compound rather than by changing the substituents. In this case, the mutual polarization of the complex components was also modified; it influences the shape of the $\Delta\mu$ vs. ΔpK_a dependence [15–18, 22].

Proton transfer in Mannich bases

From the point of view of polarity, the complexes with hydrogen bonds can be divided into three classes (A, B, and C) [18]. For weak hydrogen bonds, an increase of the dipole moment relative to the vector sum of the dipole moments of the components is less than 1 D (class A, Fig. 4).

At the other extreme, proton transfer may lead to a dipole moment increase in the order to 10 D [15] (class C). In many cases some intermediate increase of polarity is observed (class B). For such compounds, a strong dependence of the dipole moment of ΔpK_a (as well as on solvent or temperature) indicates a dynamic proton transfer equilibrium in solution [12, 15].

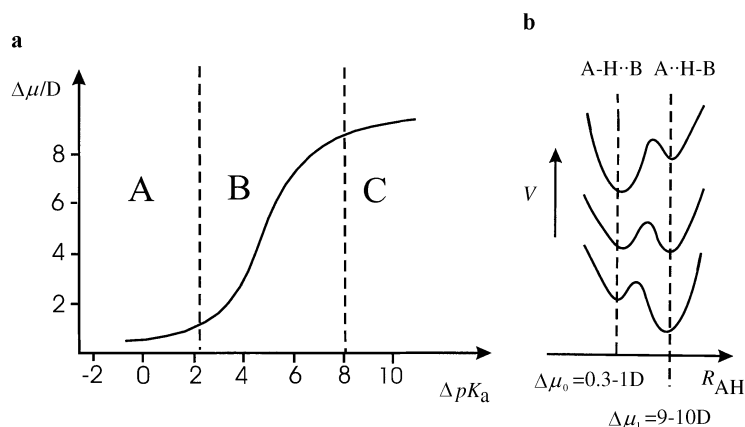


Fig. 4. a: Ranges of existence of A) molecular forms, B) proton transfer equilibria, C) ionic forms defined on the basis of the dependence of $\Delta\mu$ on ΔpK_a ; b: schematic profile of potential energy for the proton movement within the hydrogen bridge for the cases A, B, and C

According to the above studies, *Mannich* bases with intramolecular hydrogen bonds belong to class A in nonpolar solvents and some derivatives with ΔpK_a values above 3 can be assigned to class B. By variation of temperature or/and solvent polarity the proton transfer equilibrium can be shifted, thus modifying the structure of the studied species in solution.

The ^1H NMR chemical shift dependence on ΔpK_a observed for OH protons in *Mannich* bases [23] has a shape typical for systems with proton transfer equilibria. A strong influence of the surroundings on the position of the maximal chemical shifts has been stressed. Temperature decrease leads to an enhancement of effects characteristic for proton transfer.

Clear indications of proton transfer equilibria in *Mannich* bases can be found in the electronic absorption spectra of these compounds. As electronic transitions are much faster (10^{-15} s) than any chemical reaction (even extremely fast intramolecular proton transfers), it can be easily distinguished between the molecular and the ionic forms of the hydrogen bond. The electronic absorption bands of phenols and phenolates as well as naphthols and naphtholates are different [24, 25]. As an example, the spectra of 2-morpholinomethyl-naphthol-1 in different solvents are shown in Fig. 5. The spectral differences are caused by the shift of the proton transfer equilibria with variation of solvent polarity.

In some *Mannich* bases double fluorescence was observed which could be attributed to emission from the molecular and zwitterionic type of molecules [26]. Double fluorescence is also observed for molecules with weak hydrogen bonds e.g. in 6-(N,N-diethylaminomethyl)-2,3,5-trimethylphenol ($\Delta pK_a = -1.04$) [27], which does not exist in the zwitterionic form in the ground state. In the singlet excited state the proton transfer reaction proceeds to a greater extent than in the ground state, since pK_a values of phenols and naphthols may increase over six units in the excited state [26].

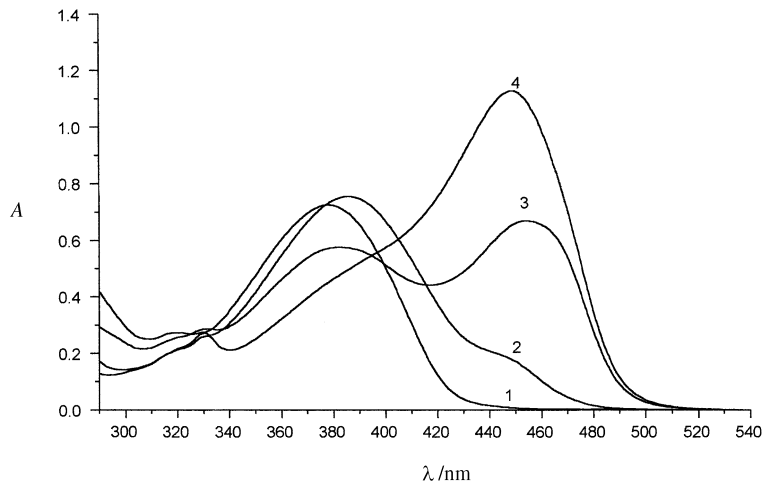


Fig. 5. Influence of solvents on UV/Vis spectra of 2-morpholinomethyl-naphthol-1 ($c = 4 \cdot 10^{-4}$ mol \cdot dm $^{-3}$ 25°C, Hitachi U-3501); 1: dioxane, 2: acetonitrile, 3: ethanol, 4: ethanol-water (10%)

It appears that also in the excited state the stabilization of the zwitterionic forms by the solvent is a necessary condition to observe the proton transfer states. In the case of the above mentioned molecule an increase of electric permittivity above 6 is a prerequisite to observe double fluorescence. Such a solvent interaction has been considered on the basis of the dielectric continuum model [28].

Proton transfer equilibrium constants and related thermodynamic parameters

Using electron absorption spectra, the amount of both forms existing in a chemical equilibrium as well as the equilibrium constant can be determined precisely. The thermodynamic characteristics of the proton transfer reaction can also be studied when temperature dependent measurements are performed [29]. Such studies are described in Refs. [4, 29, 30], and examples of estimated thermodynamic parameters in the proton transfer process [30] are presented in Table 1.

For all cases where proton transfer equilibria were detected it was found that ΔH° of the proton transfer reaction is negative within the range from -6 to -17 kJ/mol [29]. In agreement with negative values of ΔH_{PT}° , a shift of the equilibrium towards the ionic forms was observed with decreasing temperature [25]. The IR spectra also allow a direct determination of the proton transfer equilibrium position [4]. The band at 1185 cm^{-1} of 6-diethylaminomethyl-2,3,4,5-tetrachlorophenol, which has $\gamma(\text{O-H})$ bending and $\nu(\text{C-O})$ stretching character, disappears after deuteration, and a new band at 1025 cm^{-1} appears. The intensity of the 1185 cm^{-1} band was used as a measure of the amount of the molecular form. The degree of proton transfer was determined in solvents with electric permittivity ranging from 2 to 38 in dependence of temperature [4]. Linear correlations between $\log K_{PT}$ (the proton transfer equilibrium constant) and *Onsager* parameters as well as the solvent polarity parameter E_T were observed. It was shown that enhancement of the solvent polarity shifts the equilibrium in the proton transfer direction. Thermodynamic characteristics of the proton transfer reaction obtained by IR spectroscopy [4] agree well with the results of more precise UV/Vis techniques [29]. ΔS_{PT}° values are negative (within the range of -24 to $-62\text{ J/mol}\cdot\text{deg}$) with rather high absolute values as for internal proton transfer only [31], suggesting solvent

Table 1. Thermodynamic parameters of the proton transfer reaction in *Mannich* bases from derivatives of 4-nitrophenol (**1**) and 2,4,5-trichlorophenol (**2**) with benzylamines in methanol [30]

<i>R</i>	pK_a^a	$\nu/10^2\text{ \AA}^3$	$-\Delta H_{PT}^\circ/\text{kJ}\cdot\text{mol}^{-1}$		$\Delta G_{PT}^\circ/\text{kJ}\cdot\text{mol}^{-1}$		$-\Delta S_{PT}^\circ/\text{J}\cdot\text{mol}^{-1}\text{K}^{-1}$	
			1	2	1	2	1	2
CH ₃	8.91	3.66	9.20	10.60	0.083	0.498	31.64	36.80
C ₂ H ₅	9.44	2.09	8.74	9.42	2.002	0.260	36.04	32.49
C ₃ H ₇	9.40	1.47	8.32	8.62	2.40	0.54	35.96	30.72
C ₄ H ₉	9.41	1.13		8.05		0.76		29.54
C ₆ H ₁₃	9.50	0.77	7.10	7.51	3.44	1.17	35.46	29.15
C ₁₀ H ₂₁	9.45	0.47	5.89	5.65	3.81	1.63	32.69	24.43

^a pK_a value of the corresponding benzylamine; volume of the alkyl residue

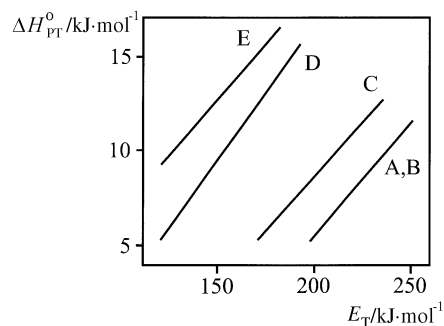


Fig. 6. Correlations between $\Delta H_{\text{PT}}^{\circ}$ and the solvent polarity parameter E_{T} [30] for A: 2-(N,N-dimethylaminomethyl)-4,6-dibromophenol ($\Delta pK_{\text{a}} = 1.1$), B: 2-(N,N-dimethylaminomethyl)-4-nitrophenol ($\Delta pK_{\text{a}} = 1.8$), C: 2-(N,N-diethylaminomethyl)-3,4,6-trichlorophenol ($\Delta pK_{\text{a}} = 2.7$), D: 2-(N,N-diethylaminomethyl)-3,4,5-tetrachlorophenol ($\Delta pK_{\text{a}} = 3.0$), E: 2-(N,N-diethylaminomethyl)-4-nitronaphthol-1 ($\Delta pK_{\text{a}} = 3.7$)

participation in the proton transfer reaction. The solvent polarity increase generally leads to an enhancement of the absolute values of $\Delta H_{\text{PT}}^{\circ}$ and $\Delta S_{\text{PT}}^{\circ}$. A linear dependence of $\Delta H_{\text{PT}}^{\circ}$ on solvent polarity (E_{T}) with more or less the same slope but distinctly different intercepts for various *Mannich* bases was found [29, 30] (Fig. 6).

A linear correlation between $\Delta H_{\text{PT}}^{\circ}$ and ΔpK_{a} was found as well [30]. The results show that there are two effects responsible for the existence and the position of the proton transfer equilibrium. The first might be called internal (see also Ref. [32]) – it depends on the relation between the electronic energy of hydrogen bonded and proton transferred forms in the gas phase. It seems that these energy levels are shifted always in favour of the molecular forms; ionic forms of *ortho-Mannich* bases in the gas phase were not detected. Theoretical calculations also yield a lower energy for the molecular forms [33]. The reason that the proton transfer forms are observed in solution is the external interaction with the solvent molecules. For weak hydrogen bonds, the electronic level distribution is so unfavourable for the proton transfer forms that even the strong interaction with a solvent cannot force the proton transfer to occur. The electronic absorption spectra of 2-(N,N'-dimethylaminomethyl)-4-chloro-5-methylphenol ($\Delta pK_{\text{a}} = -0.6$) in butanol-1 ($\epsilon = 17.8$) at its freezing temperature (110 K) did not give any evidence for the absorption of proton transfer forms [34]. Some amount of proton transfer forms in this compound was found, however, in glycerol ($\epsilon = 45.8$) at temperatures lower than 220 K.

$\Delta G_{\text{PT}}^{\circ}$ values for all studied cases were found to be small and positive at room temperature (within a range from +0.1 to 8.5 kJ/mol [29]). The relatively large negative entropy of the proton transfer reaction decreases the amount of proton transfer forms. In Ref. [35], however, all numerical values of the thermodynamic characteristics of the proton transfer process have to be considered as overestimated, because the change of electric permittivity with temperature was not accounted for.

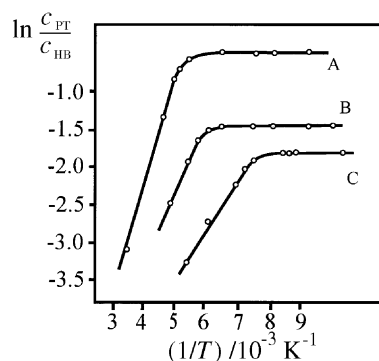


Fig. 7. Dependence of the logarithm of the concentration ratio of zwitterionic (PT) and molecular (HB) forms on $1/T$; A: 2-(N,N-dimethylaminomethyl)-4-nitrophenol in squalane, B: 2-(N,N-dimethylaminomethyl)-tetrachlorophenol in squalane, C: 2-(N,N-dimethylaminomethyl)-tetrachlorophenol in cumol

Influence of the solvent on proton transfer equilibrium

A very strong support for the hypothesis of solvent participation in proton transfer reactions arises from studies at low temperatures [34]. Crystallization of the solution prohibits the reorientation of the solvent and thus freezes the equilibrium. Similar observations were made by FTIR spectroscopy, and related conclusions were drawn [36].

The importance of solute-solvent interaction was also demonstrated in a study on the influence of steric effects on the proton transfer equilibrium of 4-nitrophenol and 2,4,5-trichlorophenol derivatives in methanol [30]. In condensation products of these phenols with secondary amines, a gradual decrease of the amount of proton transfer forms was found with increasing N-chain length (cf. Tab. 1). It was concluded that bulky substituents shield the center of the intramolecular proton transfer reaction from the polar solvent molecules. The effect was found to be inversely proportional to the molecular volume of the substituents [30], as it follows from the *Onsager* reaction field theory:

$$\Delta G_{\text{PT}}^{0(s)} = \Delta G_{\text{PT}}^{0(g)} - N_{\text{A}} \frac{\mu_{\text{PT}}^2 - \mu_{\text{HB}}^2}{a^3} \frac{\varepsilon - 1}{2\varepsilon + 1} \quad (1)$$

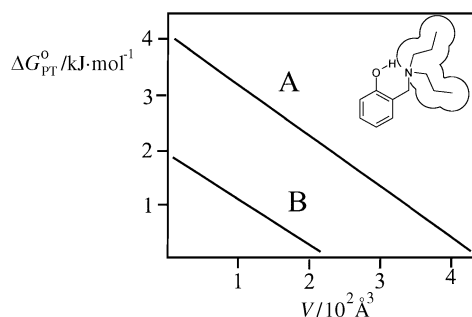


Fig. 8. Correlation between $\Delta G_{\text{PT}}^{\circ}$ and V of aliphatic chains for 2-(N,N-dialkylaminomethyl)-4-nitrophenols (A) and -3,4,6-trichlorophenols (B) in methanol

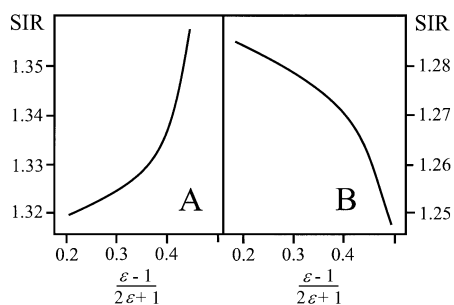


Fig. 9. Dependence of the spectroscopic isotopic ratio (SIR; A: $\nu_{\text{NH}}^+/\nu_{\text{NH}}^-$, B: $\nu_{\text{OH}}/\nu_{\text{OD}}$) on the Onsager parameter

Another example of the influence of the environment on the proton transfer equilibrium was demonstrated in Ref. [37]. Piperidinomethyl-2-naphthols form inclusion complexes with β -cyclodextrins in aqueous solution. The equilibrium constant of the proton transfer from the neutral to the zwitterionic form is strongly reduced by complexation into the cyclodextrin cavity, which is much less polar than the solvent.

In systems where the shift of the equilibrium towards one species – molecular or zwitterionic form – is complete, one can follow the influence of solvent and of temperature on the properties of particular forms of the hydrogen bond. For example, a comparison of the IR spectra of the molecular form of *Mannich* bases in the gas phase and in CCl_4 solution has been performed [7] (cf. Fig. 1). It was shown that the transfer from the gas phase to solution results in a shift of the $\nu(\text{OH})$ frequency to lower values by 100–150 cm^{-1} ; larger shifts correspond to molecules with stronger hydrogen bonds. On the basis of a correlation of ΔH° of the hydrogen bond formation with $\Delta\nu(\text{OH})$, an increase of the intramolecular hydrogen bond strength over an order of at least 4 kJ/mol was found upon passing from the gas phase to a nonactive solvent like CCl_4 [7].

A very interesting dependence of the spectroscopic isotopic ratio (SIR) on solvent polarity has been established [37]. For molecular hydrogen bonds the SIR value decreases with the solvent polarity, suggesting a strengthening of the hydrogen bond. The opposite effect was found in the case of hydrogen bonds in the zwitterionic form.

Considerations of the proton transfer potentials by IR spectroscopy

Extensive studies of the influence of the temperature on the $\nu(\text{OH})$ band shape have been performed. In the gas phase, in liquified noble gases, or in solid matrices of noble gases these bands are very broad (400–600 cm^{-1} halfwidth) [7, 39–41]. A very strong broadening was found particularly in 2,6-bis-(diethylaminomethyl)-phenols where collective proton motion can be anticipated [36, 42, 43]. A very broad absorption was also observed in monosubstituted *Mannich* bases in solvents of higher polarity, e.g. in acetonitrile [4]. The broadening was explained by a proton fluctuation mechanism and strong interactions with the environment [44]. In the gas phase and in noble gas matrices the broadening can be explained only by a coupling of the $\nu(\text{OH})$ mode with internal modes of the molecule. The low

frequency bending vibrations of the chelate ring, modulating the N \cdots O distance, were identified as those internal modes which are coupled with the $\nu_s(\text{OH})$ vibration on the basis of semiempirical force field calculations and experimental FTIR spectra [40, 41]. The band shape of the $\nu(\text{OH})$ absorption could be reproduced on the basis of this model. Weaker coupling in OD samples than in nondeuterated ones was mentioned. The temperature dependence of spectral moments, also for deuterated samples, was studied in a wide temperature range (170–380 K).

Specific properties of the hydrogen bond in Mannich bases

When discussing different aspects of the hydrogen bond on the example of *ortho-Mannich* bases, the question arises to what extent the observed properties of the hydrogen bond are of general importance, *i.e.* what are the specific features of the intramolecular hydrogen bond in *Mannich* bases.

Comparative studies of intermolecular complexes of phenols with amines and the *Mannich* bases synthesized from these components have been performed [3]. For bent intramolecular systems the $\nu_s(\text{OH})$ absorption maximum was shifted to higher frequencies by less than 100 cm^{-1} relative to analogous intermolecular systems (Fig. 10) [3].

Taking into account the weakening of the base strength in *Mannich* bases (pK_a values of benzylamines are lower than those of analogous aliphatic amines [45]), it can be concluded that the properties of both types of hydrogen bonds are very similar. The identity of the correlations between polarity ($\Delta\mu$) and ΔpK_a for *Mannich* bases and intermolecular complexes has been mentioned above.

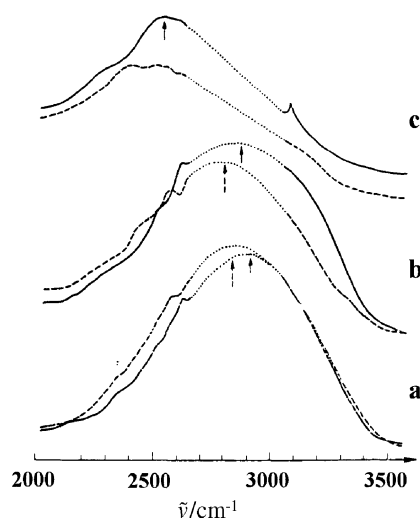
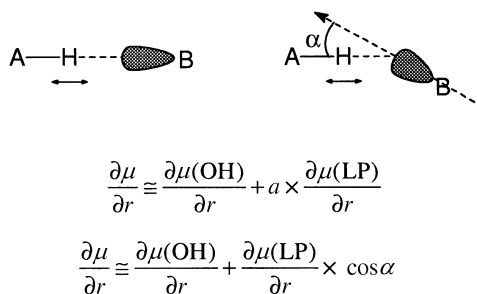


Fig. 10. Comparison of $\nu(\text{OH})$ of *Mannich* bases (full lines, $c = 0.001\text{ mol} \cdot \text{dm}^{-3}$, $d = 1\text{--}4\text{ cm}$) and complexes of related phenols and amines (dotted lines, $c = 0.01\text{ mol} \cdot \text{dm}^{-3}$, $d = 1\text{--}2.6\text{ mm}$) in CCl_4 (Perkin-Elmer 621) [3]; a: 2-(N,N-diethylaminomethyl)-2,4-dimethylphenol/2,4-dimethylphenol+triethylamine, b: 2-(N-piperidinomethyl)-4-chlorophenol/4-chlorophenol+N-methylpiperidine, c: 2-(N,N-diethylaminomethyl)-3,4,6-trichlorophenol/2,4,5-trichlorophenol+triethylamine



Scheme 1

The results of hydrogen bond studies in *ortho*-*Mannich* bases seem to be of general importance. Some peculiarities resulting from the hydrogen bridge bending in *Mannich* bases should be mentioned, however. They concern mainly the integrated intensity of $\nu(\text{OH})$ bands which are related approximately to the square of the dipole moment derivative with respect to the O–H bond stretching (Scheme 1).

The O–H stretching vibrations lead to a polarization of both proton donor and acceptor molecules (mainly the lone pair of the latter); $\partial \mu / \partial r$ is a vector sum of both components. The second takes into consideration the α with the OH axis in *Mannich* bases, lead to a decrease of the total $\partial \mu / \partial r$ value. Such suggestions follow also from semiempirical calculations. An experimental verification of these considerations is shown in Fig. 11 [46].

It can be seen that the integrated intensity in bent hydrogen bonds is reduced in comparison to analogous intermolecular, more linear hydrogen bonds. The very good linear correlation between intensity and ΔpK_a should be mentioned. The point with increased intensity (second square from left side in Fig. 11) with respect to the correlation for *Mannich* bases belongs to 2-(N,N-dimethylaminomethyl)-3,4,5-trimethylphenol, where steric repulsion by the 3-methyl group leads to hydrogen bond shortening and, therefore, strengthening [47]. The integrated intensity for this compound appears above the correlation [46] which takes into account mainly acid-base properties of the system. In more extended studies [48] these results are compared with data for analogous *Schiff* bases with direct π -electronic coupling between acidic and basic centers. The intensity was found to decrease in

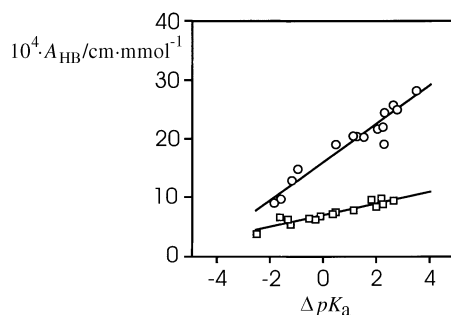


Fig. 11. Dependence of the integrated intensity of the $\nu(\text{OH})$ band of *Mannich* bases (\square) and complexes of N,N-dimethylamine with related phenols (o) on ΔpK_a

comparison to analogous *Mannich* bases, whereas the frequency shift $\Delta\nu(\text{OH})$ was larger. It can be concluded that particular hydrogen bonds of the $\text{O}-\text{H}\cdots\text{N}$ type in *Mannich* bases, *Schiff* bases, or intermolecular complexes between phenols and amines have specific individual characteristics, e.g. different slopes and intercepts for $\Delta\nu(\text{OH})$ vs. ΔpK_a , intensity of $\nu(\text{OH})$ vs. ΔpK_a , or intensity vs. $\Delta\nu(\text{OH})$ correlations. Studies of such specific collective characteristics of particular groups of hydrogen bonded systems are important because they provide a better understanding of the nature of hydrogen bonding. Parameters of such characteristics can be verified by quantum mechanical calculations.

Self-association of polar forms of Mannich bases

Some limitations in the interpretation of the results for *Mannich* bases may result from the possible self-association of their polar forms. Thus, the position of the proton transfer equilibrium of 6-(*N,N*-diethylaminomethyl)-2,5-dinitrophenol ($\Delta pK_a = 4.04$) was found to depend on concentration [49]. It was concluded that some aggregation has to be considered for solutions of such *Mannich* bases. In order to verify this conclusion, measurements of the average molecular weight by the vapor pressure osmometric technique were performed [50]; the results are depicted in Fig. 12.

6-(*N,N*-diethylaminomethyl)-2,3,4,5-tetrachlorophenol ($\Delta pK_a = 3.04$) does not show any association over the whole concentration range (up to $4 \cdot 10^{-2} \text{ mol} \cdot \text{dm}^{-3}$) in benzene solutions at room temperature. About 9% of the ionic form were found in benzene at room temperature [20]. An increase of the temperature within the range of 283–328 K leads to a decrease of the polarity of the hydrogen bond from 1.95 to 1.63 D caused by a decrease of the amount of ionic forms [21]. The dipole moment at room temperature increases from 4.9 to 5.6 D with increasing solvent polarity ($\epsilon = 2$ to 10), suggesting an increase of the amount of ionic forms

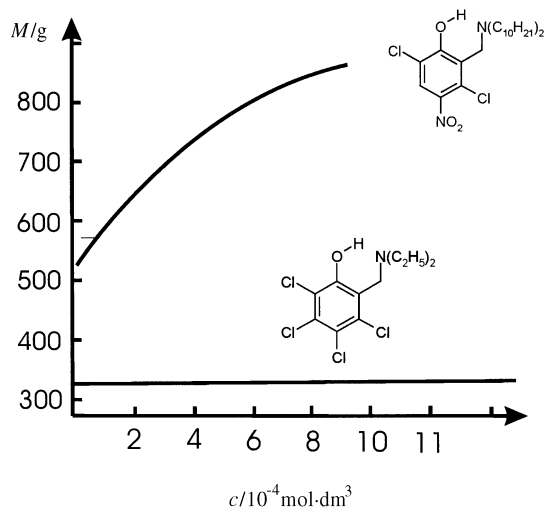


Fig. 12. Dependence of the average molecular weight (M) on the concentration of 6-(*N,N*-dipropylaminomethyl)-tetrachlorophenol and 6-(*N,N*-didecylaminomethyl)-2,5-dichloro-4-nitrophenol in benzene at room temperature

without formation of cyclic dimers. The amount of ionic forms seems to be too low to allow for self-association at these experimental conditions.

The ionization and association processes for this compound were also studied at low temperatures in CDCl_3 and CD_2Cl_2 via observation of the secondary isotope effect in ^{13}C NMR connected with D/H exchange of the OH group of *Mannich* bases. It was shown that the charge redistribution upon the proton transfer leads to an inversion of the sign of this effect [51].

In the case of 6-(N,N-diethylaminomethyl)-2,4,5,6-tetrachlorophenol, at 245 K in CH_2Cl_2 complete compensation of hydrogen bonding and proton transfer effects proceeds at about 20% contribution of the ionic form as established by US-Vis spectroscopy. Further decrease of temperature leads to an increase of the isotope effect in accordance with the increasing amount of ionic forms. At about 200 K, a surprisingly quick diminishing of these effects was observed. The authors related this to the self-association to cyclic dimers which causes a redistribution of atomic charges; the amount of ionic forms grows continuously till 178 K. In 6-(N,N-diethylaminomethyl)-2,4,5-trichlorophenol ($\Delta pK_a = 2.64$) no temperature effects were observed.

In the case of 6-(N,N-didecylaminomethyl)-2,5-dichloro-4-nitrophenol ($\Delta pK_a = 4.40$) at room temperature an enhanced molecular weight (about 10%) was detected even at such a low concentration as $1 \cdot 10^{-3} \text{ mol dm}^{-3}$ [50, 52] (Fig. 12). An increase of the concentration up to almost saturated solutions leads to molecular weights even higher than those expected for dimers. The dependence of dipole moments of this compound on concentration in benzene shows that the aggregates have a cyclic form; a decrease of the average dipole moment with increasing concentration was found. On the other hand it was stated that an increase of the concentration leads to an intensity enhancement of the electronic absorption in the region characteristic for proton transfer forms. This indicates that the proton transfer reaction is strongly coupled with the association process. A solvent polarity increase like in chloroform, dichloromethane, or dichloroethane leads to stronger association. This suggests that the solvent assisted proton transfer process is a primary effect. When the amount of the ionic forms is sufficiently large and the specific solvent interactions are not too high like, for example in alcohols, the aggregation process starts. Generally, this problems become important at room temperature only in low polar solvents and for molecules with potentially very high ability to ionization. Considering the results shown in Fig. 4 one can expect a boundary condition of $\Delta pK_a \approx 4$. At $\Delta pK_a = 4$ still an increased value of $\Delta\mu$ was observed (Fig. 3). Similarly, a radical change of $\nu(\text{OH})$ for CCl_4 solutions of *Mannich* bases was observed at $\Delta pK_a \approx 4$ [3].

General description of the proton transfer equilibria in solutions

In many of the papers mentioned above, information concerning proton transfer equilibria, in particular those of *Mannich* bases, was presented. In this chapter we aim to present a general description of this equilibrium in order to establish the regions of its existence as well as regions of existence of separate forms in dependence on solvent polarity, ΔpK_a , and temperature. Such a description can be

useful for the interpretation of experimental results and may be used in planning further experiments.

As literature shows [4, 30, 52] there exists a linear correlation between ΔH° of the proton transfer reaction and the solvent polarity parameter E_T with similar slopes for different *Mannich* bases, but shifted in relation each to other. It was also demonstrated that the distance between those correlation lines depends on ΔpK_a ; a linear correlation was found for the relation between ΔH_{PT}° and ΔpK_a in a given solvent.

A two parameter regression line was found describing the dependence of ΔH_{PT}° on both parameters at room temperature:

$$-\Delta H_{PT}^\circ = 0.106E_T + 9\Delta pK_a - 36 \quad (2)$$

No temperature dependence of ΔH_{PT}° was detected exceeding the range of the experimental error of its determination. Equation (2) reproduces the results fulfilling separate one-parameter correlation lines with a precision of ± 1 kJ/mol.

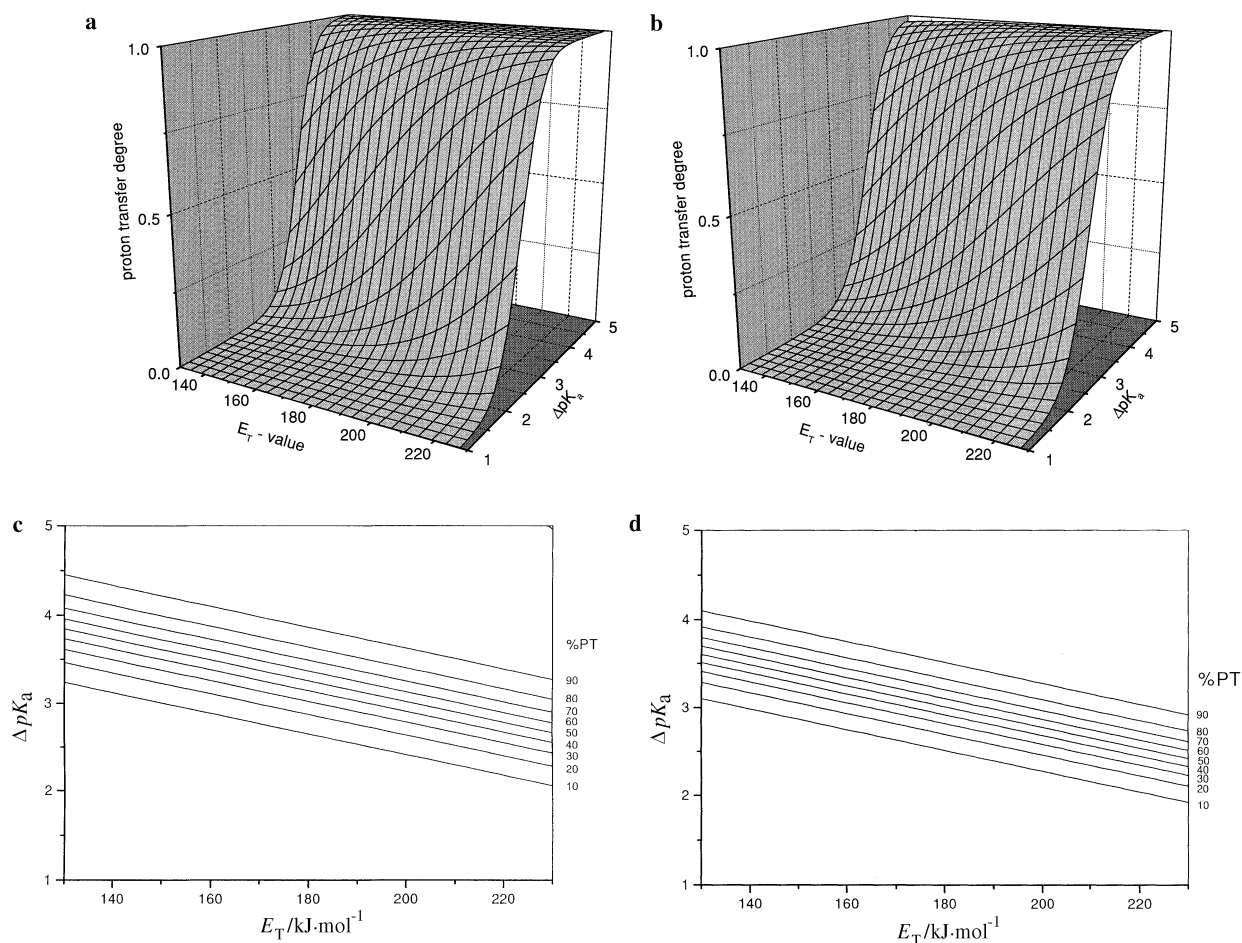


Fig. 13. Dependence of the proton transfer degree on E_T of solvents and ΔpK_a of *Mannich* bases; a: 298 K, b: 200 K, c: 298 K, 2D contour plot, d: 200 K, 2D contour plot

To account for the temperature dependence of the equilibrium constant, the above equation was combined with the *van't Hoff* relation:

$$\ln K = (0.106E_T + 9\Delta pK_a - 36) \cdot 1/(RT) + C \quad (3)$$

The parameter C was determined using the results of temperature dependence measurements of the proton transfer equilibrium in 6-(diethylaminomethyl)-2,3,4,5-tetrachlorophenol in a few solvents [4]. The C value was estimated as equal to -5 ± 0.17 .

Equation (3) was verified on results not used for its calibration. For example, the amount of ionic species of 6-(dimethylaminomethyl)-2,3,4,5-tetrachlorophenol in CCl_4 at room temperature calculated from this equation is 6% which is in accordance with the results discussed in Refs. [20, 21, 51]. The IR results [3] show a pronounced increase of the $\Delta\nu(\text{OH})$ values for *Mannich* bases in CCl_4 at room temperature at $\Delta pK_a \approx 4$. Equation (3) affords about 68% of proton transfer at these conditions, which agrees with the results presented in Ref. [3]. The equation can be presented in a graphical way, which helps to understand the influence of such parameters as the solvent polarity (E_T), ΔpK_a , and temperature on the position of the proton transfer equilibrium. Figure 13 shows such plots for 298 and 200 K.

At room temperature, the range of existence of molecules with less than 10% of proton transfer extends to $\Delta pK_a = 3.2$ for low-polar solvents. This border shifts to 2.1 for polar solvents like alcohols. 50% of proton transfer is reached at ΔpK_a values of 3.9 at room temperature in nonpolar solvents and 2.7 in highly polar solvents. Decrease of the temperature to 200 K obviously increases the regions of proton transfer and decreases the region of existence of molecular forms. Nevertheless, a large variety of molecular forms is observed at low temperatures. Steeper dependences of the degree of proton transfer with respect to ΔpK_a are observed for low temperatures than for room temperature. Figure 13 allows to estimate the proton transfer equilibrium at each state described by particular values of E_T and ΔpK_a at temperatures of 298 and 200 K. Situations at intermediate temperatures can be analyzed using Eq. (3).

Conclusions

Results obtained from investigations of intramolecular hydrogen bonding in *Mannich* bases are presented and discussed in this review. *Mannich* bases have been used as model systems to study the nature of the hydrogen bond as well as the environmental and temperature influence on hydrogen bond properties including the proton transfer reaction. The advantages of these compounds are the high stability of the hydrogen bond, the defined stoichiometry, and the presence of similar structures in different phases and solvents, and at different temperatures. Additionally, direct electronic coupling between acidic and basic centres is substantially reduced by the methylene bridge. Very specific features of so-called resonance assisted hydrogen bonds do not influence the final conclusions resulting from the experimental studies.

Evidences of the high stability of these intramolecular hydrogen bonds are provided by IR and dipole moment studies. In low polar solvents, *Mannich* bases with $\Delta pK_a < 2$ can be characterized as systems with medium to weak hydrogen

bonds. $\Delta\nu(\text{OH})$ is in the order of 600–700 cm^{-1} , and the electronic absorption spectra closely resemble those of phenols. No open forms with a free $\nu(\text{OH})$ bands are observed. Vector analysis of dipole moments suggests that the closed forms with intramolecular hydrogen bond prevail in solution. Comparison of the IR and UV-Vis spectra of *Mannich* bases in low-polar solutions with the spectra in the solid state suggests that in such solutions the molecules exist as nonionic forms with intramolecular hydrogen bonds. Dipole moments calculated for such structures precisely fit the dependence of $\Delta\mu$ on ΔpK_a . For systems with $\Delta pK_a > 2$ an increase of $\Delta\mu$ was observed which reaches the value of 2.5 D in benzene at $\Delta pK_a = 4$. At $\Delta pK_a > 3$ an increase of $\Delta\nu(\text{OH})$ was observed, and in the UV-Vis spectra a phenolate absorption appears. Solvent polarity increase and temperature decrease shift the equilibria towards ionic forms. The last fact shows that the enthalpy change upon proton transfer is negative. The observed effect does not depend on concentration. Together with an increase of dipole moments with solvent polarity this indicates that intramolecular proton transfer equilibria exist in solution.

The proton transfer equilibrium constants were determined in different solvents at various temperatures, mainly by UV-Vis spectroscopy, but also with the use of IR spectroscopy. Studies performed simultaneously by various techniques (UV-Vis, IR, NMR spectroscopy, dipole moment measurements) present very uniformly the presence of intramolecular proton transfer in *Mannich* bases. For this process, negative values of $\Delta H_{\text{PT}}^\circ$ and $\Delta S_{\text{PT}}^\circ$ were found. Participation of the solvent molecules is evident. It was shown that $\Delta H_{\text{PT}}^\circ$ correlates linearly with the solvent polarity parameter E_T .

It can be observed that – independent of temperature and solvent polarity – large regions of molecular forms exist. For molecules with ΔpK_a values above 4 the possibility of self-association at room temperature in non-polar and low-polar solvents has been demonstrated. The mechanism of this process is determined by ionization. If the concentration of zwitterionic forms is high, cyclic dimers are formed.

The increase of the polarity of the solvent up to $\epsilon = 10$ leads to an enhancement of self-association. Polarity increase in nonprotic solvents promotes the proton transfer, but specific interactions with the solute are too weak to break the aggregates. Further aggregation beyond dimers was observed as well. UV-Vis spectra show that all forms in aggregates are ionic species.

Decrease of temperature enhances the tendency to self-association. For example, *Mannich* bases with $\Delta pK_a \approx 3$ which do not associate at room temperature show some evidences of association in CH_2Cl_2 at 200 K, whereas compounds with $\Delta pK_a \approx 2.6$ do not associate under such conditions.

Due to the stability of the intramolecular hydrogen bond and the large amount of information obtained by various experimental methods, a general model of hydrogen bonding and proton transfer equilibria in *Mannich* bases was established, pointing out some universal features of hydrogen bonded systems. Informations on the role of the solvent in proton transfer processes or the influence of self-association on the position of proton transfer equilibria in low-polar solvents are obtained and can be applied to more general intermolecular hydrogen bonded systems.

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