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Structure investigation of intramolecular hydrogen bond in some substituted salicylaldehydes and 4-aminoantipyrine derivatives in solution and in the solid state

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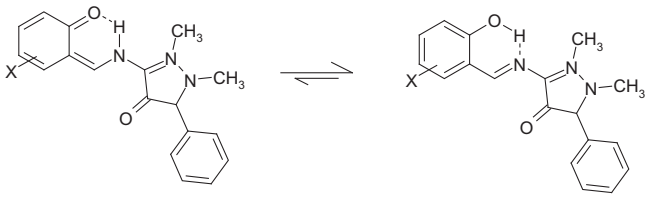
HIGHLIGHTS

- We synthesized seven o-hydroxy Schiff bases from 4-aminoantipyrine.
- We performed combined solution ^{1}H, ^{13}C and ^{15}N and solid state ^{13}C and ^{15}N NMR spectra.
- The positions of tautomeric equilibria of Schiff bases were defined.
- The pK_a measurements were done to compare with NMR data.

GRAPHICAL ABSTRACT



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ABSTRACT

Seven imine derivatives obtained by condensation of appropriate aldehydes and salicylaldehydes with 4-aminoantipyrine were investigated in terms of intramolecular hydrogen bond structure. On the base of ^{1}H, ^{13}C and ^{15}N NMR measurements in solution and in the solid state we found out that all compounds which can form such structure exist as OH forms with strong H-bonds to nitrogen atom. The structure conclusions taken from NMR study were confirmed by pK_a measurements. Surpassingly, the positions of protons in H-bridges only very slightly depend on the substituents in aldehyde used for condensation and on the phase (solution vs. solid state). The influence of antipyrine moiety seems to be the major factor defining H-bond structure.

Introduction

The imines called as the Schiff bases obtained by condensation of aldehydes and primary amines are well known since 1864 [1,2].

The unique chemical properties of those compounds are the main reason of very extensive application of Schiff bases in various areas of organic chemistry: transition metal complexes applied in homogenous catalysis [3–6], coordination chemistry [7], modern material technology (nonlinear optical materials) [3,8,9]. The Schiff bases were also used in pharmaceutical industry as the components of antibiotics, antibiotics, antiallergic, antiphlogistic and antitumor substances [2,10–12]. The imino moiety is very useful active center of many biological systems [13,14]. As a very good example of this application are extensive study of gossypol-Schiff bases derivatives studied by Przybylski et al. applying many spectroscopic, theoretical and X-ray methods [15,16].

The Schiff bases obtained from different substituted salicylaldehydes can form intra- and intermolecular hydrogen bonds, which mostly determine the chemical and physicochemical properties of those compounds [17–25]. Various studies have shown that

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Schiff bases derived from salicylaldehyde and its derivatives have considerable biological importance because of presence of many active donor atoms (N and O) in molecules of these compounds and being to some extent analogous to biological systems [26].

Imines obtained from heteroaromatic compounds containing nitrogen atoms in the ring have efficient biological activities [27]. For this reason Schiff bases derived pyrazolones are now studying as a new kind of chemoterapeutic [28].

Schiff bases obtained from 4-aminoantipyrine (4AAP) exhibit great variety of biological activities such as antitumor, fungicidal, bactericidal, antiviral, anti-inflammatory [29], antipyretic, analgesic, antiproliferative and antioxidant activities [30–32].

To perform structural studies of Schiff bases many analytical methods including all spectroscopic measurements and theoretical calculations were applied. Some of them were presented and reviewed in following papers [33–46].

For the present investigations we have chosen five 2-hydroxy aldehyde derivatives and one 2-hydroxy dialdehyde derivative (2,6-diformyl-4-methylphenol) capable to form intramolecular hydrogen bonds, and one model compound – isophtalaldehyde – which is not able to do this.

It is known, that ^{15}N NMR is a very good analytical technique to determining proton localization in hydrogen bond formed between nitrogen atom of imine group and oxygen atom from phenolic group. Signals in the spectral range from about −50 to −220 ppm are assigned to the imine groups in different stages of proton transfer process [47,48].

In our previous studies we found out that three factors influence hydrogen bond structure (proton position in the bridge): (i) substitution in aromatic ring (the major one), (ii) the amine used for the imine formation and (iii) the phase (solution or solid state) [47].

In this paper, we report the synthesis of Schiff bases obtained from 4AAP and some o-hydroxyaldehydes as well as isophtalaldehyde as the model compound for the structure without hydrogen bond, and structural study using ^{1}H, ^{13}C, ^{15}N NMR in solution and ^{13}C, ^{15}N CPMAS NMR. To confirm the results obtained by spectroscopic method the pK_a measurements in basic and acidic conditions were performer.

Experimental

Synthesis

The imine derivatives of 4-aminoantipyrine (4AAP) have been obtained by condensation in methanol solution of parent amine and appropriate aldehyde in proportions 1:1. This is the modification of the method published previously [49]. The mixture was stirred and refluxed for 1 h. Then the mixture was cooled to room temperature. After 24 h the obtained precipitate was filtered out and washed by methanol. The authenticity and purity of obtained compounds were examined by proton NMR measurements.

NMR measurements

All NMR spectra in solution have been run on Bruker DRX Avance 500 and Varian VNMRS 600 spectrometers using 5 mm TBI Z-gradient and auto XID probeheads, respectively at room temperature. The signals assignment has been done on the base of gCOSY, gHSQC and gHMBC experiments using standard Bruker and Varian procedures for both acquisition and data processing. The chemical shifts of proton and carbon signals are referred to internal TMS whereas the nitrogen-15 chemical shifts are referred to external nitromethane as a standard. The CPMAS spectra were done using Bruker Avance II 500 equipped with 4 mm MAS ^{1}H/BB probehead at room temperature. Typical CPMAS experimental conditions for ^{15}N measurements were: spectral width 25 kHz, acquisition time 30 ms, contact time 4 ms, rotation rate 6–10 kHz, relaxation delay up to 180 s depending on relaxation properties of the sample, number of scans about 300. For carbon CPMAS experiment the following conditions were applied: spectral width 31.250 kHz, acquisition time 30 ms, contact time 2 ms, rotation rate 10–11 kHz, relaxation delay up to 180 s and about 100 of scans for each spectrum were collected. For short contact time CH spectra the contact time 40 μs was applied. The basic acquisition parameters for CPMAS spectra (contact times, acquisition times, power ratio on both channels during spin-look and relaxation delays), for both carbon and nitrogen measurements, have been optimized to obtain the highest possible signal to noise ratio. Additionally the spinning rate was individually adjusted to move the rotational side bands in the region without real signals.

UV VIS spectrophotometric measurements

The measurements were carried out by means of spectrophotometric titration. Perkin–Elmer Lambda 650 UV–Vis double beam spectrophotometer, with automatic stirrer, was used for absorbance measurements. All UV–Vis spectra were recorded in 220–500 nm range, 1.00 cm quartz microcells were used. The compounds were dissolved in acetonitrile:methanol (90%:10%) mixture and titrated with methanosulfonic acid solution. The same solution was titrated with sodium hydroxide in acetonitrile:methanol (90%:10%) mixture. For each point of a known pH the absorption spectrum was recorded. pH measurements were made with Cerco-Lab system with a pH-meter using a combined glass electrode. The electrode was calibrated in the buffer system of 2,6-dinitrophenol/tetrabutylammonium 2,6-dinitrophenolate in acetonitrile. Concentrations of compounds used for all spectrophotometric measurements were around 2×10^{-5}–5×10^{-5} M. All measurements were performed at 298 K temperature.

To obtain the values of dissociation constants of measured compounds (pK_a) the resulting profile of absorbance at the wavelength of maximum absorption vs pH in each series were used to obtain the equilibrium constants of complex species tested formed in each system. All calculations were performed in OriginLab software using the Henderson–Hasselbach equation, based on change in absorption as a function of pH of the solution.

$$\mathrm{p}K\mathrm{a} = \mathrm{pH} - \log\frac{[\mathrm{B}]}{[\mathrm{BH}]} = \mathrm{pH} - \log\frac{A_\lambda - A_{\lambda\mathrm{BH}}}{A_{\lambda\mathrm{B}^-} - A_\lambda}$$

where B is compound in base form and BH is compound in acid form, $A_{\lambda B}$ is absorbance at the base form and $A_{\lambda BH}$ is the absorbance at the compound in acid form.

To define the number of equilibria present in the studied system, we analyzed the A-diagrams, which show a relationship between absorbance at two, different wavelengths. The theoretical model was fitted to experimental data presented as a relationship of absorbance vs. pH. For the evaluation of electrode parameters the STOICHIO version CVEQUID software based on the nonlinear least-squares Gauss–Newton–Marquardt algorithm was used [50–52]. The resolution of the voltage measurement was <0.1 mV.

Results and discussion

Results of all NMR measurements of all antipyrine derivatives (Fig. 1) in both solution and solid state are collected in Tables 1 and 2. The liquid state spectra were run on $CDCl_3$ solutions except 2H5MITFAB sample, where due to solubility problem DMSO was used. Additionally, some experiments in CD_3CN solution were performed to look for possible solvent effects. The proton and carbon

chemical shifts were assigned by analysis of 1D spectra and homo- and heteronuclear 2D experiments (gCOSY, gHSQC and gHMBC). The assignment of nitrogen NMR signals was done on the base of heteronuclear 2D experiments (gHMBC) and analysis of chemical shifts values characteristic for nitrogen sites present in investigated molecules. The most deshielded signals, close to −100 ppm were assigned to imine nitrogen atoms. This assignment was confirmed by correlation with protons bonded to C-7 atom. The most shielded signals were assigned to cyclic amine sites. Since both of those signals are correlated with both methyl groups in five-membered ring, the differentiation of them can be done by correlation with aromatic protons. Only signals located close to −200 ppm showed such correlation so they must be assign to N-2′ position. In the carbon and nitrogen solid-state spectra the signals assignment was done by comparison with solution spectra. Additionally, to distinguish protonated and quaternary carbon atoms the short-contact time experiments were run.

The most interesting problem in structure analysis of investigated compounds is the structure of intramolecular hydrogen bonds formed by OH groups with imine moiety. The best spectral parameter to define position of proton in hydrogen bridge is nitrogen chemical shift of imine atom. The general rule is: the most upfiels shift of this signal means the strongest proton transfer from oxygen atom to nitrogen site [53–59]. For aliphatic derivatives without H-bonds this chemical shift is about −60 ppm, relative weak H-bond can shift this signal to about −100 ppm, for compounds with strong proton transfer nitrogen signal can be shifted to about −240 ppm. Position of this signal and consequently position of the proton in the bridge are determined by two structural factors: substituents present in phenyl ring and character of base used for condensation. Generally, all substituents, which increase acidity of OH group, promote proton transfer from oxygen to nitrogen atom. The influence on amine residue on proton position is generally smaller and aliphatic derivatives promote stronger proton transfer comparing with aromatic analogues. The second parameter suitable for structure elucidation is carbon chemical shift of formally C-OH atom. In this case we observe opposite effect, strong proton transfer to nitrogen atom causes the downfield shift of this signal. This effect is much weaker than those observed for nitrogen chemical shift. For compounds without H-bonding the C-2 signal is located close to 155 ppm, proton transfer process can shift it to about 175 ppm. In contrast to imine nitrogen chemical shifts the C-2 chemical shifts are less diagnostic since they are also affected by substituents present in phenyl ring.

The analysis of spectral data should be started from nitrogen chemical shifts. The first observation is the very narrow range of changes for imine chemical shifts. For simple aliphatic amine derivatives this parameter spans much broader range. For example, for 5-Cl derivative δ_{Ns} = −90.7 ppm, for 5-NO_2 δ_{Ns} = −110 ppm, for 3-MeO, 5-NO_2 derivative δ_{Ns} = −176.1 ppm and for naphtyl derivative δ_{Ns} = −211.6 ppm [57,58]. It means that for antipyrine derivatives the position of proton in H-bridge is less sensitive on substituent in phenyl ring comparing with imines obtained from aliphatic amines. Some of nitrogen chemical shifts for antipyrine derivatives are upfield shifted comparing with aliphatic analogs, which could suggest more advanced proton transfer process. The nitrogen chemical shift of imine atom in ITFAB δ_{Ns} = −79.1 ppm can verify this suggestion. For aliphatic derivatives without H-bond

Table 1
Results of NMR measurements (^{1}H, ^{13}C, ^{15}N) of investigated compounds in chloroform (if no solvent specified) solution.

	4-Amino-antipyrine	SAAP	5-NO_2 SAAP	3,5-di-NO_2 SAAP	2HNAP	5-Cl SAAP	5-Cl SAAP + ^{1}H	ITFAB	2H5MIT FAB DMSO
N-1′	−259.5	−249.1–*246.5*	−247.1–*243.5*	−242.9	−249.7–*246.6*	−247.9–*244.9*	−232.4	−249.4	−245.8
N-2′	−199.5	−198.6–*199.4*	−199.9–*199.4*	−199.5	−199.2–*199.1*	−198.1–*199.3*	−198.5	−198.7	−199.2
C-3′	162.0	160.3	159.8			159.9	156.13	160.6	159.7
C-4′	118.8	116.2	115.0	112.1	116.3	115.7	111.15	118.2	115.7
C-5′	138.2	149.8	149.6	148.2	148.9	149.8	146.26	152.1	151.5
NH_2	−351.5[c] $^1J_{NH}$ = 78 Hz								
C-1″	135.4	134.3	134.0	133.3	–[b]	134.2	136.7	134.6	134.8
C-2″	122.8	124.6	125.1	125.7	–[b]	124.8	127.4	124.3	125.2
C-3″	129.0	129.3	129.5	129.7	–[b]	129.3	129.85	128.9	129.6
C-4″	125.8	127.3	127.6	128.4	–[b]	127.5	129.8	127.0	127.5
1′-Me	37.83	35.6	35.3	34.9	35.5	35.5	34.14	35.6	35.7
5′-Me	10.21	10.3	10.2	10.3	10.0	10.24	9.68	9.9	10.3
1′-Me ^{1}H	2.83	3.17	3.25	3.32	3.18	3.17	3.32	3.10	3.17
5′-Me ^{1}H	2.14	2.41	2.45	2.51	2.45	2.39	2.41	2.46	2.42
H-2								8.33	
H-3		6.95	7.01		–[a]	6.87	6.97		
H-4		6.89	8.17	8.88	–[a]	7.20	7.38	7.88	7.57
H-5		7.28			–[a]			7.44	
H-6		7.35	8.29	8.45	–[a]	7.28	7.52	7.88	7.57
H-7		9.8	9.87	9.90	10.84	9.73	9.36	9.81	9.80
5-Me ^{1}H									2.28
C-1		120.2	119.5	121.6	–[b]	121.1	119.6	138.2	122.8
C-2		*160.5*	*165.9*	*162.2*	*162.3*	*159.0*	*158.9*	*127.3*	*157.8*
C-3		116.7	117.6	137.4	–[b]	118.2	118.56	138.2	122.8
C-4		119.1	127.0	123.7	–[b]	131.5	133.6	129.0	131.0
br.									
C-5		131.9	140.2	137.4	–[b]	123.6	124.06	128.9	128.2
C-6		132.0	127.6	130.9	–[b]	130.8	131.69	129.0	131.0
br.									
C-7		160.6	158.2	155.4	156.8	158.8	158.5	156.3	154.1
5-Me									20.5
OHN		13.33	14.4	–	13.0	13.3	–	–	13.78
Ns	–	−108.5–*104.9*	−105.6–*103.3*	−124.1	−123.4–*116.0*	−104.6–*102.0*	−134.2	−79.1	−92.3

Nitrogen chemical shifts in CD_3CN solution are presented in italics.
[a] Unresolved pattern of aromatic protons signals.
[b] Unresolved pattern of aromatic carbons signals.
[c] Results obtained in DMSO solution, since in chloroform solution the NH proton signal was too broad to obtain effective polarization transfer.

Table 2
^{15}N and ^{13}C CPMAS NMR data of investigated compounds.

	4-Amino-antipyrine	SAAP	5-NO_2SAAP	3,5-di-NO_2SAAP	2HNAP	5-ClSAAP	2H5MIT FAB
N-1′	−261.5	−249.8	−244.9	−243.1	−242.6	−238.8	−235.4 −250.7
N-2′	−200.3	−199.5	−199.1	−196.5	−202.4	−200.6	−197.3 −203.4
C-3′	160.9	156.8	160.1	155.8 ov.	157.0	159.9	159.2[a] 157.8[a]
C-4′	120.9 ov.	116.2	111.4	109.0	110.9	111.9	111.9 119.7
C-5′	135.4	151.1	152.7	148.8	144.8	148.6	153.7 147.2
NH_2	−353.2						
C-1″	134.0						
C-2″	122.9 120.9 ov.						
C-3″	130.2						
C-4″	125.3						
1′-Me	41.0	35.2	34.0	36.1	33.3	33.8	37.7 31.8
5′-Me	8.7	12.0	9.4	9.9	9.0	9.9	8.9 6.8
Ns	–	−110.5	−110.1	−143.8 br.	−115.2	−108.5	−86.3 −106.7
C-2		160.6	164.1	164.3	161.2	160.9	159.6[a]
C-7		156.6	150.7	155.8 ov.	149.8	153.6	156.4 149.9

ov – Overlapped signals.
br – Broad signal.
Assignment of some aromatic CH signals is impossible due to overlapping.
[a] Assignment can be reversed.

δ_{Ns} is close to −60 ppm. The almost 20 ppm upfield shift in ITFAB is caused by pyrazol-3-one ring. If we consider this effect for the other antipyrine derivatives it will clear that in all compounds the proton transfer is less effective than in aliphatic analogs. This statement is consisting with general rule that in aromatic and pseudoaromatic imines the proton transfer is weaker than in aliphatic analogs. Very interesting is the last compound in Table 1: 2H5MITFAB. In this case the δ_{Ns} = −92.3 ppm value suggests the smallest proton transfer in all investigated compounds. This is not true, because in this compound two proton-acceptor centers are present and the observed δ_{Ns} value is time averaged chemical shift for two positions: with hydrogen bond and without such structure. Considering this, and using δ_{Ns} = −79.1 ppm value for non-bonded imine, one can estimate the proper value for hydrogen bonded structure in this compound as close to δ_{Ns} = −105 ppm, which is in good agreement with the remaining values. For 5-methyl- substituted derivative (2H5MITFAB) the δ_{Ns} value close to those obtain for SAAP was expected.

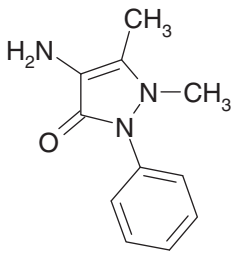
Basically, the proton position in the H-bonded systems can be determined by coupling constants analysis too. For the Schiff bases two couplings: homonuclear $^3J_{HH}$ and heteronuclear $^1J_{NH}$ involving tautomeric proton can be considered. Unfortunately, this approach is useful only for the systems where proton is significantly shifted to nitrogen atom [58]. In considered here compounds the tautomeric protons are located on oxygen atoms and mentioned couplings are very small and consequently difficult to measure. In all investigated compounds the signals of H-7 protons are slightly broadened singlets without measurable splittings. This broadening is enough to provide effective proton transfer in GHMBC experiment but not enough to show coupling constants in 2D experiments. In GHSQC experiments we do not observe polarization transfer from formally OH proton to imine nitrogen atom in all investigated compounds. Only one successful coupling constant measurement was done with 4-aminoantipyrine in DMSO solution, but it do not provide valuable information, it can only confirm signal assignment. In solid state spectra we do not observe any splittings since all the spectra were run with proton decoupling.

The next interesting issue is structural transformation connected with phase change from solution to the solid state. For imines derived from aliphatic amines with relatively strong H-bonding, such transformation causes strong proton transfer to nitrogen atom, which can be monitored by nitrogen chemical shift. For 5-NO_2 derivative nitrogen signal is shifted from δ_{Ns} = −110 ppm to δ_{Ns} = −200.9 ppm and for 3-MeO,5-NO_2 compound from δ_{Ns} = −176.1 ppm to δ_{Ns} = −207.9 ppm [57]. For investigated antipyrine derivatives such transformation changes nitrogen chemical shifts less extensive. Only for 5-NO_2 derivative this effect exceeds about 20 ppm, the most unexpected behavior was found for naphtyl derivative 2HNAP, where practically no effect of phase transfer was observed, which means that in both phases the OH form is dominant one. The Schiff base obtained from naphtylaldehyde and methylamine in both chloroform solution and in solid state exists as NH form (δ_{Ns} = −211.6 ppm in solution and δ_{Ns} = −247.3 ppm in the solid state) [58]. For the 2H5MITFAB sample in the solid state nitrogen CPMAS spectrum two signals were detected: δ_{Ns} = −86.3 ppm and δ_{Ns} = −106.7 ppm. Since in this compound two imine sites and only one OH group exist, we can state that in the solid state the proton transfer between those sites is frozen and consequently signal δ_{Ns} = −86.3 ppm should be assign to non-hydrogen bonded imine and signal δ_{Ns} = −106.7 ppm to hydrogen-bonded site. This is very close to the δ_{Ns} values in solution calculated above, it means that the proton position in hydrogen bridge is almost the same in both phases. The position of the proton in hydrogen bridge can be estimate by analysis of carbon chemical shifts too. Is known the best estimation is provided by C-2 chemical shift. For antipyrine derivatives the major problem is with carbon signal assignment in the solid state spectra. Practically, comparing regular and short contact time spectra we can assign only C-7 signals. The other interesting quaternary carbon signals (C-3′, C-2) are located in very narrow range between 156 and 166 ppm and there is no argument to assign them unmistakably. The position of those signals can lead only to the conclusion that proton is located close to the oxygen atom (for NH form the C-2 signals should be downfield shifted to about 170 ppm). The

remaining quaternary carbon atoms signals (C-4′ and C-5′) are in typical position close to 120 and 150 ppm respectively and can be assigned. Unfortunately, those chemical shifts do not provide valuable structure information.

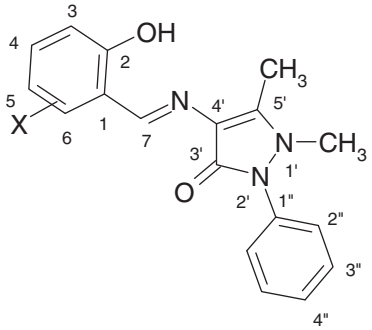
For the compounds containing more than one nitrogen atom it is very interesting to decide, where those compounds would be protonated. For such experiment the 5-ClSAAP derivative was chosen. The results of NMR measurements of protonated 5-ClSAAP are presented in Table 1. The analysis of carbon chemical shifts shows that the biggest differences between neutral and protonated forms are observed in antipyrine ring and in 1″ and 2″ position in phenyl ring. It means we can expect that protonation site is in antipyrine ring. To confirm this suggestion we can compare the chemical shifts of C-7 atom close to possible protonation site on imine atom. In both neutral and acidic conditions this parameter is completely unchanged. Much better insight into protonation process can be made on the base of nitrogen chemical shifts. The $\delta_{Ns} = -134.2$ ppm value for protonated species (the appropriate value for neutral compounds is $\delta_{Ns} = -102.0$ ppm) suggest some structure changes in this position, but it cannot be protonation reaction. In the case of full protonation one can expect much stronger effect. In simple Schiff bases [53] protonation process shifts nitrogen atom upfield to $\delta_{Ns} = -180$ ppm. Much smaller effect observed for 5-ClSAAP can be caused be solvent (pK_a) effect. The decision which amine nitrogen atom was protonated can be done using nitrogen chemical shifts of those atoms. The chemical shift of N-2′ atom is practically unchanged whereas those for N-1′ is shifted downfield about 12 ppm. In contrast to protonation of imine atom, where strong upfield effects are observed, the nitrogen chemical shifts of tertiary amines are much less sensitive on protonation and additionally this effect can be upfield or downfield [48,54–56]. Since the effect of this range was found on N-1′ atom we can state that this is protonation site.

To establish the influence of pH on shape and intensity of UV–Vis spectrum and pK_a values of substituted salicylic aldehydes and 4-aminoantipyrine derivatives a group of four compounds was chosen (5-ClSAAP, 5-NO_2SAAP, 2HNAP and ITFAP).



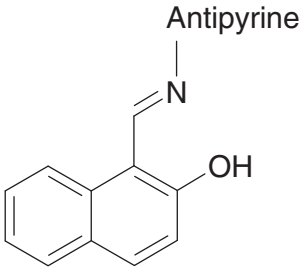
4-Amino-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one

4-Aminoantipyrine

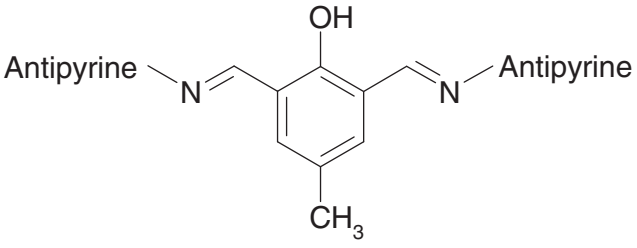


4-{[1-(2-Hydroxy-phenyl)-methylidene]-amino}-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one

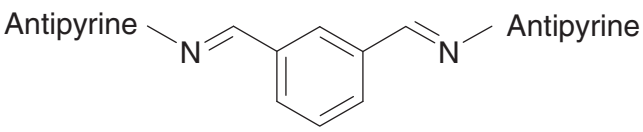
X=H	SAAP
X=5-NO_2	5-NO_2SAAP
X=3,5-diNO_2	3.5-diNO_2SAAP
X=5-Cl	5-ClSAAP



2HNAP



2H5MITFAP



ITFAP

Fig. 1. Compounds under investigations.

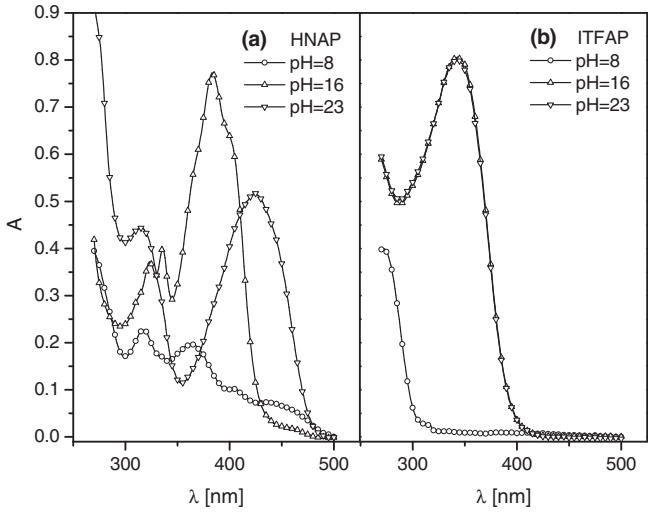


Fig. 2. Absorption spectra of HNAP (a) and ITFAP (b) in different pH.

Investigated compounds, 5-ClSAAP, 5-NO_2SAAP, 2HNAP and ITFAP in acetonitrile:methanol (9:1) solution exhibit strong changes in position and intensity of UV–Vis spectra, when the pH is changed from basic to acidic. For example for 2HNAP a shift of the long-wave band from 364 nm in pH = 8 to 383 nm in pH = 16 and to 425 nm in pH = 23 was observed (Fig. 2a). Generally all investigated compounds show similar changes of UV–Vis spectra. In alkaline solution we observe a batochromic shift, whereas in acidic solution there is a hypsochromic shift present. In case of ITFAP derivative there are no changes of the spectrum in alkaline solution (Fig. 2b).

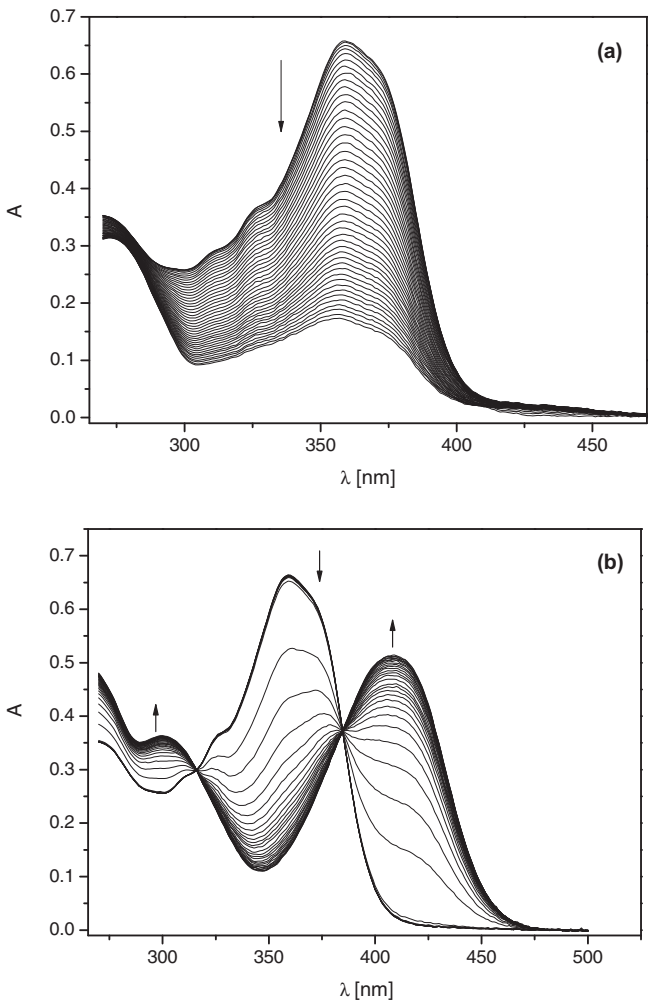


Fig. 3. Titration spectra of 5-ClSAAP in mixture acetonitrile:methanol (9:1) in pH range: (a) 8–16 and (b) 16–23.

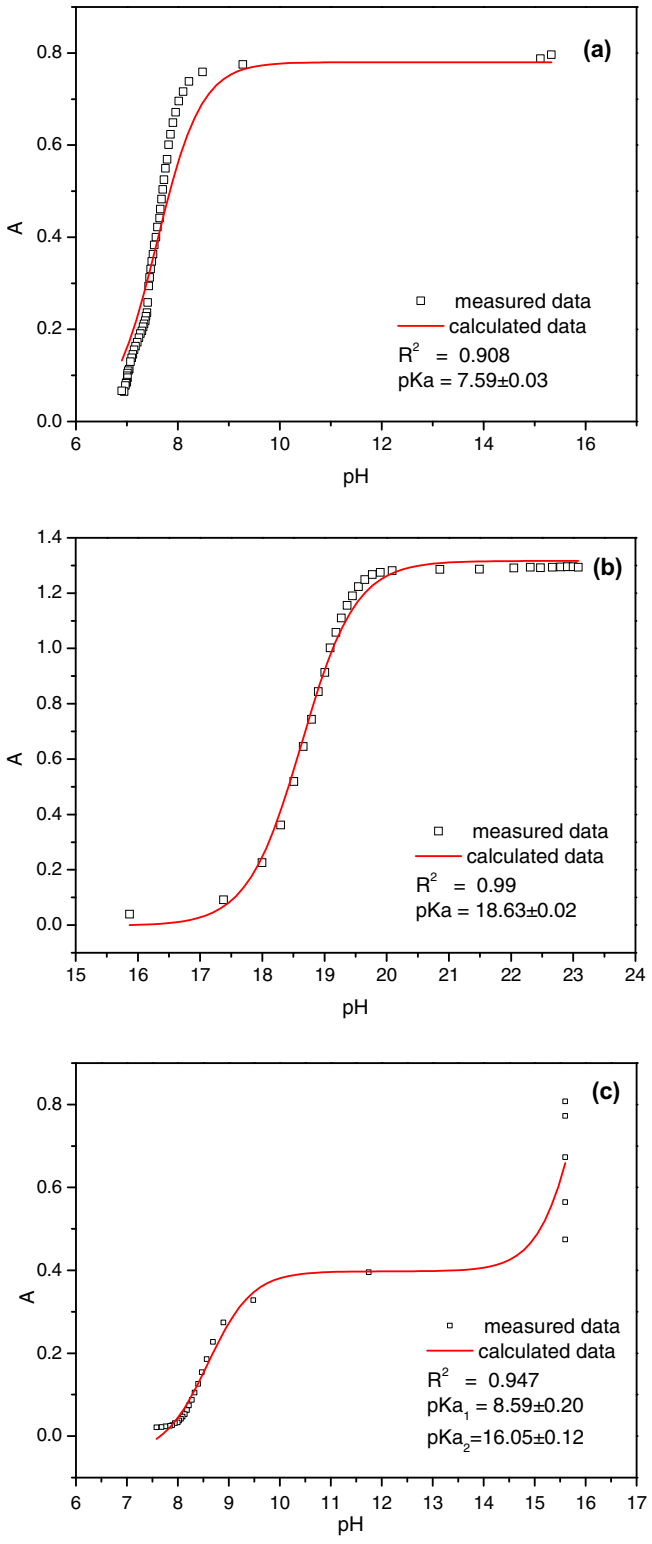


Fig. 4. Spectrophotometric titration curves – A vs pH curves for: (a) 5-NO_2SAAP at λ = 385 nm in pH range 8–16, (b) 5-NO_2SAAP at λ = 433 nm in pH range 16–23, and (c) ITFAP at λ = 343 nm in pH range 8–16.

Table 3
pK_a values with uncertainties obtained for 5-ClSAAP, 5-NO2SAAP, 2HNAP and ITFAP in mixture acetonitrile:methanol (9:1).

Compound	pK_{a1}	pK_{a2}
5-ClSAAP	7.76 ± 0.02	20.03 ± 0.06
5-NO_2SAAP	7.59 ± 0.03	18.63 ± 0.02
2HNAP	8.05 ± 0.04	20.35 ± 0.06
ITFAP	8.59 ± 0.20	16.05 ± 0.12

UV–Vis spectra of these molecules were recorded in pH range 8–23 (Fig. 3a and b). Observed spectral changes suggest the presence of two acid–base equilibria for all investigated compounds. The complex character of the acid–base equilibria are consistent with the changes of absorption as a function of pH, where for selected wavelength there are inflections visible, suggesting presence of minimum three protolytic forms. For 5-ClSAAP, 5-NO_2SAAP and 2HNAP one equilibria was determined in acidic solution (Fig. 4a) and the second one in alkaline solution (Fig. 4b), whereas for ITFAP both equilibria were established in acidic solution (Fig. 4c). This is the result of the compound structure. ITFAP is not a salicylaldehyde derivative. The acid–base equilibria present in alkaline solution results from dissociation of the phenolic substituent in the salicylaldehyde group, whereas the one present in acidic solution is associated with the aminoantipyrine group. Analyze of the pH-spectroscopic titration curves indicates, that in higher concentration of acid there is not only protonation of the compound present, but presumably also hydrolysis of the C–N bond. This hinders the quantitative analysis of these changes.

Values of the first dissociation constant of the investigated molecules, 5-ClSAAP, 5-NO_2SAAP, 2HNAP and ITFAP differ insignificantly in range 7.59–8.59 (Table 3). For 5-ClSAAP, 5-NO_2SAAP and 2HNAP pK_{a1} value reflects the alkaline properties of the molecule, while pK_{a2} value reflects the acidic properties of the molecule. ITFAP derivative containing two aminoantipyrine groups, both capable of proton acceptance, exhibit stronger alkaline properties than their derivatives with salicylic aldehyde group. Comparison of the pK_{a2} values of salicylic aldehyde derivatives suggests that the presence of nitro group (5-NO_2SAAP) in *para* position to hydroxyl group increases the acidity of the phenolic group (pK_{a2} = 18.63) in relation to compounds containing chloride atom (pK_{a2} = 20.03) in this position or being 1-hydroxynaftoic aldehyde derivative (pK_{a2} = 20.35) (5-ClSAAP and 2HNAP).

Conclusions

On the base of the previous investigation [57–59] of the structure of intramolecular hydrogen bond in Schiff bases obtained from aromatic aldehydes and different amines (aliphatic or aromatic) depends on three factors. First, the main factor are substituents in aromatic ring, second is amine used for condensation (aromatic or aliphatic), and finally the third factor; the phase (solution or solid state). Generally, in the solid state the position of the proton is much more shifted to nitrogen site. In contrast to above statements the Schiff bases obtained by condensation of aromatic aldehydes and 4-aminoantipyrine have quite different properties. First of all the dependence of proton position in the bridge on the substituents in aldehydes used in much smaller. Practically, all investigated antipyrine derivatives should be defined as OH forms with strong hydrogen bond (the difference in nitrogen chemical shifts between 5-Cl and naphtyl derivative is only 18.8 ppm in $CDCl_3$ solution), for aliphatic derivatives this difference is 120.9 ppm. The second major difference is very small difference between H-bond geometry in both solution and solid state. For 5-Cl and 5-NO_2 derivatives this difference is close to 5 ppm, the biggest one was found for 3,5-diNO_2 derivative, and for naphtyl derivative we observe opposite effect, in solid state proton is shifted less to nitrogen atom then in chloroform solution.

Concluding, we can state that the antipyrine substituent is the most important part of the molecule under study. The electron effects created by this substituent are so strong that can minimize influence of acidity of OH group on the H-bond structure. Additionally, this substituent successfully prohibits all structural changes which could promote the proton transfer from oxygen to nitrogen site in the solid state, which leads to the situation that in both phases we observe almost the same structure.

On some quantitative level the protonation site can be define on the base of pK_a value measurements. In all investigated compounds the pK_a values in acidic solution are very close one to another. This suggest that that protonation takes place on the fragment of the same structure. In the case of protonation on imine atom the intramolecular hydrogen bond of different structure should modify this parameter. The amine sites in antipyrine ring are almost equal in all derivatives and should have similar basicity and consequently similar pK_a values. Unfortunately, on the base on available data in is impossible to decide which amine atom in protonated.

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