

Application of a Schiff Base Derived from Sulfanilamide as an Acid-Base Indicator

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The present paper firstly announces the possibility of using a Schiff base as an acid-base indicator. This surprising phenomenon can be considered as an interest due to the fact that Schiff bases are usually unstable in solutions and definitely undergo hydrolysis. It was found that such a specific observation depends merely upon the chemical structure and type of the substitute of amine that reacts with aldehyde to give the Schiff base. The latter reagent 4[(4-dimethylamino-benzylidene)-amino]-benzene sulfonamide was synthesized from the condensation of sulfanilamide with *p*-dimethylaminobenzaldehyde. The reagent solution shows a reproducible change in its color due to the addition of acid and base. A UV-Vis spectroscopic characterization and acid-base equilibrium study of the reagent for its possible use as an indicator were investigated. The results show that the reagent is an amphoteric which possesses four ionization constants K_{a1} , K_{a2} , K_{b1} and K_{b2} of weak dibasic and diacidic properties. The value of pK_{a2} (9.80) is parallel to the observed transition interval pH 9.5 (yellow) and pH 10.5 (colorless), which is considered to be the indicator exponents pK_i . It was concluded that the benzyl sulfonamide group plays a key role in the stability of the reagent towards hydrolysis and also for indicator characteristics through breaking the conjugation.

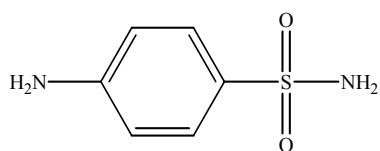
Keywords: Acid-base indicator, Sulfanilamide, *p*-Dimethylaminobenzaldehyde, Schiff base, 4[(4-Dimethylamino-benzylidene)-amino]-benzene sulphonamide

INTRODUCTION

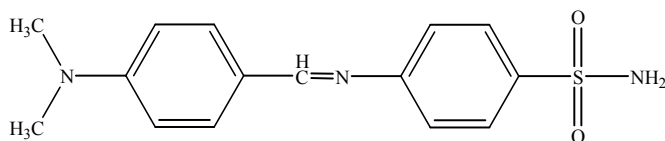
Sulfanilamide (**1**) is well known as the simplest molecule that belongs to sulfa drugs or sulfonamide derivatives. Recently, we have studied the effect of the presence of surfactant on the kinetic of reaction of six sulfonamides with *p*-dimethylaminobenzaldehyde (DAB) at pH = 2 [1]. Such investigations were carried out through following the increases in the visible absorption due to the formed Schiff base with time. Surprisingly, it was noticed that there is a reproducible change in the color of solution through the addition of base and acid. Indeed, the hydrolysis of imine group of the Schiff base makes such phenomenon quite unexpected. More

recently, we have extended our investigations of the above reaction through using bromhexine drug [2,3] and three β -lactams antibiotics [4] instead of sulfonamide. The colored solutions of these molecules do not show the above observed phenomenon of sulfanilamide. Therefore, it seems quite interesting to synthesis the Schiff base from condensation of (**1**) with DAB and then separate it in a bulk form as 4[(4-dimethylamino-benzylidene)-amino]-benzene sulfonamide (**2**). This is followed by the study of its acid-base equilibrium in order to establish whether it could be used as an acid-base indicator. It should be noted that such investigations can be considered as extension to our previous work but for phthalide derivatives substances [5,6]. A relative study was carried out by Alonso *et al.* for dihydroxynaphthalene derivative [7].

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(1)



(2)

EXPERIMENTAL

Reagents

Sulfanilamide (1) was obtained in highly pure form from State Drug Industry (SDI), Samara-Iraq. All other reagents were analytical grade commercial products purified when necessary by standard procedures. Distilled water and 99.99% ethanol were used for preparation of all solutions.

Instruments

All UV-Vis spectra were recorded on a Shimadzu UV-Vis Spectrophotometer UV-1650 PC, using 1 cm quartz cuvettes. The IR investigations were performed on Bruker FTIR Spectrophotometer model tensor 27. Potentiometric titrations were carried out using Hana Instruments Microprocessor pH meter. To control the temperature within ± 0.1 °C, a thermostated water bath Haake NK22 was used.

Synthesis of the Reagent

The Schiff base (2) was prepared by reaction of equimole (1.163×10^{-3}) of (1) and DAB. Each reactant was dissolved in a minimum amount of ethanol, then mixed together and followed by addition of 5 ml ethanol. The solution was refluxed for 24 h then left overnight for standing. The solid product was collected through filtration and then dried using drying oven at 80 °C. The product was redissolved in ethanol for recrystallization and then dried to give a yellow product of m.p.: equal to 222-225 °C with yield of 88.15%. The identification of the product was confirmed through FTIR spectroscopy which gives an apparent sharp peak at 1603.09

cm^{-1} due to the presence of imine group.

Acid-Base Equilibrium Study

The stock solutions of 1.0×10^{-3} M of the reagent (2) and 0.1 M of KCl in 25% ethanol were prepared. 8.0×10^{-4} M of both KOH and HCl in 0.1 M KCl and 25% ethanol were also prepared.

For determining the ionization constants, 15 ml of 1.0×10^{-3} M of the reagent in 25% ethanol and presence of 0.1 M KCl was titrated with HCl and KOH. KCl was added to the solutions in order to prevent the effect of ionic strength. 30-31 data points were used in each titration and at least two runs were carried out to check the reproducibility of the data. A sufficient time (2-3 min.) was allowed between successive additions of KOH and HCl solutions to permit equilibrium to be reached. The ionizations constants (pK_a and pK_b) were calculated from the intercept of pH vs. $\log([\text{salt}]/[\text{acid}])$ and $\log([\text{salt}]/[\text{base}])$, respectively [8]. The pK_b was calculated from subtracting pH from 14 for converting pH to pOH. All measurements were carried out at constant temperature of 25 °C.

RESULTS AND DISCUSSIONS

Due to the very low solubility of the compound (2) in neutral aqueous solution, an aqueous ethanolic solution was used. The effect of pH upon the UV-Vis absorptions of the reagent has been investigated. Figure 1 illustrates this effect upon the absorptions of the reagent at the Vis region. The UV region was excluded from this figure due to the apparent complicating that appeared when merging these spectra at this region. However, the spectra indicate the occurrence of different forms of the compound at the pH studied and the existence of more than one pK_a and pK_b values. In addition, it is apparent that the absorption of the broad peak at 410 nm undergoes a substantial successive decrease with both increasing and decreasing the pH from neutral ($\text{pH} = 7.05$). The reason for this phenomenon may in generally be attributed to the reduction that occurs in conjugation. The spectra clearly show that at high pH ($\text{pH} = 11$ and over) the solution color turn from yellow to colorless. Indeed, this is the basis for the use of this reagent as an acid-base indicator. While, at low value of pH ($\text{pH} = 2.3$) there is a strong red shift to a well

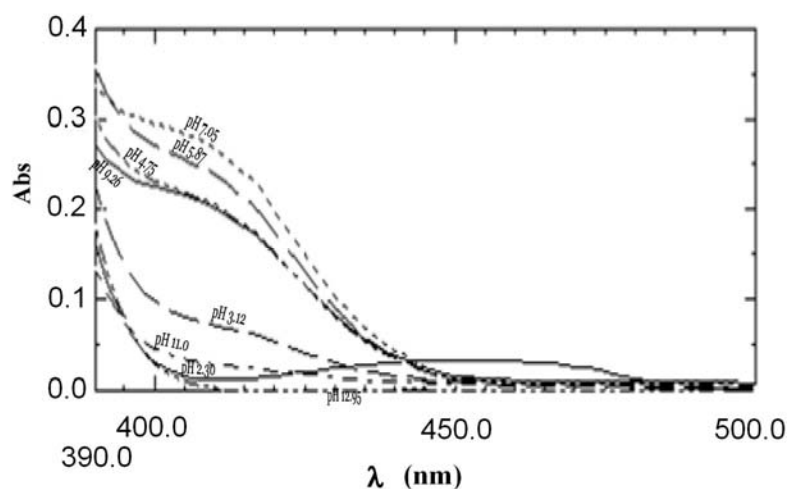


Fig. 1. Visible absorption spectra of the reagent (9.333×10^{-5} M) in 25% ethanol at different pH (2.30, 3.12, 4.75, 5.87, 7.05, 9.26, 11.0 and 12.95).

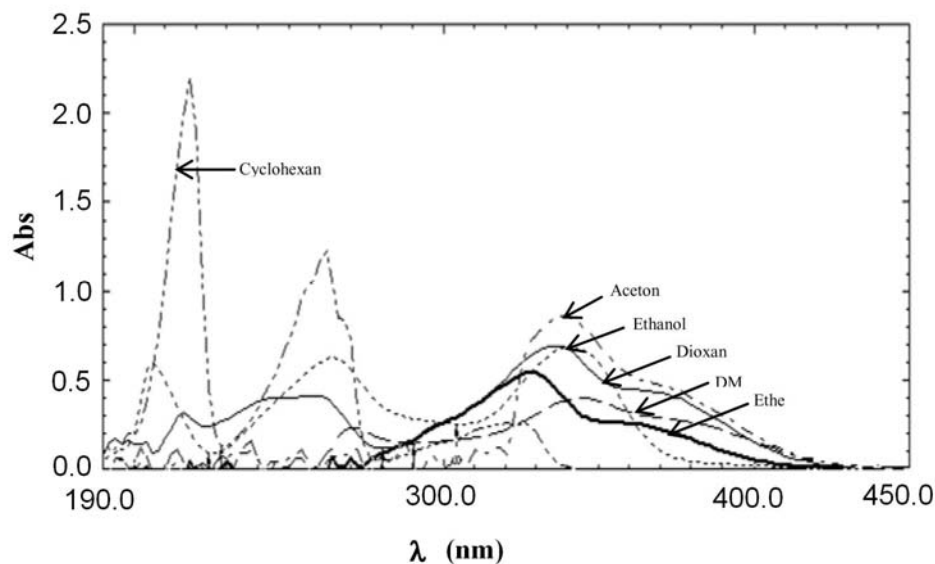


Fig. 2. UV-Vis spectra of the reagent in various organic solvents (3.3×10^{-4} M).

defined weak broad band at 447 nm which may be attributed to the protonation of the nitrogen of imine group [1,9].

A study of the UV-Vis absorption spectra of the reagent (2) in various organic solvents was carried out and the results are illustrated in Fig. 2 and Table 1. The results indicate that the substance (2) possesses a remarkable solvatochromism (solvent sensitive) that makes it quite difficult to write any

correlation between the dielectric constant of solvent with absorption peak. However, band II undergoes a bathochromic shift with the decreases in solvent polarity due to the presence of conjugation. On the other hand, the not well defined III and IV bands at UV region for relatively polar solvents, in contrast to that for cyclohexane, may be attributed to the interaction of the reagent with the solvent molecules. Furthermore, the

Table 1. UV-Vis Data for the Reagent in Various Organic Solvents (3.3×10^{-4} M)

Solvent	ϵ^a	Band I	Band II	Band III	Band IV
DMF	37.6 [10]	365 (3107)	344 (4275)	270 (2507)	-
EtOH	24.3 [11]	-	340 (7328)	264 (6718)	206 (6396)
Acetone	20.7 [11]	372 (5250)	340 (9203)	-	-
Ether	4.3 [11]	362 (2785)	328 (5807)	-	-
Dioxane	2.2 [11]	368 (5143)	336 (7393)	258 (4425)	-
C ₆ H ₁₂	2.0 [11]	-	326 (2742)	262 (13136)	218 (23550)

^adielectric constant at 25 °C.

deformations of the UV bands in acetone may be attributed to change in the equilibrium of keto-enol tautomerism caused by the presence of the reagent in contrast to that in the blank solution.

As it can be seen clearly above, the Vis spectra of the reagent change considerably with both increasing and decreasing pH of the solution. Therefore, the acid-base equilibrium study using potentiometric titrations was carried out twicely with acid and base. The results indicated that the reagent is an amphoteric which possesses dibasic and diacidic properties as illustrated in Figs. 3 and 4, and Table 2. This phenomenon was expected since the reagent solution gives a neutral pH (7.05). The values of ionization constants indicate that the acidic and basic behavior of the reagent is quite weak. For example, K_{a1} and K_{a2} are somewhat comparable to K_{a2} of phosphoric acid ($K_{a2} = 6.3 \times 10^{-8} \text{ M}^{-1}$) [11] and K_a of glycine ($K_a = 1.6 \times 10^{-10} \text{ M}^{-1}$) [12], respectively. While K_{b1} is comparable to K_b of aniline ($K_b = 4.2 \times 10^{-10} \text{ M}^{-1}$) [12], the value of K_{b2} denotes that the basicity is lower than quinoline ($K_b = 3.0 \times 10^{-10} \text{ M}^{-1}$) [12] and much higher than pyrrole ($K_b \approx 2.5 \times 10^{-14} \text{ M}^{-1}$) [12]. K_{b1} of the presented reagent may be attributed to the protonation of the amine nitrogen substituted by two methyl groups. The latter releasing electrons groups may stabilize the ion of positive charge as illustrated in Scheme 1. K_{b2} could be attributed to the protonation of imino nitrogen according to its confirmed visible peak at 447 nm. The amino group of sulfonamide may hardly protonated due to the presence of SO_2 group.

The value of $\text{p}K_{a2}$ agrees with observed transition interval between pH 9.5 (yellow) and pH 10.5 (colorless) which should be lying at $\text{pH} = \text{p}K_a \pm 1$ (or $\text{pH} = 14 - \text{p}K_b \pm 1$) [13]. Therefore, $\text{p}K_{a2}$ can be considered as the indicator exponents ($\text{p}K_i$) for the

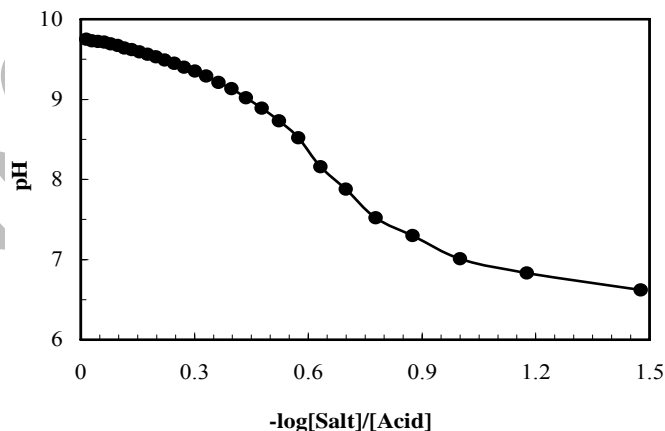


Fig. 3. potentiometric plot of the reagent upon titration with KOH at 25 °C.

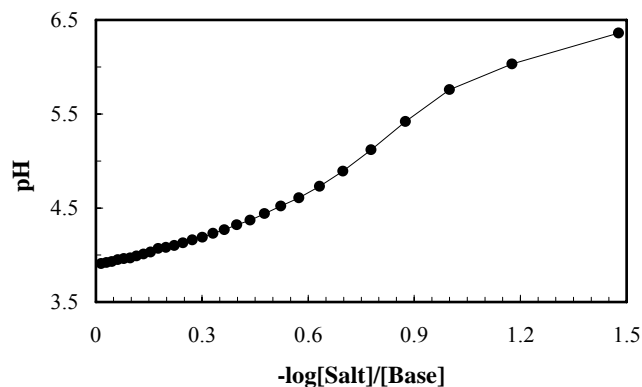
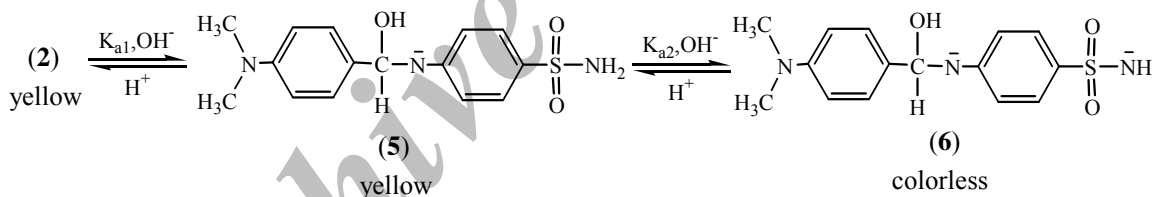
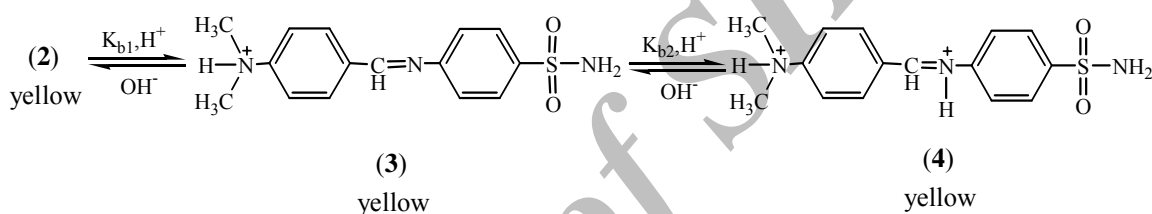


Fig. 4. potentiometric plot of the reagent upon titration with HCl at 25 °C ($\text{pOH} = 14 - \text{pH}$; $\text{p}K_b = 14 - \text{intercept}$).

Table 2. Ionization Constants with the Related Statistical Parameters of the Reagent at 25 °C

pK (Ionization constant)	Value (M ⁻¹)	r (Correlation coefficient)	S.E. (Standard error)
pK _{a1} (K _{a1})	7.80 (1.58 × 10 ⁻⁸)	0.994	0.0392
pK _{a2} (K _{a2})	9.82 (1.51 × 10 ⁻¹⁰)	0.991	0.0471
pK _{b1} (K _{b1})	14 - 4.54 = 9.46 (3.46 × 10 ⁻¹⁰)	0.996	0.0291
pK _{b2} (K _{b2})	14 - 3.87 = 10.13 (7.41 × 10 ⁻¹¹)	0.995	0.0299



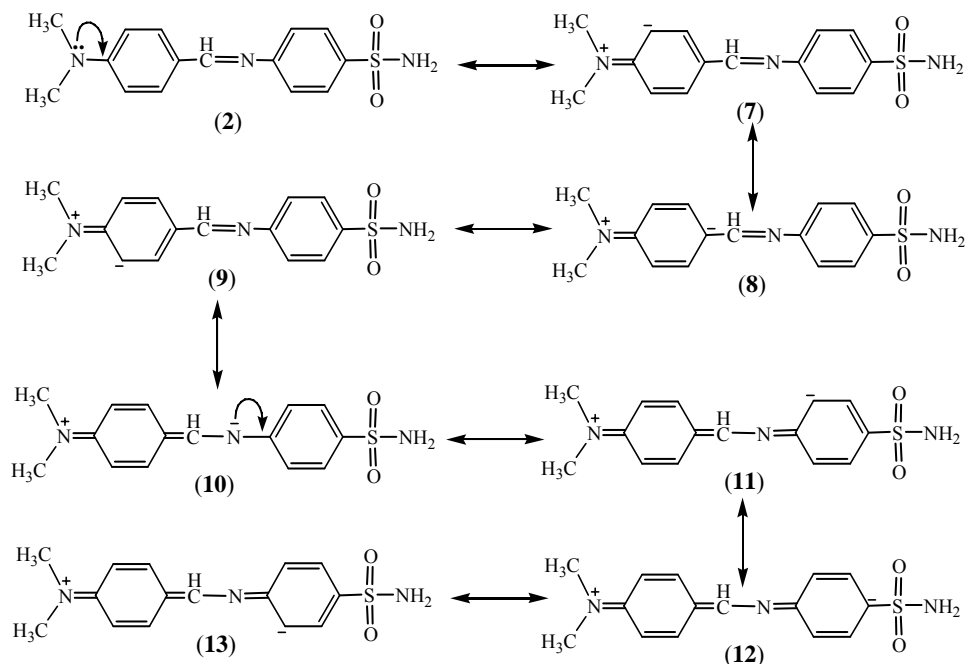
presented reagent. Obviously, it is not easy to give a straight forward interpretation for such phenomenon. However, K_{a1} may be interpreted by the attack of OH^- group to the imine carbon atom as presented in Scheme 2. While K_{a2} may be related to the deprotonation of one hydrogen atom from sulphonamide amino group as shown in the latter Scheme.

Thus, the different colors shown by species (6) from both (5) and (2) involved in the equilibrium of Scheme 2 allows the use of compound (2) as an acid-base indicator, placing the transition interval between pH 9.5 (yellow) and pH 10.5 (colorless). The yellow color of the reagent (2) in neutral state may be attributed to the conjugation as illustrated by the resonance structures of Scheme 3. While, the yellow color exhibited by species (3) could also be related to the conjugation phenomenon as presented by Scheme 4.

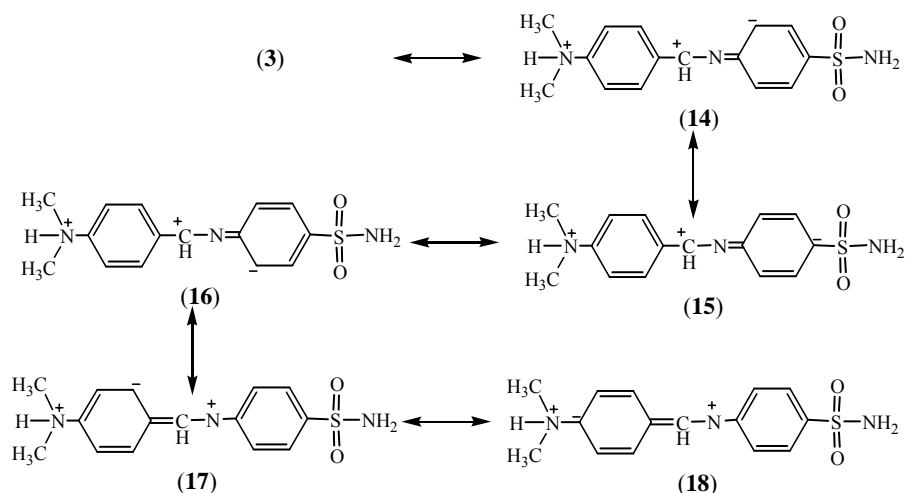
It is apparent from Schemes 3 and 4 that species (3) possesses less conjugation than (2) which gives the reason for the decreased Vis absorption followed by a blue shift (Fig. 1) when the pH decreased. While, the strong red shift of species (4) caused by protonation of imine nitrogen was already defined and confirmed in the literature [9,14].

The yellow color of species (5) could also be attributed to the conjugation as explained by Scheme 5. The especially stable structure of species (20) may give the specific reason for the resistant of the presented Schiff base towards hydrolysis. The decrease in conjugation of species (5), in contrast to that of (2), gives also the reason for the decrease in the Vis absorption (Fig. 1) which are followed by a blue shift when the pH increased above the neutral form.

The colorless of species (6) may be related to the absence



Scheme 3



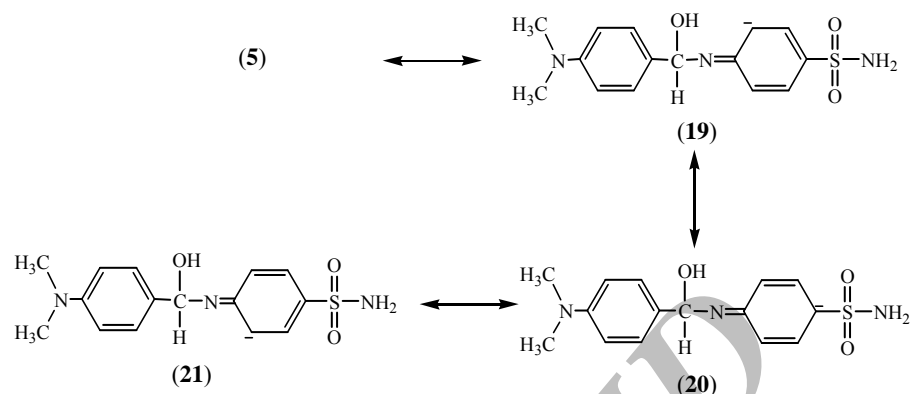
Scheme 4

of conjugation in its structure. The latter phenomenon can be raised from the especially unstable structure of species (23) due to the closeness of two negative charges as shown in Scheme 6. Such a phenomenon could definitely eliminate the conjugation of the reagent.

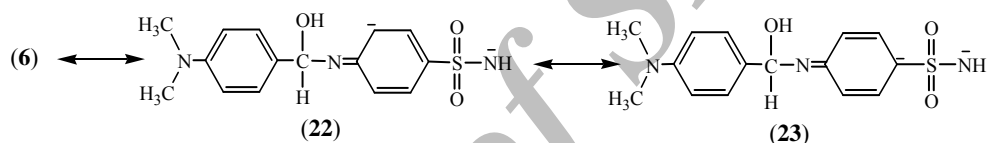
Thus, the color of the reagent solution remains yellow at pK_{b1} , pK_{b2} and pK_{a1} , while turn to colorless at pK_{a2} .

In general, indicators can be defined as those acids and bases molecules possessing considerable change in their distribution of electrons if the molecule donates or accepts a proton. Thus, our presented reagent is quite parallel to that category. From the indicators sensitivity point of view, the reagent is considered to be an acid-sensitive indicator. This is due to the fact that the transition point that lies in the alkali-pH

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Scheme 5



Scheme 6

range in a similar manner to those of alpha blue, 2,4,6-trinitrophenylacetylhydrazine, *p*-xylenolphthalein, thymolphthalein, thymoltetrachlorophthalein and guaiacolphthalein [13]. On the other hand, the sensitivity of the presented reagent towards hydrogen ions is $10^{-9.8}$ g ion l^{-1} , whereas against hydroxyl ions is $10^{-4.2}$ g ion l^{-1} [13]. Therefore, a series of acid-base titrations between carried out acetic acid and NaOH suggested that only few drops of 0.1% indicator solution (25% (v/v) ethanol-water) is required for each 100 ml solution to be titrated. The satisfactory results thus obtained may be attributed to the narrow range of pH transition interval (9.5-10.5) of the presented reagent.

CONCLUSIONS

On the basis of our results, we can conclude that the use of Schiff bases as an acid-base indicator is quite possible. For this purpose, the Schiff base must possess a specific substituent at definite position to prevent its hydrolysis. In our investigations, we have found that the presence of sulfonamide group in the *para*-position of imine nitrogen is responsible for the indicator characteristics of the presented reagent (2). It should be noted that the use of acid-base indicator is not

captured by titration method but also used to adjust the fine pH through pH indicator paper and the color of solution. Furthermore, it may seem interesting to introduce an acid-base indicator that derived from a pharmaceutical active material.

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