Chromogenic Chemosensors Based on Phenolic Imines for the Detection of Alkylamines and Lidocaine in Water and in the Vapor Phase

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Three imines comprised of 5-nitrothiophen-2-yl as electron-accepting and phenols as electron-donating groups were synthesized and used as chromogenic chemosensors to detect alkylamines. The compounds are colorless in water, but their deprotonation by the alkylamines generates the corresponding colored phenolates, which can be used to detect those analytes. The addition of cetyltrimethylammonium bromide (CTAB) causes bathochromic shift of the perichromic band of the phenolates, indicating that the compounds are transferred into the micelles. In addition, CTAB lowers the $pK_a$ of phenols and increases the stability of the phenolates, improving their performance as chemosensors. Applications were prospected with the chromogenic chemosensors adsorbed on strip papers to detect alkylamines in water and in the vapor phase. The compounds were also used in solution for the quantification of lidocaine in water. Thus, the versatility of the compounds studied allows to think about applications in industrial, environmental, and pharmaceutical areas.

Keywords: amines, chromogenic chemosensors, perichromism, vapochromism, volatile organic compounds, lidocaine

Introduction

Amines are among the most important neutral target analytes in terms of naked eye and quantitative detection. This is due to their roles in chemical, biochemical, and industrial processes. For instance, the amino functional group is present in amino acids, which are the building blocks for the formation of protein chains. The biogenic amines, which are produced from the enzymatic decarboxylation of amino acids or in amination and transamination processes, are important for the evaluation of food quality. The degradation of fish and meat releases volatile amines. Many pharmaceutical drugs have amino substituents in their molecular structures. For instance, lidocaine has a tertiary amino group in its molecular structure, being one of the most utilized local anesthetics.

The literature presents different methods of detection/quantification of amines, such as gas chromatography-mass spectrometry (GC-MS) and high-performance liquid chromatography (HPLC). Although these methods are recognized for their sensitivity and efficiency, they have disadvantages, such as their availability, difficulties in their operation, high cost, and the analyses are time-consuming and laborious. The design of molecular and supramolecular optical devices for the detection of neutral analytes has recently been gaining importance. The detection of amines with the use of molecular and supramolecular devices has been intensively explored due to their simplicity, reliability, precision, and low cost.

Thus, the design of chemosensors for the detection of amines is important for planning low cost and simple assays to verify the purity of chemical compounds, for setting up tests for clinical diagnostics, for monitoring levels of environmental pollutants, and to perform the quality control of foods and drugs. In this sense, the search for simple chromogenic chemosensors for the detection of amines in a purely aqueous medium represents a very important challenge.

A very interesting application for the chemosensors can be observed when exposed to vapors of volatile organic compounds (VOCs). These vapochromic systems in contact with VOCs change their optical properties, indicating the presence of the organic analyte. This strategy has been studied and aimed at vapors that are toxic or harmful to human health.
Merocyanines and merocyanine-like dyes are heterocyclic compounds recognized by their perichromic properties, which have been utilized in recent years in the design of many detection optical devices. Classical examples of these compounds are provided by the pyridinium N-phenolate betaine dye 1 (Figure 1), better known as Reichardt’s dye, and Brooker’s merocyanine 2. These and other perichromic dyes are capable to probe very small changes in their microenvironment, in the form of visually perceptible color changes, making them potentially attractive to be utilized in strategies for the detection of several analytes. These compounds can be utilized directly in solution (organic or aqueous medium) or associated with different materials, such as silica, polymers, hydrophobic porous membranes, polystyrene resins, organically modified silicas, mesoporous silica, glass previously treated with silanizing agents, and ionic liquids.

A very simple strategy to be designed for the detection of analytes using perichromic dyes involves the use of the protonated form of the dye, which is colorless, in solution or anchored/adsorbed in a polymeric matrix. If the system is brought into contact with an analyte that is sufficiently basic to cause the detection unit to deprotonate, the dye is generated. The appearance of color indicates the presence of the analyte in the medium, which can be visually detected and quantified. This strategy is based on the rationalization of Steiner that all hydrogen bonds (HBs) can be seen as occurring through incipient proton-transfer processes and in the case of strong HBs these processes are in a very advanced stage.

These observations led us to investigate whether it would be possible to use the same systems for the detection of amines in solution. Thus, the protonated form of compounds 1 and 2 were investigated in organic solvents (dichloromethane, acetonitrile, and dimethyl sulfoxide (DMSO)). The two compounds were capable to detect alkylated amines in the solvents, while aromatic amines did not cause any effect. The level of interaction of the protonated dyes with the amines revealed to be dependent on the basicity of the amine, on the molecular structure of the dye, and on the medium. However, these systems could not be utilized in the investigation of amines in aqueous solution, due to practical problems related to the low solubility of the compounds used and to the fact that the acidity-basicity of the species involved does not show compatibility in those experimental conditions.

Thus, the research for compounds exhibiting better solubility in water and with compatible acidity to be deprotonated by the amines represents an interesting challenge for the development of detection strategies for those analytes in aqueous medium. In this sense, we have studied the solvatochromism of some families of merocyanine-like dyes. Some of these compounds are imine dyes comprised of 5-nitrothiophen-2-yl as electron acceptor and phenolate as electron donor group. Herein we describe the synthesis of compounds 3a-5a (Scheme 1) and their use as chromogenic chemosensors for the detection of alkylamines in water. The rationale here is consider that compounds 3a-5a are colorless in water, but their deprotonation by basic amines generates the corresponding colored species 3b-5b, which can be used to detect those analytes. The differences in the use of this strategy in water in the absence and presence of a cationic surfactant were investigated. All findings were explained here in the light of a model that considers the molecular structure of the chemosensor, the micropolarity of the medium, and the basicity of the amine. Applications were prospected with the use of the chromogenic chemosensors adsorbed on strip papers in the detection of alkylamines in
vapor phase and in water, and in solution for the detection of lidocaine in water.

**Experimental**

**Materials**

All reagents were analytically pure and were obtained from Sigma-Aldrich (St. Louis, USA) and Vetec (Duque de Caxias, Brazil). The amines (n-butylamine (BTA), diethylamine (DEA), triethylamine (TEA), aniline (ANI), N-methylaniline (NMA), and N,N-dimethylaniline (NNDM)) were purchased from Sigma-Aldrich (St. Louis, USA), and distilled twice immediately before use. Lidocaine (pharmaceutical standard, > 99%) was purchased from Sigma-Aldrich (St. Louis, USA). Commercial lidocaine hydrochloride, at a 20 mg mL⁻¹ solution, stored in a 5 mL ampoule, and without the presence of vasoconstrictor, was obtained from Hypofarma (Ribeirão das Neves, Brazil). Cetyltrimethylammonium bromide (CTAB) was purchased from Sigma-Aldrich (St. Louis, USA). Ethanol (Honeywell, HPLC grade, Muskegon, USA) and acetone (Synth, Diadema, Brazil) were purified according to the procedure described in the literature 73,74 and were stored on molecular sieves (4 Å, Sigma-Aldrich, St. Louis, USA). Water used for all measurements was deionized, boiled, and bubbled with nitrogen and kept in a nitrogen atmosphere to avoid the presence of carbon dioxide.

**Methods**

The UV-Vis studies were performed using an Agilent Technologies Cary 60 and a Hewlett Packard 8452A diode array UV-Vis spectrophotometers (Palo Alto, USA). The temperature was kept at 25.0 °C in the cuvette in all measurements by coupling a thermostated water bath (MicroQuimica, model MQBTC 99-29, Palhoça, Brazil). Quartz cuvettes with 1 cm of optical path were used, being closed with a rubber septum, which was used to avoid contamination with CO₂.

Nuclear magnetic resonance (NMR) spectra were recorded with 200 MHz Bruker AC-200F and with 400 MHz Bruker Avance 400 spectrometers (Massachusetts, USA). Chemical shifts were recorded in ppm with the solvent resonance as the internal standard and data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet), integration, and coupling constants (Hz). Infrared (IR) spectra were obtained with an FT Varian 3100 spectrometer (Palo Alto, USA), by using KBr pellets. High-resolution mass spectra (HRMS) were obtained with a Bruker OTOF-Q II 10243 electrospray ionization-quadrupole time-of-flight mass spectrometer (HR ESI-MS QTOF). The melting points were determined by means of differential scanning calorimetry (DSC) analysis, by using a Shimadzu DSC-50 apparatus (Oregon, USA). The samples were dried under vacuum for 24 h before analysis.

The determinations of pKₐ values were performed at 25.0 ± 0.1 °C using a Kasvi bench pH meter, model K38-2014B (São José dos Pinhais, Brazil), with a combined glass electrode. The measurements were performed using buffer solutions, previously prepared, according to the pKₐ of each compound.

Liquid chromatography-mass spectrometry (LC-MS) measurements were performed using a LCMS-2020 single quadrupole liquid chromatography mass Shimadzu apparatus (Oregon, USA), with a Phenomenex C18 column (particle size = 5 µm; internal diameter = 4.6 mm; length = 150 mm). The sample of the compound was prepared in acetonitrile. The eluent was used an acetonitrile:water mixture (4:1; v/v) containing formic acid (1%), in a flow rate of 0.2 mL min⁻¹, and a column temperature of 27 °C.

**Synthesis of the compounds**

Compounds 3a and 4a were synthesized according with a previously described procedure. 71 4-Amino-2,6-di-tert-butyphenol was prepared in two steps. Firstly 2,6-di-tert-butylbenzo-1,4-quinone-4-oxime was prepared, according with Kharasch and Joshi,75 which was further reduced, following the procedure of Uliana et al.,76 to obtain the desired amine.

(E)-2,6-Di-tert-buty-4-(((5-nitrothiophen-2-yl)methylene)methylene) amino)phenol (5a)

5-Nitrothiophene-2-carboxaldehyde (0.04 g, 0.25 mmol), 4-amino-2,6-di-tert-butyphenol (0.05 g, 0.25 mmol), and ethanol (5 mL) were placed in a round-bottomed flask and 2 drops of glacial acetic acid were added. The reaction mixture was refluxed at 70 °C for 2 h. After the end of the period of reaction, the system was cooled to room temperature and the precipitate formed was filtered. The obtained solid was recrystallized from n-hexane. The filtrate was washed with ice-cold n-hexane. Brown solid; yield 66%; mp obtained 178.1 °C; IR (KBr) νmax / cm⁻¹ 3627 (OH free), 3400 (OH), 3090, 2961 (CH), 2871 (CH₂), 1615 (C=N), 1497 (C=C), 1335 (CH₃), 1229 (C=O), 1146 (Ar–H), 889 (C=C), 7.90 (d, 1H, J 4.4 Hz), 7.32 (d, 1H, J 4.4 Hz), 5.37 (s, 1H), 7.18 (s, 2H), 7.15 (s, 1H), 7.12 (d, 1H, J 4.4 Hz), 7.10 (d, 1H, J 4.4 Hz), 7.05 (s, 1H); ¹H NMR (400 MHz, CDCl₃) δ 1.48 (s, 18H), 5.37 (s, 1H), 7.18 (s, 2H), 7.32 (d, 1H, J 4.4 Hz), 7.90 (d, 1H, J 4.4 Hz), 8.55 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 154.3, 149.9, 147.7, 141.4, 137.1, 128.8, 128.4,
118.7, 118.7, 77.5, 77.2, 76.8, 34.7, 30.4; HRMS (ESI, TOF) m/z, calcd. for C_{19}H_{25}N_{2}O_{3}S [M + H]^+: 361.1580, found: 361.1578.

Influence of CTAB on the studied systems

Firstly, a stock solution of CTAB (2.0 × 10^{-2} mol L^{-1}) in water was prepared. In a quartz cuvette, sealed with a rubber septum, 2 mL of a previously prepared solution containing both the chemosensor (4.0 × 10^{-3} mol L^{-1}) and BTA (4.0 × 10^{-4} mol L^{-1}) were placed. Then, increasing volumes of the CTAB stock solution were added to the cuvette with a microsyringe, until no changes in the Vis spectrum were verified. The absorbances in the their maximum wavelength (λ_{max}) values for each experiment were plotted as a function of the concentration of CTAB.

Determination of pK_{a} values

A stock solution for each compound (3a-5a) was prepared at a concentration of 2.0 × 10^{-3} mol L^{-1} in anhydrous acetone. Aliquots of these solutions were transferred to glass vials. The concentrations of these aliquots corresponded to 5.0 × 10^{-5} mol L^{-1}. Afterwards, distilled water at different pH values was added. The different pH values (3.0-13.5) were adjusted by dripping KOH or HCl solutions (0.1 mol L^{-1} and/or 1.0 mol L^{-1}). The UV-Vis spectra were recorded at 25.0 °C for each solution at different pH values. The absorbance values in λ_{max} values for each experiment were plotted as a function of pH. With the application of a sigmoidal equation, the inflection point allowed collecting the pK_{a} values for each compound. In micellar systems, the pK_{a} values of the compounds were determined based on the same procedure already described, using CTAB at a concentration of 1.0 × 10^{-3} mol L^{-1}.

Self-aggregation assays

Studies were carried out observing the influence of the concentration of compounds 3a-5a on the absorbance values at the wavelength maxima. Solutions of the compound (2.0 × 10^{-3} mol L^{-1}) in anhydrous acetone were prepared. Then, in a cuvette sealed with a rubber septum, 2.0 mL of distilled water were added and then BTA to a concentration of 5.0 × 10^{-3} mol L^{-1}. With the aid of a microsyringe, small volumes of the stock solution of the compound were added, generating a new spectrophotometric reading with each addition. The absorbance values corresponding to the maximum wavelengths in each solvent were collected and used to perform absorbance plots as a function of the concentration of the compound. BTA in excess was added to ensure that the total concentration of the compound present in the medium was in the deprotonated form (3b-5b).

Study of the compounds as chromogenic chemosensors

Initially, a stock solution of each compound (3a-5a) was prepared in anhydrous acetone at a concentration of 2.0 × 10^{-3} mol L^{-1}. The same procedure was performed for the preparation of the stock solution of the different amines, but with a concentration of 3.0 × 10^{-2} mol L^{-1}. Then, aliquots of the stock solution of the compound were transferred to different volumetric flasks partially filled with water. After homogenizing the system, an aliquot of the stock solution of each amine was transferred to the flasks. The contents of the flasks were again homogenized, and the volumes were completed with water. The concentrations in the volumetric flasks were 5.0 × 10^{-4} mol L^{-1} for the chemosensors and 5.0 × 10^{-4} mol L^{-1} for the amines. Subsequently, the digital images of the solutions were made and the UV-Vis spectra were collected at 25.0 °C. The same procedure was followed for the studies containing CTAB, utilizing water in the stock solutions with c (surfactant) = 1.0 × 10^{-3} mol L^{-1}.

Stability of the compounds in aqueous and micellar medium

Firstly, a stock solution of the chemosensors at a concentration of 2.0 × 10^{-3} mol L^{-1} in anhydrous acetone was prepared. In parallel, an aqueous solution of BTA (2.0 × 10^{-4} mol L^{-1}) was prepared. Then, 2 mL of the aqueous solution containing the amine were transferred to a quartz cuvette, which was properly sealed with a rubber septum. The cuvette was inserted into the spectrophotometer and a few minutes were waited until the thermal equilibrium had been reached.

An aliquot of the stock solution of the chemosensor was transferred to the cuvette, and the concentration of the compound in the cuvette was 4.0 × 10^{-3} mol L^{-1}. Then, several UV-Vis spectra were made at 25.0 °C during time intervals and the absorbance values were recorded at λ_{max}. The proportions between the compounds and the amine were kept constant in all stability tests. The micellar tests were carried out using the same procedure described above, but the water was replaced by an aqueous CTAB solution with a concentration of 1.0 × 10^{-3} mol L^{-1}.

Spectrophotometric titrations

The titration experiments were carried out at 25.0 °C with the amines that changed the color of the solutions of the compounds. Firstly, a stock solution of each compound
and another of the amine were prepared in anhydrous acetone. An aliquot of the stock solution of compound was used to prepare a diluted solution in an aqueous medium with a concentration on the order of $5.0 \times 10^{-3}$ mol L$^{-1}$. Then, 2 mL were transferred to a quartz cuvette closed with a rubber septum and sealed with parafilm. Increasing volumes of the amine stock solution were then added repeatedly to the system, until no changes occurred in the absorbances at the $\lambda_{\text{max}}$ corresponding to the deprotonated compounds. In the experiments with a surfactant, water was replaced by a stock solution containing CTAB ($c = 1.0 \times 10^{-3}$ mol L$^{-1}$). In micellar systems, UV-Vis spectra were collected more than once to ensure that the system was in equilibrium.

The collected data were used to plot the titration curves with absorbance as a function of the concentration of the amine or anion.

### Determination of equilibrium constants and stoichiometries

The equilibrium constants ($K_{11}$, $K_{12}$, and $K_{13}$) of compounds $3a$-$5a$ with the amines were obtained using the mathematical model of Connors through linear and non-linear regressions using the Origin 6.1® software. Equations 1-3 were used to determine the equilibrium constants $K_{11}$, $K_{12}$, and $K_{13}$ for the systems in which complexes were formed with stoichiometries 1:1, 1:2, and both 1:2 and 1:3 between the chemosensor and the amine, respectively.$^{67,79}$

\[
\text{Abs} = \frac{\text{Abs}_b + K_{11}c(\text{amine})}{1 + K_{11}(\text{amine})} \quad (1)
\]

\[
\text{Abs} = \frac{\text{Abs}_b + Abs_{12}K_{12}(c(\text{amine}))^2}{1 + Abs_{12}K_{12}(c(\text{amine}))^2} \quad (2)
\]

\[
\text{Abs} = \frac{\text{Abs}_b + Abs_{12}K_{12}(c(\text{amine}))^2 + Abs_{13}K_{13}(c(\text{amine}))^3}{1 + K_{12}(c(\text{amine}))^2 + K_{13}K_{12}(c(\text{amine}))^2} \quad (3)
\]

In these equations, Abs is the absorbance value after each addition of the amine, $\text{Abs}_b$ is the initial absorbance without the addition of the amine, $\text{Abs}_{12}$ is the maximum absorbances obtained considering the interaction of 1 equiv of the compound for every 2 equiv of the amine, $\text{Abs}_{13}$ is the maximum absorbances obtained considering the interaction of 1 equiv of the compound for every 3 equiv of the amine, and $c$ (amine) corresponds to the concentration of the amine after each addition.

Job’s method was also employed. Several volumes (0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0 mL) of the solution of the compound ($4.0 \times 10^{-3}$ mol L$^{-1}$) were placed in 5 mL volumetric flasks. The volume of each flask was completed with the corresponding amine solution ($4.0 \times 10^{-3}$ mol L$^{-1}$) and the solutions were homogenized.

The UV-Vis spectra were collected at 25.0 °C and the absorbances were collected at $\lambda_{\text{max}}$ corresponding to the dyes ($3b$-$5b$). Finally, the absorbance values were plotted as a function of the mole fraction of the amine.

### Limits of detection and quantification

The linear segment obtained on the titration curve of each compound was used to calculate the LOD (limit of detection) and LOQ (limit of quantification) values. The procedure described in the literature$^{80-82}$ was applied, using equations 4 and 5.

\[
\text{LOD} = 3 \times S_b / S \quad (4)
\]

\[
\text{LOQ} = 10 \times S_b / S \quad (5)
\]

where $S_b$ represents the standard deviation of the blank solution and $S$ is the slope of the calibration curve.

### Tests with solid support

Symmetrical strips of Whatman® quantitative filter papers were cut out. The strips were dipped for 5 s in a previously prepared solution of compound $3a$ ($1.0 \times 10^{-3}$ mol L$^{-1}$) in anhydrous acetone. After the evaporation of the solvent, the strips were immersed in aqueous solutions containing different concentrations of BTA.

### Detection of amines in the vapor phase

Glass vials were washed and dried under vacuum for 24 h. The previously prepared paper strips were placed inside the glass vials, which were immediately closed with a rubber septum. An argon (99.99%) flow was passed through each system for 20 s and different amounts of BTA were cautiously placed at the wall of the vials, with the aid of a microsyringe. The ratio between the amount of BTA and the volume of each vial was used to determine the amine concentrations.

### Assays with lidocaine

The assays with lidocaine were performed according to the procedures described above. The concentration of lidocaine in the stock solutions was $3.0 \times 10^{-2}$ mol L$^{-1}$.

For the assays using commercial lidocaine hydrochloride in solution the drug was neutralized using sodium
bicarbonate. Then, the aqueous solution was extracted with dichloromethane for three times. The extracts were combined, dried with anhydrous magnesium sulfate, and the organic solvent was evaporated.

**Results and Discussion**

**Synthesis of the compounds**

Compounds 3a-5a were synthesized as shown in Scheme 2, using a methodology described by Stock *et al.*, through the condensation of 5-nitro-2-thiophenecarboxyaldehyde with the corresponding amine in ethanol as the solvent and in the presence of acetic acid as the catalyst. Compounds 3a and 4a had already been synthesized and characterized by de Melo *et al.* Compound 5a is a novel compound and was characterized using IR, 1H NMR, 13C NMR, HRMS, and DSC techniques (Figures S3-S7, Supplementary Information (SI) section).

Interaction of the chemosensors with the amines

Figure 2 shows photographs for the solutions of compounds 3a-5a in water in the absence and presence of aliphatic and aromatic amines. Only the alkylamines (BTA, DEA, and TEA) changed the color of the solutions of 3a and 4a, from colorless or pale yellow to red, while no color changes were verified for the solutions of 5a with the addition of the amines. The UV-Vis spectra of the solutions were obtained, revealing that the colored species correspond to the deprotonated species 3b and 4b (Figures S8-S10, SI section). Table 1 displays the $\lambda_{\text{max}}$ and the molar absorptivity coefficient ($\varepsilon_{\text{max}}$) values for dyes 3b-5b in water. For instance, compound 3b has $\lambda_{\text{max}} = 490$ nm and $\varepsilon_{\text{max}} = (1.804 \pm 0.006) \times 10^4$ L mol$^{-1}$ cm$^{-1}$ and dye 5b has

**Table 1.** Values of $\lambda_{\text{max}}$ and $\varepsilon_{\text{max}}$ for dyes 3b-5b in water at 25.0°C in the absence and presence of CTAB (1.0 × 10$^{-3}$ mol L$^{-1}$)

| Compound | Water | Aqueous CTAB solution | $\Delta\lambda_{\text{max}} / \text{nm}$ |
|----------|-------|-----------------------|-------------------------------------|
| 3b       | 490   | 515                   | +25                                 |
| 4b       | 480   | 508                   | +28                                 |
| 5b       | 615   | 668                   | +53                                 |

*$\Delta\lambda_{\text{max}} = \lambda_{\text{max}}$ (aqueous CTAB solution) − $\lambda_{\text{max}}$ (water). CTAB: cetyltrimethylammonium bromide; $\lambda_{\text{max}}$: maximum wavelength; $\varepsilon_{\text{max}}$: molar absorptivity coefficient.*
λ_{\text{max}} = 615 \text{ nm} \quad \text{and} \quad ε_{\text{max}} = (1.774 \pm 0.012) \times 10^6 \text{ L mol}^{-1} \text{ cm}^{-1} \quad \text{(Figures S11-S16, SI section), while 3a and 5a have λ_{\text{max}} of 405 and 430 nm.}

Compounds 3a-5a act as chemosensors according to the acid-base strategy, therefore being sensitive to the pH of the medium in which the analyte is found. The use of these chemosensors in water will depend on the pH of the medium, in the absence of the amine, being below the pK_a of the compounds in the protonated form. Thus, it is crucial to determine the pK_a of each compound to define its range of action in solution. Table 2 displays the pK_a values for compounds 3a-5a (Figures S17-S22, SI section). The pK_a value of 3a in water is 9.12 ± 0.01, while for dye 4a the pK_a is lowered to 5.91 ± 0.01, which is expected due to the presence of the chloro electron-withdrawing substituents. The presence of the tert-butyl groups, which are electron-donating substituents, increases the pK_a value to 12.25 ± 0.02.

**Table 2.** Values of pK_a determined for compounds 3a-5a in water at 25.0 ºC in the absence and presence of CTAB

| Compound | pK_a (without CTAB) | pK_a (with CTAB)* |
|----------|---------------------|-------------------|
| 3a       | 9.12 ± 0.01         | 8.57 ± 0.01       |
| 4a       | 5.91 ± 0.01         | 4.40 ± 0.01       |
| 5a       | 12.25 ± 0.02        | 10.08 ± 0.04      |

* (surfactant) = 1.0 × 10^{-3} mol L^{-1}. CTAB: cetyltrimethylammonium bromide.

The results obtained suggest that the reactivity of the compounds could be modified in a medium containing surfactant. Figure 3 exhibits photographs for the solutions of the chemosensors in aqueous CTAB solution. Data show that the solutions of 3a are pale yellow in the absence and in the presence of the aromatic amines but are pale ruby in the presence of the alkyl amines. Differently from it was verified in purely aqueous medium, 4a is colored even in absence of the amine. It means that the compound in anionic form is more polarizable and that it is interacting firmly with the positively charged groups of the surfactant molecules. 88

Another aspect to be considered is that species 3b-5b are perichromic, 71 exhibiting reverse solvatochromism. For example, for 3b, changing from water to aqueous CTAB solution, a bathochromic shift from 490 to 515 nm occurs (Table 1), which corresponds to a shift of +25 nm. Comparing the results with those obtained by de Melo et al., 71 this would correspond to leaving water and going to a less polar microenvironment, which is situated between methanol and ethanol (493.8 and 524.6 nm, respectively). For compound 5b, the value of λ_{\text{max}} changes from 615 nm in water to 668 nm in aqueous CTAB solution. This then tells us that the compound must be incorporated inside the micelle. Moreover, the analysis of the UV-Vis spectra shows very clean, not enlarged bands, which suggest the incorporation of practically all the dye molecules inside the CTAB micelles.

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![Figure 3. Solutions of compounds 3a (a), 4a (b), and 5a (c) in aqueous CTAB solution in the absence and after the addition of aliphatic and aromatic amines at 25.0 ºC. The concentrations of the amines and CTAB were 2.0 × 10^{-4} and 1.0 × 10^{-3} mol L^{-1}, respectively.](image)
CTAB medium is sufficiently acidic to be predominantly in the deprotonated form (see also Figure S23, SI section). Thus, the use of compound 4a as chemosensor in this medium should be discarded. Other interesting result is that compound 5a, pale yellow in aqueous CTAB solution, now is deprotonated if the alkylamines are added, generating blue colored solutions of 5b. These observations are a result of the changes in the pK, values of the compounds with the use of CTAB above its CMC.

Some experiments were performed to verify the stability of the compounds in water at pH = 7.0 and 25.0 °C in the absence and presence of CTAB. The tests showed that for compound 4b the UV-Vis spectrum underwent little change as a function of time, which reflects the maintenance of color in the system (Figure S24, SI section). However, for compound 3b, the absorbance value at 490 nm starts to decrease after 200 s, indicating the hydrolysis of the imine, thus showing the superior stability of imines replaced with chlorine substituent. Layer reported greater stability for imines replaced with electron withdrawing substituents when compared to electron donor groups. The addition of CTAB caused an important influence on the stability of 3b, as no changes in the λmax at 515 nm were observed over an interval of 1800 s (Figure S25, SI section). Consequently, micelles can contribute to reduce the reactivity of the imine group in the compounds, increasing the stability of these species in an aqueous medium. Thus, the surfactant could contribute by increasing the stability of the compounds and causing a decrease in the degradation of 3b in water.

Figure 4a shows UV-Vis spectra of 3a in the absence and presence of amines in aqueous CTAB solution. Compound 3a exhibits a band with maximum at 410 nm. This band disappears if the alkylamines are added to the system, simultaneously with the appearance of other band with λmax = 515 nm, being the latter related to the generation of 3b species. The influence of the addition of the alkylamines on the UV-Vis spectrum of 5a is shown in Figure 4b. The band with λmax = 430 nm, associated with the protonated species is changed to other band with maximum at 668 nm related to 5b species. Figures 4c and 4d show the relative absorbances for the appearance of the deprotonated compounds (3b and 5b) after the addition of the amines on the solutions of the chemosensors, being verified that only the alkylamines deprotonate the compounds.

Figure 5a compares the pK, values of 3a-5a in water with those of the protonated amines used in this paper (Table S1, SI section). Data show that the protonated aromatic amines have pK, values between 4.58-5.06, meaning that...
these amines are not sufficiently basic to deprotonate the chemosensors. However, the protonated alkylamines exhibit $pK_a$ values between 10.59 and 10.98, being sufficiently basic to deprotonate $3a$ and $4a$. Compound $5a$ is not sufficiently acid to be deprotonated by the amines in these experimental conditions. On the other hand, in micellar medium (Figure 5b), $4b$ is the predominant species even in the absence of the amines. The lowering in the $pK_a$ of $5a$ makes the compound able to act as chemosensor for the aliphatic amines in micellar medium. In these conditions, $3a$ is also deprotonated by the aliphatic amines.

Titrations of the chemosensors with the amines

The influence of the alkylamines on the UV-Vis spectra of the chemosensors in water and in aqueous CTAB solution was studied. These data allowed to obtain the equilibrium constants, which were used to understand the level of interaction of the chemosensors with the amines. Figure 6a shows UV-Vis spectra related to the titration of $3a$ in water with increasing amounts of BTA. Data show that the amine addition led to a reduction in the absorbance values of the band with $\lambda_{\text{max}} = 405$ nm simultaneously with an increase in the absorbances of the band with a maximum of 490 nm. The bands at $\lambda_{\text{max}}$ values of 405 and 490 nm are related to the protonated and non-protonated forms of the compound, respectively, and an isobestic point occurs at 438 nm, suggesting an equilibrium between the two species. Figure 6b exhibits the corresponding titration curve, in the form of a plot of the absorbance values at $\lambda_{\text{max}} = 490$ nm as a function of $c$ (BTA). The Job plot was obtained for $3a$ and BTA (inset in Figure 6b), suggesting a 1:2 chemosensor:amine stoichiometry. The sigmoid shape in the titration curve corroborates the stoichiometry verified in the Job experiment.

Figure 7a shows the UV-Vis spectra for the titration of $5a$ with BTA in aqueous CTAB solution. The band with maximum at 432 nm, related with $5a$, decreased on the addition of BTA, with the simultaneous appearance of the band at $\lambda_{\text{max}} = 668$ nm, related with the formation of deprotonated species $6b$. An isobestic point was verified at 505 nm. The corresponding titration curve shown in Figure 7b exhibits a sigmoidal shape, suggesting a 1:2 chemosensor:amine stoichiometry. The Job plot (inset in Figure 7b) exhibited a maximum at 0.71, which is between 0.67 (1:2 stoichiometry) and 0.75 (1:3 stoichiometry). This
suggested that the system is best represented as presenting 1:2 and 1:3 stoichiometries.

The trends verified in the titration curves shown in Figures 6 and 7 are typical for all titrations performed with 3a-5a and the alkylamines in water and in aqueous CTAB solution (see also Figures S26-S38, SI section). The titration curves obtained allowed, with the use of equation 2, to calculate $K_{12}$ values of 3a and 4a with the amines. The titration curves with 5a in aqueous CTAB solution were fitted using equation 3, providing $K_{12}$ and $K_{13}$ values.

The results are given in Table 3 and show very good fits for all systems studied (standard deviation (SD) < 9.818 × 10⁻⁵). For instance, $K_{12} = (1.463 ± 0.048) \times 10^8$ L² mol⁻² (determination coefficient ($r^2$) = 0.998 and SD = 5.02 × 10⁻³) was obtained for 3a with BTA in water while 5a with the same amine in water/CTAB system provided $K_{12} = (8.959 ± 0.219) \times 10^7$ mol⁻¹ and $K_{13} = (2.012 ± 0.043) \times 10^5$ L³ mol⁻³ ($r^2 = 0.997$ and SD = 6.62 × 10⁻³).

Scheme 3 summarizes the behavior of the chemosensors in the presence of the alkylamines, showing two possibilities. The alternative (a) indicates 2 equiv of amine to completely abstract the proton. This model is in line with several studies published by different research groups which have investigated the influence of anionic species on chemosensors with an acidic H-atom in their molecular structure. 67,70,79,84,92-94

The abstraction of the proton with only 1 equiv of the amine requires a sufficiently strong base and a sufficiently acid chemosensor. However, 2 equiv of the amine (alternative (a)) may be required to deprotonate each equivalent of the chemosensor if the analyte is not a sufficiently strong base. Thus, the alternative (a) involves firstly 1 equiv of amine to interact with the phenolic moiety of the chemosensor through hydrogen bonding. This interaction weakens the O–H bond, and by adding a second equivalent of the amine the proton is abstracted, forming a [R₃N…H…NR₃]⁺ complex.

The titration curves of 5a with the amines could be fitted only with the use of equation 3, suggesting that the amines can also interact with the chemosensor through the alternative (b). Compound 5a is less acidic than compounds 3a and 4a. In addition, the compound has in its molecular structure lipophilic tert-butyl groups as substituents. Thus, the data suggest that, in addition to the CTAB’s role in reducing the pKₐ of 5a, the first equivalent of the amine can interact with the phenolic moiety of the compound by hydrophobic effect. This interaction occurs previously to the addition of the 2 equiv of the amine required to the full abstraction of the proton.

Table 3. Values of equilibrium constants $K_{12}$ for 3a-5a and $K_{13}$ for 5a with the amines in water at 25.0 °C

| Compound | BTA | DEA | TEA |
|----------|-----|-----|-----|
| 3a       | $K_{12}$ (L² mol⁻²) | (1.463 ± 0.048) × 10⁸ | (1.070 ± 0.027) × 10⁸ | (1.729 ± 0.055) × 10⁸ |
| 3a'      | $K_{12}$ (L² mol⁻²) | (1.162 ± 0.050) × 10⁸ | (1.173 ± 0.049) × 10⁸ | (8.511 ± 0.262) × 10⁷ |
| 4a       | $K_{12}$ (L² mol⁻²) | (8.797 ± 0.191) × 10⁶ | (1.721 ± 0.044) × 10⁷ | (2.237 ± 0.080) × 10⁷ |
| 4a'      | $K_{12}$ (L² mol⁻²) | (8.959 ± 0.219) × 10⁷ | (1.240 ± 0.279) × 10⁸ | (1.844 ± 0.325) × 10⁸ |
| 5a'      | $K_{13}$ (L³ mol⁻³) | (2.012 ± 0.043) × 10⁵ | (7.160 ± 0.182) × 10⁶ | (7.780 ± 1.099) × 10⁶ |

*With cetyltrimethylammonium bromide (CTAB) 1.0 × 10⁻⁵ mol L⁻¹. BTA: n-butylamine; DEA: diethylamine; TEA: triethylamine.

Figure 7. (a) UV-Vis spectra at 25.0 °C showing the behavior of 5a (4.0 × 10⁻⁵ mol L⁻¹) in aqueous CTAB solution (1.0 × 10⁻³ mol L⁻¹) with the addition of increasing amounts of BTA. (b) Corresponding titration curve with BTA. The final concentration of BTA was 1.07 × 10⁻⁴ mol L⁻¹ and the absorbance values were collected at 668 nm. The inset displays a Job plot for 5a and the amine.
Scheme 3. Proposed model for stoichiometries of the chemosensors with the amines in pure water and in aqueous CTAB solution. In (a) compounds 3a and 4a interact with the amines following a 1:2 chemosensor:amine stoichiometry while the 1:3 stoichiometry (b) occurs with 5a in CTAB system in the presence of the alkylamines.

The titrations curves were used to estimate the values of LOD and LOQ for the systems (Table 4 and Figures S39-S53, SI section). The lowest LOD and LOQ values were obtained for compounds 3a and 5a in aqueous CTAB solution. For comparison, the values of LOD for the detection of BTA with 3a were $2.36 \times 10^{-6}$ and $6.89 \times 10^{-7}$ mol L$^{-1}$ in water and aqueous CTAB solution, respectively. The lowest value of LOD ($4.64 \times 10^{-7}$ mol L$^{-1}$) was obtained for 5a in the detection of BTA in aqueous CTAB solution. A compilation of LOD values for the detection of aliphatic amines in water using different techniques is shown in Table 5. The data show that the determinations obtained using the GC and HPLC techniques offer the lowest limits of detection, but the values reported here, using compounds 3a-5a, are in general less than those obtained using other techniques. Thus, the results obtained here illustrate the interesting potential for the application of these compounds considering the simplicity, versatility, and low cost of the technique used.

Applications

Compound 3a was chosen to be used in three different applications involving detection of amines. Strips of Whatman$^\text{®}$ filter paper containing the compound were used for the analysis of BTA in water and in the form of vapor. Another potential application was the use of 3a for the detection of lidocaine in water and for the quantification of lidocaine in a commercial sample.

Detection of vapors of amines

An assay was elaborated using paper strips containing 3a to evaluate the potential of the system to act as...

Table 4. Values of limit of detection (LOD) and quantification (LOQ) for compounds 3a-5a with the amines in water at 25.0 $^\circ$C

| Compound | BTA | DEA | TEA |
|----------|-----|-----|-----|
|          | LOD (mol L$^{-1}$) | LOQ (mol L$^{-1}$) | LOD (mol L$^{-1}$) | LOQ (mol L$^{-1}$) | LOD (mol L$^{-1}$) | LOQ (mol L$^{-1}$) |
| 3a       | $2.36 \times 10^{-6}$ | $7.88 \times 10^{-6}$ | $1.61 \times 10^{-5}$ | $5.36 \times 10^{-6}$ | $1.45 \times 10^{-5}$ | $4.18 \times 10^{-6}$ |
| 3a$^*$   | $6.89 \times 10^{-7}$ | $2.29 \times 10^{-6}$ | $5.29 \times 10^{-7}$ | $1.76 \times 10^{-6}$ | $6.27 \times 10^{-7}$ | $2.09 \times 10^{-6}$ |
| 4a       | $9.71 \times 10^{-7}$ | $3.23 \times 10^{-6}$ | $1.84 \times 10^{-6}$ | $6.54 \times 10^{-7}$ | $1.42 \times 10^{-6}$ | $4.75 \times 10^{-6}$ |
| 5a$^*$   | $7.00 \times 10^{-7}$ | $2.33 \times 10^{-6}$ | $6.99 \times 10^{-7}$ | $2.33 \times 10^{-6}$ | $5.08 \times 10^{-7}$ | $1.69 \times 10^{-6}$ |

$^*$With cetyltrimethylammonium bromide (CTAB) $1.0 \times 10^{-3}$ mol L$^{-1}$. BTA: n-butylamine; DEA: diethylamine; TEA: triethylamine.
Vapochromic chemosensors for the detection of amines. The strips were left in contact with the BTA vapors in a closed system. Figure 8 shows the images of the papers exposed to different concentrations of BTA. The strips containing $3a$ had their color changed after the addition of BTA to the wall of the flask. The change in color of the paper allows to estimate concentrations of BTA vapors above $4.5 \times 10^{-4}$ mol L$^{-1}$.

Detection of amines in water

The paper test strips containing $3a$ were immersed in aqueous solutions containing BTA in different concentrations (Figure 9). The strips dipped in the solutions had their color changed, allowing qualitative detection of $c$ (amine) > $1.0 \times 10^{-4}$ mol L$^{-1}$. No leaching of the chemosensor from the paper to the solution was verified: the solution containing the amine remained colorless after the paper strip was dipped.

Detection of lidocaine

Figure 10 shows solutions of compound $3a$ in the presence of lidocaine in water and in aqueous CTAB solution. The data show that lidocaine deprotonates $3a$, making the solutions colored, orange in water (Figure 10a) and pink in aqueous CTAB solution (Figure 10b).

Figure 11a shows UV-Vis spectra for the titration of $3a$ in aqueous CTAB solution with increasing amounts of standard pharmaceutical lidocaine. The addition of the drug led to the reduction in the absorbances of the band with $\lambda_{\text{max}} = 418$ nm, corresponding to $3a$, simultaneously with an increase in absorbance of the band with a maximum of 515 nm, related to the formation of $3b$. An isosbestic point was verified at 454 nm, which suggests an equilibrium between $3a$ and $3b$ in solution.

The absorbance values at $\lambda_{\text{max}} = 515$ nm on each spectrum were plotted as a function of $c$ (lidocaine) (Figure 11b). Equation 1 was used to fit the experimental data, providing $K_{11} = (2.333 \pm 0.004) \times 10^{4}$ L mol$^{-1}$ ($r^2 = 0.999$ and SD = $4.805 \times 10^{-4}$). Values of LOD and LOQ were calculated (Figure S52, SI section), being equal to $5.35 \times 10^{-6}$ and $1.78 \times 10^{-5}$ mol L$^{-1}$, respectively. The Job plot (inset in Figure 11b) suggests also a 1:1 $3a$:lidocaine stoichiometry. The same stoichiometry was also verified in pure water (Figure S36, SI section). These observations disagree with what was verified for the same compound in the presence of the alkyamines in water.

Some experiments were carried out to compare the pH of aqueous CTAB solution, $3a$, and lidocaine at concentrations of $1.0 \times 10^{-3}$, $4.6 \times 10^{-3}$, and $9.7 \times 10^{-3}$ mol L$^{-1}$.
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3.3 \times 10^{-4} \text{ mol L}^{-1}, \text{ respectively. The starting pH for the distilled water used in the tests was equal to } 5.9, \text{ the same being verified for an aqueous CTAB solution and for water containing both CTAB and } 3a. \text{ The pH of an aqueous CTAB solution of lidocaine was } 9.1, \text{ while for the mixture of CTAB, } 3a, \text{ and lidocaine a value of } 8.7 \text{ was obtained. Thus, the } \Delta(pH) = 0.4 \text{ verified by comparing the lidocaine solutions in the absence and in the presence of the chemosensor is due to the neutralization of } 3a, \text{ with the formation of the colored species } 3b.

The pK_a value of protonated lidocaine in water is 7.8,^{103} \text{ being lesser than the pK}_a \text{ for protonated TEA (10.65). Data suggest that lidocaine has a molecular structure capable to make with } 3a, \text{ previously to the proton abstraction, a 1:1 complex by means of both hydrophobic effect (using its phenyl group) and hydrogen bonding. This complex could weaken the OH bond in the phenolic moiety of the chemosensor, which would facilitate the abstraction of the proton, such as suggested in Scheme 4.}

Tests were carried out to verify the application of } 3a \text{ as a chromogenic chemosensor for commercial lidocaine samples. A calibration curve was obtained by LC-MS measurements (Figures S54-S58, SI section), using the standard pharmaceutical lidocaine, in order to find a comparison with the titration curve of Figure 11b. Figure 12A shows UV-Vis spectra for different concentrations of a commercial sample of lidocaine. The

\textbf{Figure 11.} (a) Influence of the addition of increasing amounts of a standard pharmaceutical lidocaine on the UV-Vis spectrum of } 3a (4.0 \times 10^{-4} \text{ mol L}^{-1}) \text{ in water containing CTAB (1.0 \times 10^{-3} \text{ mol L}^{-1}) \text{ at } 25.0 \text{ °C. (b) Corresponding titration curve for the absorbances collected at 515 nm. The inset displays a Job plot for } 3a \text{ and lidocaine.}

\textbf{Figure 12.} (A) UV-Vis spectra of } 3a \text{ in water with CTAB (1.0 \times 10^{-3} \text{ mol L}^{-1}) \text{ at } 25.0 \text{ °C without (a) and with 1.02 \times 10^{-5} (b), 3.04 \times 10^{-5} (c), and 6.99 \times 10^{-5} \text{ mol L}^{-1} (d) of a commercial sample of lidocaine. (B) Titration curve at 515 nm for the titration of } 3a (5.0 \times 10^{-5} \text{ mol L}^{-1}) \text{ with increasing amounts of a standard pharmaceutical lidocaine. The red circles correspond to the commercial samples of lidocaine.}

\textbf{Scheme 4.} Proposal for the interaction of } 3a \text{ with lidocaine in solution.
absorbances at 515 nm were collected and the values were applied in the curve shown in Figure 12B (red points in the curve) to obtain the concentrations of lidocaine. Data were compared to the LC-MS calibration curve, showing a good agreement between the two techniques. The LOQ and LOD values were very close when both techniques were compared. Compound 3a was also efficient in the evaluation of lidocaine in purely aqueous medium (Figure S59, SI section).

Conclusions

Compounds 3a-5a were synthesized and studied as chromogenic chemosensors for the detection of alkylamines in water based on the acid-basic approach, in which the basicity of the analytes was used as a property to generate the colored phenolates in solution. The acidity of the compounds could be increased with addition of CTAB to water above its CMC, which enabled the use of compound 5a as chromogenic chemosensor. Thus, the use of the compounds as chemosensors depends on the molecular structure of the phenols, the basicity of the amines, and the medium.

The studies performed in water in the presence of CTAB revealed that the compounds in their deprotonated form (3b-5b) are perichromic. The λmax values in the Vis region of the dyes are shifted to longer wavelengths if CTAB is added to the medium, indicating that the dyes are incorporated in less polar media than pure water. These data suggest that these compounds and other dyes with related molecular structures can be used as probes for the detection of surfactants in water. The addition of CTAB also increases the stability of phenolate 3b, improving the performance of the system as chemosensor.

The titration curves obtained for the compounds and the alkylamines showed that compounds 3a and 4a interact with the amines in a 1:2 chemosensor:amine stoichiometry, requiring 1 equiv of amine to interact with the phenolic moiety of the chemosensor through hydrogen bonding, which weakens the O–H bond, and a second equivalent of the amine for the full abstraction of the proton. Data for 5a show 1:2 and 1:3 chemosensor:amine stoichiometries, which was explained by a combination of two aspects, the lower acidity of the compound compared to the others and the presence of the lipophilic tert-butyl groups as substituents. In this case, one equivalent of the amine can interact with the compound, through hydrophobic effect, previously to the addition of the other 2 equiv of the amine required to abstract the proton.

The versatility of the compounds studied was demonstrated for the design of chemosensors for the naked-eye and quantitative detection of alkylamines in aqueous and vapor phases. The systems were also applied for the quantitative detection of lidocaine in water. The use of the systems on solid support, as vapochromic chemosensors or for the detection of amines in water, allows to think about their applications in industrial, environmental, and pharmaceutical areas.

Supplementary Information

Supplementary data (characterization data; UV-Vis studies; self-aggregation assays; pKa determinations; determination of equilibrium constants; determination of limits of detection and quantification; stability of compounds; and chromatography assays) is available free of charge at http://jbc.ssbq.org.br as PDF file.

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