



## Multi-wavelength spectrophotometric determination of acidity constant of some newly synthesized Schiff bases and their QSPR study

Bahram Hemmateenejad\*, Leila Emami, Hashem Sharghi

Department of Chemistry, Shiraz University, Adabiat Four-way, Shiraz, Fars 71454, Iran

### ARTICLE INFO

#### Article history:

Received 27 January 2009

Received in revised form 21 October 2009

Accepted 26 October 2009

#### Keywords:

Schiff base

Acidity constant

Chemometrics

Methanol–water

Quantitative structure–property relationship

### ABSTRACT

The acidity constants of some newly synthesized Schiff base derivatives were determined by hard-model based multivariate data analysis of the spectrophotometric data in the course of pH-metric titration in 50% (v/v) methanol–water binary solvent. The employed data analysis method was also able to extract the pure spectra and pH-dependent concentration profiles of the acid–base species. The molecules that possess different substituents (both electron donating and withdrawing) on the ortho-, meta- and para-positions of one of the phenyl ring showed variable acidity constants ranging from 8.77 to 11.07 whereas the parent molecule had an acidity constant of 10.25. To investigate the quantitative effects of changing of substitution pattern on the acidity constant, a quantitative structure–property relation analysis was conducted using substituent constants and molecular descriptor. Some models with high statistical quality (measured by cross-validation  $Q^2$ ) were obtained. It was found that the acidity constant of the studied molecules in the methanol–water mixed solvent not only is affected by electronic features of the solutes but also by the lipophilic interaction between methanol part of solvent and the deprotonated solutes.

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### 1. Introduction

Schiff bases represent an important class of chelating ligands, the metal complexes of which have been widely studied [1]. These complexes play an important role in the development of coordination chemistry related to catalysis and enzymatic reactions, magnetism and molecular architectures [2]. Since these mentioned properties are related to the acid–base behavior of the compounds, determination of acidity constant is highly important and let us to understand other properties better. In addition, knowledge of ionization constant ( $pK_a$ ) of substance is very important in the pharmaceutical industry and drug design, in the new chemical manufacturing industry (environmental impact compliance) and in the environmental field (environmental fate of toxic substances) [3].

Among the available analytical methods for determination of acidity constant, spectroscopic methods are, in general, highly sensitive and are as such suitable for studying chemical equilibria. However, in many cases, the spectral responses of two and sometimes even more components overlap considerably and analysis is no longer straightforward. Since the introduction of chemometrics methods in analytical chemistry the problem of spectral overlapping has been diminished thanks to the resolving power of various multivariate data analysis methods [4–9]. Multivariate

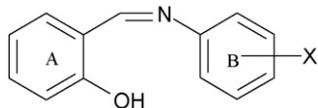
curve resolutions are a group of chemometrics methods dealing with extracting concentration profiles and pure spectra of the species coexisted in reaction system (both kinetic and equilibrium studies) [10–14]. The application of these methods for studying acid–base equilibria has now become popular in chemistry [15–18]. In this context, there are available some commercial programs such as SQUAD [19], SPECFIT [20] and DATAN 2.1 [17,21] that can be used to calculate acidity constants from spectrophotometric–pH-metric titration data. In the last year, in our research group we are involved in the use of different curve resolution methods for studying acid–base and complexation equilibria [22–25] as well as the photodegradation kinetics of drugs [26,27].

Low solubility in aqueous solutions and low values of acidity constants are two main drawbacks in determination of acidity constants of organic molecules. Therefore, in order to enhance the acidity constants in one hand and to increase the solubility on the other, we forced to choose mixed solvents. Mixed solvents are interesting, because when two solvents are mixed a solvent with quite different properties, both, physically (dielectric, density and viscosity) and chemically (acid–base and donor–acceptor properties) is produced [28].

Much of the theoretical foundation of modern organic chemistry is based on the observation of the effects on the acid–base equilibria of changing molecular structure. The history is come back to the Hammett law relating changing in acidity of substituted carboxylic acids to electronic substituent constant, which was then explored as field effect, resonance, lipophilic and steric substituent constants. The quantitative relationships between

\* Corresponding author. Tel.: +98 711 6137360; fax: +98 711 2286008.  
E-mail address: [hemmatb@sums.ac.ir](mailto:hemmatb@sums.ac.ir) (B. Hemmateenejad).

**Table 1**  
Structure and acidity constant of the substituted Schiff bases used in this study.



No.	X	pK <sub>a</sub>
D <sub>1</sub>	H	10.25 ± 0.01
D <sub>2</sub>	2-Me	9.89 ± 0.01
D <sub>3</sub>	2-Cl	10.22 ± 0.01
D <sub>4</sub>	2-Br	10.27 ± 0.01
D <sub>5</sub>	2-CN	10.61 ± 0.03
D <sub>6</sub>	2-CF <sub>3</sub>	11.07 ± 0.03
D <sub>7</sub>	2-OMe	10.14 ± 0.01
D <sub>8</sub>	2-CO <sub>2</sub> H	8.94 ± 0.01
D <sub>9</sub>	3-Cl	10.46 ± 0.01
D <sub>10</sub>	3-Br	10.49 ± 0.06
D <sub>11</sub>	3-CN	10.36 ± 0.03
D <sub>12</sub>	3-F	10.46 ± 0.01
D <sub>13</sub>	3-OMe	10.53 ± 0.07
D <sub>14</sub>	3-NO <sub>2</sub>	10.25 ± 0.01
D <sub>15</sub>	3-CO <sub>2</sub> H	10.62 ± 0.01
D <sub>16</sub>	4-Cl	10.33 ± 0.01
D <sub>17</sub>	4-Br	10.42 ± 0.03
D <sub>18</sub>	4-CN	10.13 ± 0.02
D <sub>19</sub>	4-Me	10.27 ± 0.01
D <sub>20</sub>	4-NO <sub>2</sub>	10.15 ± 0.01
D <sub>21</sub>	4-OMe	10.61 ± 0.01
D <sub>22</sub>	4-F	10.56 ± 0.01
D <sub>23</sub>	4-CO <sub>2</sub> H	10.16 ± 0.01
D <sub>24</sub>	2-OH	pK <sub>a1</sub> = 9.37 ± 0.02 pK <sub>a2</sub> = 10.77 ± 0.02
D <sub>25</sub>	3-OH	pK <sub>a1</sub> = 8.57 ± 0.03 pK <sub>a2</sub> = 10.07 ± 0.003

molecular properties (such as acidity, polarity, and stability) and substituent constants are currently known as quantitative structure property relationship (QSPR) analysis [29,30]. In modern QSPR methods, in addition to substituent constants, molecular descriptors obtained from whole molecular structures are used to obtain structure–property relationships. Now a day, thousands of molecular descriptors, describing different aspects of molecular structures can be calculated for each molecule [31]. A successful strategy for the prediction of acidity constants is the construction of quantitative structure–property relationships (QSPRs) [32–35]. These relationships take an approach to identification and isolation of the most important structural descriptors that affect acidity constants. Very recently, Roy and Popelier developed a QSPR model for acid dissociation constant of phenols in methanol–water binary solvents [36].

In this work, the acid dissociation constant of 26 newly synthesized substituted Schiff bases were determined by spectrophotometric–pH-metric titration followed by multivariate data analysis of the recorded absorbance spectra. The effects of variation in the substituent patterns on the calculated acidity constants were investigated using firstly substituent constants and then molecular descriptors.

## 2. Experimental

### 2.1. Reagents

Extra pure methanol (MeOH, Merck) was used as received. Acetic acid, boric acid, phosphoric acid and potassium nitrate (all from Merck) were used for preparing of buffer solutions. The basic chemical structure and structural details of the Schiff bases used in this study are shown in Table 1. The compounds, which recently synthesized in the research group of Professor Sharghi [37], are con-

taining different substitutions like Br, Cl, CN, CO<sub>2</sub>H, OH, F, OMe, NO<sub>2</sub>, Me and CF<sub>3</sub>. The stock solution of the compounds (1.0 × 10<sup>-4</sup> M) was prepared by dissolving their appropriate amounts in pure methanol.

### 2.2. Instrument and software

The electronic absorbance spectra were recorded by a HP8452A diode-array spectrophotometer equipped with a 10-mm quartz cell and a circulated water bath thermostated at 25.0 ± 0.1 °C. Measurements of pH were done with a Metrohm 780 pH-meter using a combined glass electrode.

Data analysis was performed in the MATLAB (Math works, Inc.) environment using written programs in our Lab. Hyperchem software (Hyper-cube, Inc.) was employed for entering molecular structures into computer and subsequent geometry optimization and calculation of molecular descriptors.

### 2.3. Procedure

#### 2.3.1. Spectrophotometric–pH-metric titration

Calibration of the pH-meter in the 50% (v/v) binary methanol–water solvent was performed using two aqueous standard buffer solutions of pH 4.0 and 7.0. The recording pH values in the binary methanol–water solvent were corrected using the following equation:

$$\text{pH}^* = \text{pH}(\text{R}) - \sigma \quad (1)$$

where pH\* is the corrected pH, pH(R) is the pH-meter reading obtained in a the binary solvent, and  $\sigma$  is the correction term [38] for accounting differences between transfer activity coefficient and junction potential of aqueous and binary solvents. In all experiments, the ionic strength of the solutions was kept constant at 0.1 M using potassium nitrate as the supporting electrolyte.

For each compounds, to a series of 5.0 mL volumetric flasks a fixed volume of the stock methanolic solution of Schiff base and 2.5 mL aqueous buffer solution of desired pH (prepared from 0.04 M universal buffer) were added and diluted to the mark with methanol. The pH of the resulting solutions was measured and then their absorbance spectra were recorded in the wavelength interval of 300–500 nm versus buffer blank. It should be noted that there are differences in pH between the aqueous buffer solutions and the obtained solutions for the spectrophotometric measurements. The real pH values are those measured by pH-meter after mixing of solutions and we used these values for subsequent data analyses. The absorbance spectra were digitized in 1.0 nm intervals and collected in a data matrix **D** with dimension of ( $n_{\text{pH}} \times n_{\lambda}$ ), where  $n_{\text{pH}}$  and  $n_{\lambda}$  are the number of absorbance spectra recorded at various pH through a titration and number of absorbance reading per each spectrum, respectively.

#### 2.3.2. Multivariate data analysis for determination of acidity constant

We used a hard-model data analysis method based on equilibrium law of acid dissociation constant and Beer–Lambert law of additive absorbencies. For an acid–base reaction system composed of  $k$  absorbing species (i.e., HA and A<sup>-</sup> for monobasic acids and H<sub>2</sub>A, HA<sup>-</sup> and A<sup>2-</sup> for dibasic acids), the recorded absorbance at each wavelength is assumed to be the sum of contributions of all components:

$$d_j(\lambda) = \sum_{i=1}^k s_i(\lambda) c_{ij}, \quad (i = 1 : n_{\text{pH}}) \quad (2)$$

where  $d_j(\lambda)$  is the absorbance of sample  $j$  at wavelength  $\lambda$ ,  $s_i(\lambda)$  is the molar absorptivity of component  $i$  at wavelength  $\lambda$  and  $c_{ij}$  is the

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