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Potentiometric p*K*a determination of biological active phenothiazine in different aqua-organic solvents

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Abstract : Potentiometric titrations of phenothiazines derivatives were performed in methanol-water, ethanol-water, acetonitrile-water and dioxane-water mixtures with varying contents of organic solvent. All titrations were performed in aqua-organic medium at constant ionic strength (0.15 mol·dm−3) and at different temperatures (25 to 45 °C). The pKa were determined at different aqua-organic proportions. Effect of temperature and dielectric constant on dissociation constant has been compared. The p*K*a values were then obtained by Yasuda-Shedlovsky extrapolation.
Keywords : Aqua-organic, pka, Potentiometry, Phenothiazine.

Introduction

It is observed that 70-80 % of drugs molecules are ionizable and thus the acid dissociation constant (pKa) is an important physicochemical property [1-2]. Several key physicochemical properties that regulates absorption and distribution processes, such as lipophilicity and solubility, are pKa dependent [3]. The ionization state is a key parameter. When the drug interacts with the biological target, the interaction occurs in aqueous environment at physiological pH. pKa can be important in determining the rate and the site of drug metabolism [4]. Finally, in drug formulation the ionization constant is important for choosing the correct excipients and counterions. Therefore, pKa should be accurately evaluated during drug optimization.

Ionization constant can be measured by several methods, including potentiometric and UV–visible spectrophotometric titrations which are frequently used. These methods require a lot of skills for both monitoring the ionization state of the molecule while changing pH and interpreting the experimental data taking full account of chemical equilibria theory, sample solubility, and overlapping pKa values. This explains the paucity of experimental data on the ionization constant of drug-like molecules. Several pKa prediction models have been proposed, based on different descriptors, including atomic charges, topological distances, chemical reactivity models, and group philicity. However, the predicted values sometimes could be much off and can only be used as estimates [5-6].

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The aqua-organic method is the most widely used procedure for the p*K*a determination of water-insoluble compounds. The solubility of some unionized molecules can be enhanced by mixing solvents such as methanol, dioxane or acetonitrile with water.

Experimental

GLpKa automated p*K*a analyser (Sirius Analytical Instruments Ltd., Forest Row, UK) fitted with combination Ag/AgCl pH electrode was used for determination of dissociation constants. The p*K*a values were calculated by Refinement ProTM software (Sirius Analytical Instruments Ltd., Forest Row, UK).

The four-parameter technique (Four PlusTM method) was used for electrode calibration in aqua-organic mixtures. The titrations were carried out at constant ionic strength (*I* = 0.15 M KCl) and temperature (t = 25.0 ± 0.5 ºC), and under nitrogen atmosphere. The p*K*a values of samples were calculated by Refinement ProTM software.

The dissociation constants (p*K*a values) of the compounds were determined in methanol-water, ethanol-water, acetonitrile-water and dioxane-water mixtures with varying between 15-56 wt %.

To obtain the best p*K*a value from data three different extrapolation methods have been tried. First, the traditional plot of p*K*a versus *R* (wt% of organic solvents) was applied using p*K*a = a *R*wt% + b equation.

The second extrapolation method is based on the linear relation between p*K*a and the dielectric constant (ε) of mixture.

$pKa = a/\varepsilon + b$

The third method known as Yasuda-Shedlovsky extrapolation also establishes a correlation with the dielectric constant but uses a modified equation:

$psKa + \log[H_2O] = a/\varepsilon + b$

Where log $[H_2O]$ is the molar water concentration of the given solvent mixture.

Result and Discussion:

pKa values were determined by potentiometric titration using the Sirius GLpKa (Sirius Analytical Instruments Ltd., Forest Row, East Sussex, UK). All experiments were carried out at 25 ± 0.5 _C under a slow argon flow to avoid CO_2 absorption at high pHs. To measure pKa values, a right amount of each compound was dissolved in ionic strength adjusted water (0.15 M KCl) to achieve final sample concentration. The low aqueous solubility of the investigated compounds required pKa measurements to be performed in the presence of water as cosolvent. The solutions were then titrated with 0.5 M KOH to pH 11. The pH change per titrant addition was limited to 0.2 pH units and pH value in each point was collected when the pH-drift was lower than 0.002 pH per minute. Check of the pH-electrode with measurement of voltage in Orion pH 7.00 buffers and electrode calibration (Four-PlusTM parameters) by a blank titration were everyday performed. The initial estimates of the pKa values, which are the apparent ionization constants in the mixed solvent, were obtained by Bjerrum plots. These values were then refined by a weighted non linear least-squares procedure (Refinement Pro 1.0 software) to create a multiset, where the refined values were extrapolated using the Yasuda–Shedlovsky equation.

Table 1: Data for obtaining formation curve & proton – ligand stability constant of 2-(2-oxo-2-(10H-phenothiazin-10-yl) ethyl) isoindoline-1, 3-dione

Medium: Acetonitrile - water **Temp: 298 ^{0} K** **μ = 0.15M**

% solvent	H_20	Dielectric constant (Є)	Concentration	pKa+log(H_20)	pKa
10.41	48.0	74.6	3.16×10^{-4}	11.208	9.527
20.62	41.3	70.2	3.34×10^{-4}	11.584	9.968
33.61	33.0	63.2	3.56×10^{-4}	11.758	10.239
43.52	27.3	58.1	4.47×10^{-4}	12.057	10.621
51.76	22.8	54.0	5.18×10^{-4}	12.230	10.873

Medium: Dioxane - water **Temp: 298 ^{0} K** **μ = 0.15M**

% solvent	H_20	Dielectric constant (Є)	Concentration	pKa+log(H_20)	pKa
10.34	49.8	69.6	2.63×10^{-4}	11.514	9.417
20.58	44.2	60.5	3.18×10^{-4}	11.982	9.837
32.22	37.3	48.5	3.85×10^{-4}	12.132	10.141
43.05	31.9	39.5	4.99×10^{-4}	12.258	10.454
51.48	27.2	32.1	5.96×10^{-4}	12.534	10.599

Medium: Ethanol - water **Temp: 298 ^{0} K** **μ = 0.15M**

% solvent	H_20	Dielectric constant (Є)	Concentration	pKa+log(H_20)	pKa
10.36	48.3	72.4	2.86×10^{-4}	10.583	9.200
20.59	41.6	66.3	2.99×10^{-4}	10.836	9.516
33.47	33.7	58.4	3.22×10^{-4}	11.642	10.114
43.34	28.0	52.6	3.79×10^{-4}	11.950	10.402
51.73	23.4	47.7	4.40×10^{-4}	12.470	10.600

Medium: Methanol - water **Temp: 298 ^{0} K** **μ = 0.15M**

% solvent	H_20	Dielectric constant (Є)	Concentration	pKa+log(H_20)	pKa
10.20	48.5	73.9	2.71×10^{-4}	10.656	8.971
20.56	41.7	69.5	5.18×10^{-4}	10.708	9.088
41.20	29.3	60.1	5.70×10^{-4}	10.790	9.223

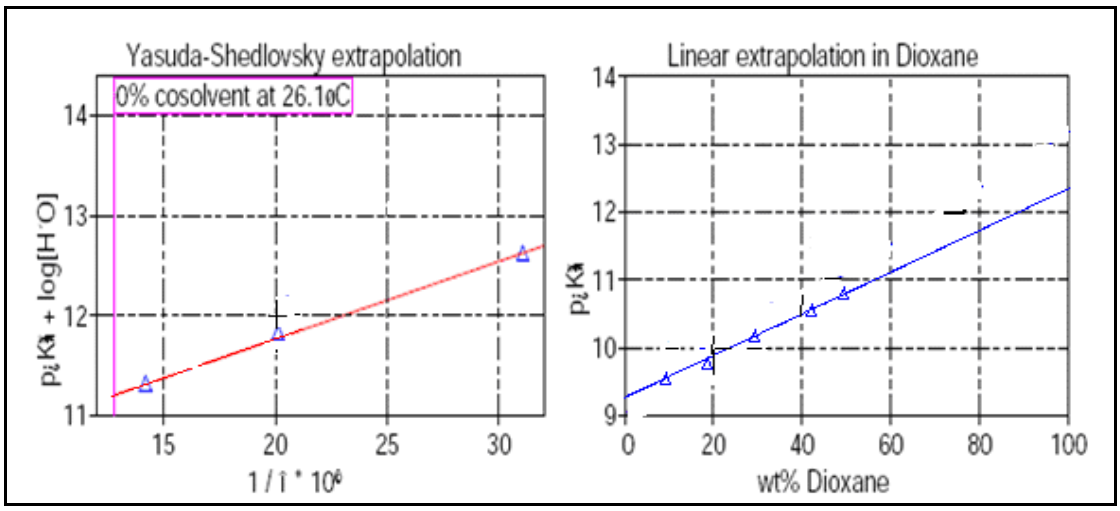

Figure 1: pH titration curve of 2-(2-oxo-2-(10H-phenothiazin-10-yl) ethyl) isoindoline-1, 3-dione (R_5) in different percentage of Dioxane – water medium at 298 ^{0} K and 0.150 M ionic strength.

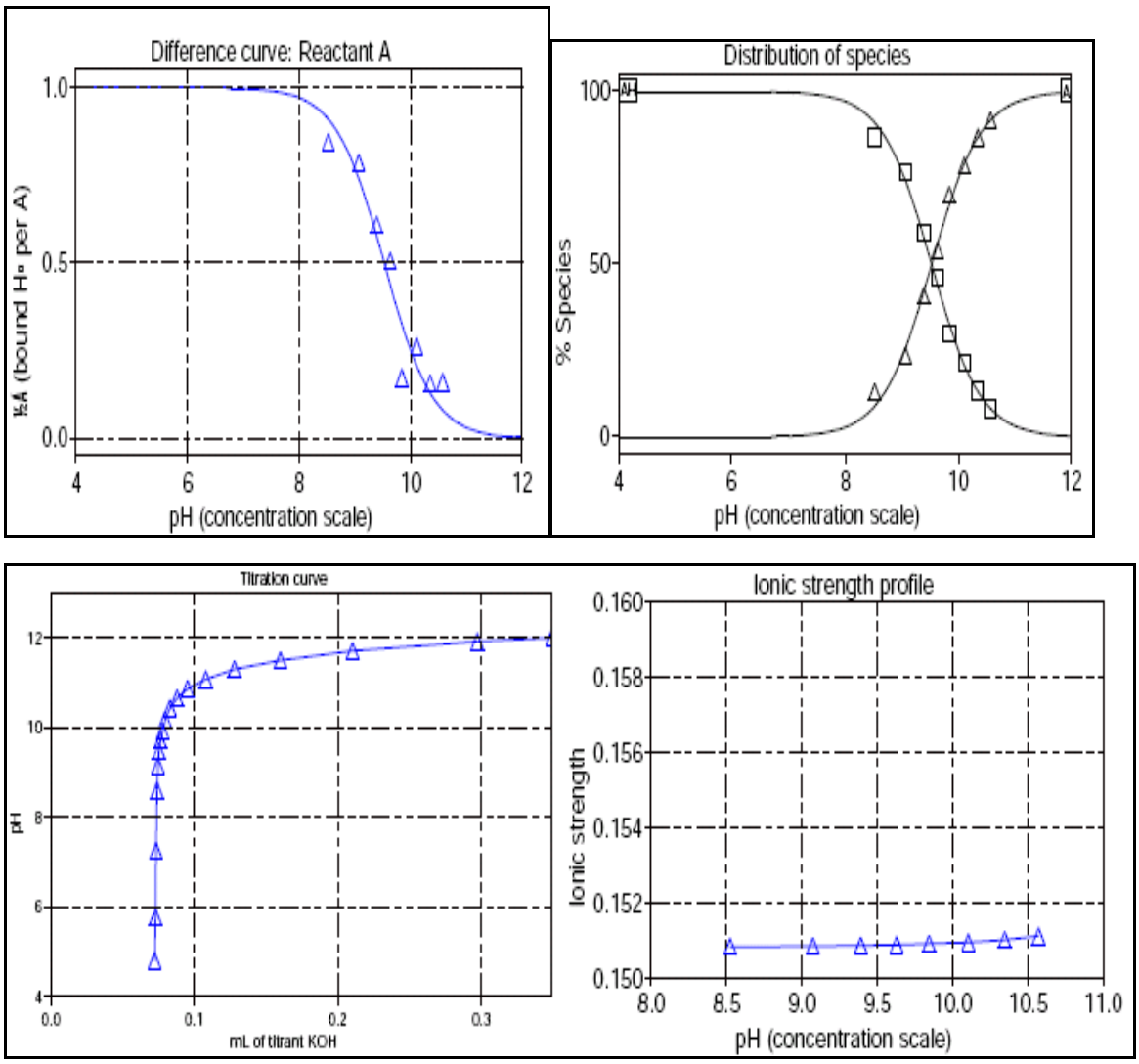

Figure 2: pH titration curve of 2-(2-oxo-2-(10H-phenothiazin-10-yl) ethyl) isoindoline-1, 3-dione in 10% Dioxane –water medium at 298 ^{0} K and 0.150 M ionic strength.

Table 2 Data for obtaining formation curve & proton – ligand stability constant of 2-(2-oxo-2-(10H-phenothiazin-10-yl) ethyl) isoindoline-1, 3-dione at various temperature.

Medium: 40% Methanol - water $\mu = 0.15$ M

Temperature	Concentration	pKa
25.42	5.37×10^{-4}	9.126
38.53	3.37×10^{-4}	8.950
44.78	3.89×10^{-4}	8.796

Conclusion:

The application of aqua–organic solvent mixtures improves the solubility of poorly water soluble drugs thus their p*K*a values can be measured in lower proportion of organic solvent. The dissociation constants (p*K*a) of phenothiazine derivatives were determined in different aqua–organic mixtures by potentiometric method. The Yasuda–Shedlovsky extrapolation procedure was proposed to obtain the p*K*a values. The extrapolated data are in good agreement with p*K*a values. In this way the proposed different aqua-organic methods can be applied to those compounds which are not soluble in aqueous solutions and can be easily adopted in drug discovery laboratory for the determination of dissociation constant.

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