

Barium Diphenylamine-4-Sulfonate (BDPA) Ion-Ion Interactions and Solvation Volumes in Acetonitrile–Water Mixed Solvents

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Abstract: The aim of this work is to calculate ion-ion interaction, density of organic-aqueous mixtures of Acetonitrile-water (AN-H₂O), density of saturated solutions of BDPA, solvation volumes (Van der Waals volume V_w , molar volume V_M and electrostriction volume V_e) and solvated radii (r_o) from solubility experiments. It was found that values of the log activity coefficient (γ_+) of BDPA in (AN-H₂O) mixture were decreases by increasing in the content of the organic solvent used. The values of the log γ_+ found to decrease with the increase in temperature. The densities and the molar volumes of the saturated solutions of BDPA decrease by increasing ratio of AN and also increases by increasing in temperature. All the electrostriction volumes calculated for BDPA having negative values. The electrostriction volumes increase in negativity on increasing the percentages of the organic solvent. The solvated radii of BDPA are increased as the organic solvent content increase and as the temperature increase.

Keywords: Ion-Ion Interactions, Barium Diphenylamine 4-Sulfonate, Acetonitrile, Solubility, Solvation Volumes

1. Introduction

Low aqueous solubility and reduced dissolution rates are a common property of many new drug candidates, and these properties create a number of challenges during drug discovery and development. An understanding of the determinants of solubility and dissolution provides a framework from which approaches to enhance solubilization may be developed. In subsequent sections of this review, we first address the complexities of working with poorly water-soluble drugs in vitro and subsequently summarize the approaches that can be taken to assist in the development of both parenteral and oral formulations. The main body of the review follows and provides a detailed account of the technological approaches that can be taken to support the development of effective formulations for poorly watersoluble drugs. Comment is made as to the many

different approaches that might be taken during lead optimization and preclinical development and also those strategies that are also appropriate for extension into clinical development and ultimately to the market. To constrain the scope of this review, synthetic medicinal chemistry approaches to solubility manipulation are not addressed and the discussion is limited to approaches that do not result in the generation of a fundamentally new chemical entity. For more information on approaches to solubility manipulation via structural modification [1-5].

A further application of the solubility-permeability relationship to oral drug absorption is the Biopharmaceutics Classification System (BCS) originally developed. [6] with subsequent variations [7-9]. The principles of the BCS are well described elsewhere [10-12], but in brief, the BCS

allows classification of drug molecules as a function of their solubility and permeability properties. A lot of published data [13-20] for BDPA and other substances that shows that they are very important materials for different fields.

2. Materials and Methods

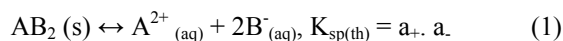
High grade of Barium diphenylamine sulfonate (BDH), ethanol were supplied from Merck, double distilled water that have measured specific conductance $2 \times 10^{-7} \text{ S cm}^{-1}$.

The mixed solvents, (AN + H₂O by percent values of AN = 0, 20, 40, 60, 80 and 100% by volume), were prepared from double distilled water and fairly pure AN. Then, saturated solutions of BDPA were prepared by dissolving different amounts in closed test tubes containing different (AN + H₂O) mixtures. The tubes were placed in a shaking thermostat (Model Gel) for a period of four days till equilibrium reached. The solubility, S (mole/Kg.solvent), of BDPA in the mixed solvent at different temperature was determined gravimetrically by the solvent evaporating method. All the solubility experiments were repeated at least three times and the results were averaged.

3. Results and Discussion

3.1. Ion-Ion Interaction Calculations

For an ionic compound, with the formula AB₂, we may consider the following equilibrium in its saturated solution at a given constant temperature.



Where $K_{\text{sp}(\text{th})}$ denotes the thermodynamic solubility product constant and a_{+} and a_{-} refer to activity of A^{2+} and B^{-} in the solution, respectively. If the solubility of AB₂ is very low, it may replace the activity of each ion by its concentration, so,

$$K_{\text{sp}(\text{th})} = 4s_0^3 \quad (2)$$

Where s_0 represents the molarity of BA₂ in the very dilute solution. The electrostatic interaction becomes very small and the ion association phenomenon may be negligible (the activity coefficient $\gamma_{\pm} \sim 1$) [13-16].

Ion-ion interaction is a function of the mean activity coefficient (γ_{\pm}) of the ions. There are several theoretically-based expressions that can be used to estimate the activity coefficients. At very low concentration, the electrostatic interaction becomes very small and the ion association phenomenon may be negligible (the activity coefficient $\gamma_{\pm} \sim 1$) [21-23].

At low concentration, the activity coefficient may be determined by using the Debye-Hückel limiting law:

$$\log \gamma_{\pm} = -Z_{+}Z_{-}A\sqrt{I} \text{ applicable for } I < 10^{-2} \text{ M} \quad (3)$$

Where Z_{+} and Z_{-} are the charges of ions in solutions, $A =$

$1.823 \times 10^6 (\epsilon T)^{-3/2}$, the ionic strength, I , defined as,

$$I = \frac{1}{2} \sum_i m_i z_i^2 \quad (z_i \text{ is the charge on ion } i, \text{ and } m_i \text{ is the}$$

molality of ion i) and the ionic strength, I emphasizes the charges of ions because the charge numbers occur as their squares.

At relatively high concentration, the electrostatic interaction becomes very large [24-25]. The activity coefficient may be determined using the extend Debye-Hückel law:

$$\log \gamma_{\pm} = -\frac{Z_{+}Z_{-}A\sqrt{I}}{I + Br^o\sqrt{I}} \text{ for } I < 10^{-1} \text{ M} \quad (4)$$

Where $B = 50.29 \times 10^8 (\epsilon T)^{-1/2}$, and r^o is the solvated radius.

At high concentrations, activity coefficients of electrolyte solutions can be determined by using the Davies equation [21] which is an empirical extension of Debye-Hückel theory. The final form of the equation gives the mean molal activity coefficient, γ_{\pm} , of an electrolyte which dissociates into ions having charges z_{+} and z_{-} as a function of ionic strength, I .

$$\log \gamma_{\pm} = -Z_{+}Z_{-}A\left(\frac{\sqrt{I}}{I + \sqrt{I}} - 0.3I\right) \quad (5)$$

The second term, $0.3 I$, goes to zero as the ionic strength goes to zero, so the equation reduces to the Debye-Hückel equation at low concentration. However, as concentration increases, the second term becomes increasingly important, so the Davies equation can be used for solutions too concentrated to allow the use of the Debye-Hückel equation.

The results of the ionic strength for BDPA in (AN-H₂O) mixture are illustrated in Table 1. The values of the $\log \gamma_{\pm}$ for BDPA in (AN-H₂O) mixture are illustrated in Table 2 are shown in Figure 1.

Table 1. Ionic strength (I) for BDPA in (AN-H₂O) mixed solvents at different temperatures.

AN vol. %	X_s	I			
		293.15 K	298.15 K	303.15 K	308.15 K
0	0	0.604	0.6369	0.6704	0.6884
20	0.0788	0.0479	0.0564	0.0647	0.077
40	0.1857	0.0412	0.0454	0.0537	0.0705
60	0.3391	0.0383	0.0428	0.0515	0.0689
80	0.577	0.0315	0.0363	0.0454	0.0684
100	1	0.0304	0.0355	0.0407	0.0459

Table 2. Log activity coefficient ($\log \gamma_{\pm}$) for BDPA in (AN-H₂O) mixed solvents at different temperatures.

AN vol. %	X_s	$\log \gamma_{\pm}$			
		293.15 K	298.15 K	303.15 K	308.15 K
0	0	0.55119	0.5513	0.551646	0.5494
20	0.0788	0.663206	0.6443	0.626893	0.6052
40	0.1857	0.655435	0.6403	0.61861	0.5857
60	0.3391	0.623203	0.6046	0.581267	0.5424
80	0.577	0.566068	0.544	0.520782	0.4557
100	1	0.364617	0.3413	0.31364	0.2917

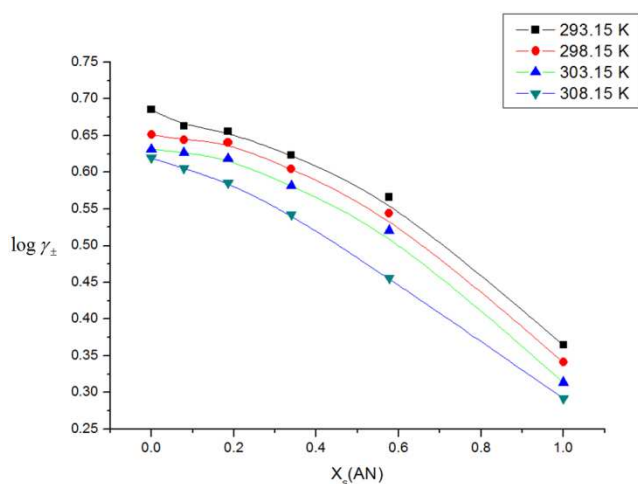


Figure 1. Relation between the activity coefficient ($\log \gamma_{\pm}$) of BDPA and the mole fraction of AN (X_s) in mixed solvents at different temperatures.

It was found that values of the $\log \gamma_{\pm}$ of BDPA were decreases by increasing in the content of the organic solvent used (AN) due to decrease in its solubility which lead to a decrease of the electrostatic interaction becomes and the ion association. The values of the $\log \gamma_{\pm}$ found to decrease with the increase in temperature due to a decrease of the electrostatic interaction becomes and the ion association.

3.2. Density Measurements

3.2.1. Density of the Saturated Solutions

Table 3 show the density of the saturated solutions of BDPA in (AN-H₂O) mixtures, at different temperatures (293.15, 298.15, 303.15 and 308.15 K). It is obvious that the densities of the saturated solutions of BDPA decrease by increasing ratio of AN and also increases by increasing in temperature.

Table 3. Density (d) of saturated solution of BDPA in (AN-H₂O) mixed solvents at different temperatures.

AN vol. %	(d)			
	293.15 K	298.15 K	303.15 K	308.15 K
0	1.53	1.61	1.734	1.835
20	0.966	0.974	0.981	0.994
40	0.943	0.95	0.954	0.963
60	0.887	0.897	0.9	0.912
80	0.846	0.853	0.859	0.863
100	0.776	0.781	0.793	0.81

3.2.2. Calculation of the Solvation Volumes and the Solvated Radii

From density and molal solubility measurements of the saturated solutions of BDPA in (AN-H₂O) mixtures, the molar volumes (V) [24-25] are calculated, at different temperatures (293.15, 298.15, 303.15 and 308.15 K) according to equation (6)

$$V = \frac{M}{d} \quad (6)$$

Where M is the molecular weight of BDPA, d is the

density of the solution;. The molecular weights of the binary solvents are calculated using equation (7)

$$M = X_{S(1)(H_2O)} \cdot M_{(H_2O)} + X_{S(2)(O.S)} \cdot M_{(O.S)} \quad (7)$$

Where $M_{(H_2O)}$ and $M_{(OS)}$ are the molecular weights of water and organic $X_{S(1)(H_2O)}$ $X_{(OS)}$ solvent, respectively, and are the mole fractions of water and the organic solvents used by are calculated by applying equation (8):

$$X_{S(1)} \text{ by wt.} = \frac{\frac{\text{Vol. \% (1)} \cdot X \cdot d(1)}{M_1}}{\frac{\text{Vol. \% (1)} \cdot X \cdot d(1)}{M_1} + \frac{\text{Vol. \% (2)} \cdot X \cdot d(2)}{M_2}} \quad (8)$$

Where $d_{(1)}$ and $d_{(2)}$ are the densities of the organic solvent and water, respectively, and M_1 and M_2 are the molecular weights of the organic solvent and water respectively, vol.% (1) and vol.% (2) are the volume percentages of the organic solvent and water, respectively.

The packing density (i.e., the relation between the Van der Waals volumes and the partial molar volumes) of relatively large molecules (more than 40) is found to be constant. Therefore, it is possible to calculate the Van der Waals volumes (V_w) of BDPA in (AN-H₂O) salt mixtures in at different temperatures (293.15, 298.15, 303.15 and 308.15 K) by applying equation (9).

$$\text{Packing density (P)} = \frac{V_w}{V} = 0.661 \pm 0.017 \quad (9)$$

Where V_w and V are the Van der Waals and partial molar volumes, respectively.

The electrostriction volume (V_e) [25-27] which is the volume of the solute compressed by the solvent is calculated by using equation (10).

$$V_e = V_w - V \quad (10)$$

The values of V , V_w and V_e of BDPA in (AN-H₂O) mixtures; at different temperatures (293.15, 298.15, 303.15 and 308.15 K) are listed in Tables 4-5 respectively.

In comparing the data of solvation, it is was observed that the values of the molar volume of ethanol mixtures with water are increased by increasing the organic solvents content in the mixtures due to the increase in the volume of organic solvent compared to water.

All the electrostriction volumes calculated for BDPA in (AN-H₂O) mixtures having negative values. The electrostriction volumes increase in negativity on increasing the percentages of the organic solvent, indicating the more work (energy) is done by the solvent on the solvation sheaths of the salts.

The solvated radii of the organic–aqueous mixtures; (AN-H₂O) at different temperatures (293.15, 298.15, 303.15 and 308.15 K) were calculated using equation (11) by considering the spherical form of the solvated molecules [25-27].

$$V = \frac{4}{3} \pi N \sigma^3 \quad (11)$$

Where V is the molar volume calculated from the densities as described before and σ is the solvated diameter. The solvated radii of BDPA in mixtures were calculated by adding the crystal radius of the salt to the radii of solvent in BDPA (AN-H₂O) mixtures at different temperatures (293.15,

298.15, 303.15 and 308.15 K).

The calculated values of the solvated radii of BDPA (AN-H₂O) mixtures at different temperatures (293.15, 298.15, 303.15 and 308.15 K) as well as the solutions of BDPA in (AN-H₂O) mixtures are listed in tables 4 and 5.

Table 4. Molar volume (V), Van der Waals volume (V_w), electrostriction volume (V_e) and Solvated radii (r_o) of BDPA in different (AN-H₂O) mixed solvents at 293.15K and 298.15K. ($\text{Cm}^3.\text{mol}^{-1}$).

AN vol.%	V	V _w	V _e	r _o	V	V _w	V _e	r _o
at 293.15K					at 298.15K			
0	412.87	272.90	-140.0	4.6246	392.22	259.26	-133.0	4.5467
20	657.38	434.53	-222.9	5.3907	651.05	430.35	-220.7	5.3759
40	673.20	444.98	-228.2	5.4342	667.64	441.32	-226.3	5.4208
60	717.78	474.45	-243.3	5.5463	708.40	468.26	-240.1	5.5255
80	752.40	497.33	-255.1	5.6344	744.62	492.20	-252.4	5.6189
100	817.14	540.13	-277.0	5.7990	811.13	536.16	-275.0	5.7866

Table 5. Molar volume (V), Van der Waals volume (V_w), electrostriction volume (V_e) and Solvated radii (r_o) of BDPA in different (AN-H₂O) mixed solvents at 303.15K and 308.15K. ($\text{Cm}^3.\text{mol}^{-1}$).

AN vol.%	V	V _w	V _e	r _o	V	V _w	V _e	r _o
at 303.15K					at 308.15K			
0	365.57	240.582	-123.4	4.4325	343.76	227.22	-116.5	4.3527
20	646.17	426.974	-219	5.3425	637.01	421.06	-215.9	5.3396
40	664.46	439.206	-225.3	5.40012	657.79	434.79	-223	5.3963
60	704.32	466.296	-239.1	5.5022	695.25	459.56	-235.7	5.4951
80	737.94	488.223	-250.4	5.6021	734.61	485.57	-249	5.5972
100	799.36	527.194	-270.4	5.7321	779.37	515.16	-264.2	5.7167

It is obvious that the solvated radii of BDPA in (AN-H₂O) mixtures are increased as the organic solvent content increase and as the temperature increase. This may be due to the excess solvation processes, and the higher solvated radii of the organic solvent used than those of water and also to the increasing in the electronic clouds around the solvated molecules as a result of the increase in their vibration and rotation motions with increasing the temperature.

4. Conclusion

In this work we calculate ion-ion interaction, dielectric constant, density of organic-aqueous mixtures of ethanol-water solvents, density of saturated solutions of BDPA, salvation volumes (Van der Waals volume V_w , molar volume V_M and electrostriction volume V_e) and solvated radii from solubility experiments. It was found that values of the $\log \gamma_{\pm}$ of BDPA in (AN-H₂O) mixture were decreases by increasing in the content of the organic solvent used (AN). The values of the $\log \gamma_{\pm}$ found to decrease with the increase in temperature. The densities of the saturated solutions of BDPA decrease by increasing ratio of AN and also increases by increasing in temperature. The values of the molar volume of ethanol mixtures with water are increased by increasing the organic solvents content in the mixtures due to the increase in the volume of organic solvent compared to water. All the electrostriction volumes calculated for BDPA having negative values. The electrostriction volumes increase in negativity on increasing the percentages of the organic solvent. The solvated radii of BDPA are increased as the organic solvent content increase and as the temperature increase.

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