Monatsh Chem (2010) 141:381–386
DOI 10.1007/s00706-010-0277-5

ORIGINAL PAPER

Solvent effect on protonation constants of salicylic acid in mixed aqueous organic solutions of DMSO

Ali Farajtabar · Farrokh Gharib

Received: 23 August 2009 / Accepted: 22 February 2010 / Published online: 18 March 2010

Abstract The first protonation constant of salicylic acid in water–DMSO solutions containing 0–50% (v/v) DMSO has been determined by spectrophotometric and potentiometric methods at 25 °C and an ionic strength of 0.1 M sodium perchlorate. The results indicate that the pK_a value of salicylic acid increases with increasing proportion of DMSO in the mixed solvent. The variation of pK_a value over the media composition range was explained by a linear solvation energy relationship, and correlations between pK_a values and the Kamlet–Taft parameters α (hydrogen bond donor acidity), π^* (dipolarity/polarizability), and β (hydrogen bond acceptor basicity), and the dielectric constant were calculated by means of multiple linear regression. The equations obtained can be used to estimate the first protonation constant of salicylic acid in a water–DMSO solvent from the relationship between the pK_a values and the Kamlet–Taft parameters of the solvent. Also, the pK_a value in aqueous medium was calculated by use of the SPARC online calculator and was compared with the value determined experimentally.

Keywords Solvent effect · Protonation constant · Water–DMSO · Spectroscopy · Potentiometry

A. Farajtabar (✉)
Department of Chemical Engineering, Islamic Azad University, Jouybar Branch, Jouybar, Iran
e-mail: a_farajtabar@yahoo.com

F. Gharib
Chemistry Department, Faculty of Sciences, Shahid Beheshti University, Evin, Tehran, Iran

Introduction

Acid ionization constants are important for the qualitative and quantitative treatment of systems involving acid–base equilibria in solution and knowledge of these values is essential in a wide range of research areas in chemistry, biochemistry, and pharmacology. For example, many compounds used as drug candidates have acidic or basic functionalities and the extent to which the drugs enter the blood stream is controlled by their pK_a values [1]. It has been shown that the activity of enzymes and acid–base homeostasis of living organisms is strongly dependent on the protonation constants of the compounds present in the cell and in the body [2]. So a knowledge of pK_a values is necessary for numerical understanding and stability constant determination of the interaction between acidic or basic ligands and metal ions in complexes [3–7].

The combination of pure solvents as mixed solvents substantially increases the diversity of reaction media. Among the various different solvents, dimethyl sulfoxide and its mixtures, particularly with water, are of special interest among scientists not only because of its manifold applications as solvents and reaction media in general and analytical chemistry, physical chemistry, biology, and medicine, but also because of its important role in biochemical processes [8, 9]. DMSO is highly polar, very weakly acidic, and fairly basic whereas water is also highly polar but acidic and negligibly basic. DMSO can interact strongly and specifically with water through hydrogen bonds, thus, like alcohol, it is miscible with water in all proportions. Aqueous mixtures of DMSO have extraordinary penetration properties and can impel cell fusion and intensify cell permeability; these properties are used in drug-delivery systems [10, 11].

Systematic investigations of solvent effects on thermodynamic and kinetic functions are interesting both experimentally and theoretically in chemical and biochemical analysis. The study of solvent effects on chemical and physical processes in binary mixtures is more complicated than in pure solvents, because the solute–solvent and solvent–solvent interactions can create new solvent properties leading to preferential solvation. Preferential solvation occurs when the solutes interact more specifically with one of the components of the mixture and when this difference in interactions is reflected in the composition of the solute microenvironment [12, 13].

The use of empirical scales is a suitable method for describing solvation interactions at a microscopic level. Among these, some of the most extensively used parameters are the solvatochromic parameters (α, β, and π^*) developed by Kamlet, Abboud, and Taft (KAT) to reflect specific and non-specific solute–solvent interactions [14–16]. α, β, and π^*, which quantify the hydrogen bond acidity, hydrogen bond basicity, and dipolarity–polarizability of the solvent, are calculated from the wavenumbers of maximum absorption of the UV–vis spectroscopic shifts of appropriate solvatochromic indicators. The shifts of absorption maxima with changing solvent composition reveal the nature of solvent–solute interaction in cybotactic regions of solutes. Linear solvation energy relationships (LSER) have been successfully proposed for relating the KAT parameters to diverse processes in solvents, for example protonation equilibria [17].

In continuation of our previous work [18, 19], in this study the protonation constants of salicylic acid have been determined in different water–DMSO mixtures to examine the dependence of acid–base equilibria on solvent composition.

Results and discussion

The acid–base equilibrium of salicylic acid is described in terms of the protonation of the Bronstedt base A^- according to the equation:

$$\mathrm{HA} \leftrightarrow \mathrm{H}^+ + \mathrm{A}^- \tag{1}$$

Because the objective was to determine the protonation constants, the potentiometric cell used to do so was calibrated for each binary mixture to measure the hydrogen ion concentration and the calibration constants.

Calibration of the potentiometric cell with aqueous binary mixtures

All measurements were performed at 25 °C and constant ionic strength of 0.1 mol dm^{-3} sodium perchlorate. The protonation constants were evaluated from measurements of absorbance versus emf (electromotive force) by titration of 25 cm^3 salicylic acid (2.5×10^{-4} mol dm^{-3}) with 0.1 mol dm^{-3} sodium hydroxide solution both at the same ionic strength and mol fraction of organic solvent (0–50% (v/v) DMSO).

In the first step, the electrode system calibration was performed by Gran's method [20, 21]. For this purpose a measured amount of an acidic solution, at the same conditions of temperature, ionic strength, and solvent composition to be used in later experiments, was placed in the double-wall thermostated vessel. The electrode was immersed in the solution in the vessel and the acidic solution was titrated with small additions of the sodium hydroxide solution with same proportion of organic solvent and the same ionic strength. The potential was allowed to stabilize after each addition of titrant and the recorded emf values were then used to obtain $E°$. In the second step, 25 cm^3 of an acidic (0.01 mol dm^{-3} $HClO_4$) solution of salicylic acid (2.5×10^{-4} mol dm^{-3}) at the same conditions of temperature, ionic strength, and solvent composition was titrated with a sodium hydroxide solution (0.1 mol dm^{-3}). The emf and the absorbance (in the interval 200–400 nm) values were then determined. The procedure was continued up to the required pH (around 7).

The recorded emf values were then converted to p_cH ($-\log\,[H^+]$) using the method described in literature [22]. In acidic solution, the measured potential of the cell, E_{cell}, can be written as:

$$E_{\mathrm{cell}} = E^\circ_{\mathrm{cell}} + k\log a_{\mathrm{H}^+} + E_{\mathrm{LJ}} \tag{2}$$

or

$$E_{\mathrm{cell}} = E^\circ_{\mathrm{cell}} + k\log[\mathrm{H}^+] + k\log\gamma_{\mathrm{H}^+} + E_{\mathrm{LJ}} \tag{3}$$

where $E^\circ{}_{\mathrm{cell}}$ is the standard potential of the cell, E_{LJ} is the liquid junction potential, $k = 2.303\ RT/F$ in which R, T, and F have the usual meaning, a_{H^+} is the activity of the hydrogen ion, and γ_{H^+} is the activity coefficient of the hydrogen ion. Difficulties in computing the activity coefficients of the hydrogen ion in different aqueous mixtures of organic solvents lead to measurement of emf versus H^+ concentration in solution. Because the ionic strength of the solution is kept constant, the activity coefficient of hydrogen ion is constant, also. The non-ideality of solutions is then included in k_a (the specific constant of the potentiometric cell in the acidic region), and thus:

$$E_{\mathrm{cell}} = k_{\mathrm{a}} + k\log[\mathrm{H}^+] \tag{4}$$

with k_a being $E^\circ_{\mathrm{cell}} + k\log\gamma_{\mathrm{H}^+} + E_{\mathrm{LJ}}$. The use of a glass electrode (with an aqueous inner solution) in non-aqueous media introduces a deviation from ideality, but it has been shown that the deviation is negligible and the glass electrode is always usable in such media to measure H^+

concentrations with a linear relationship between E_{cell} and log $[\mathrm{H}^+]$ [23].

In the acidic region the hydrogen ion concentration can be expressed as:

$$[\mathrm{H}^+] = (\mathrm{M}_{\mathrm{HClO}_4}\mathrm{V}_0 - \mathrm{M}_{\mathrm{NaOH}}\mathrm{V}_1)/(\mathrm{V}_0 + \mathrm{V}_1) \qquad (5)$$

where $\mathrm{M}_{\mathrm{HClO}_4}$ and $\mathrm{M}_{\mathrm{NaOH}}$ are the molarities of perchloric acid and sodium hydroxide, and V_0 and V_1 are the initial volume of perchloric acid and the added volume of sodium hydroxide solution, respectively. Finally:

$$\mathrm{p_cH} = (k_\mathrm{a} - E_{\mathrm{cell}})/k \qquad (6)$$

Computing ionization constants using spectroscopic titration data

The spectrophotometric data (every 0.5 nm) obtained during the titration as a function of H^+ concentration were processed with the computer software STAR [24]. The stoichiometric formation constants were computed from the data using the software. The number of experimental points (absorbance versus $\mathrm{p_cH}$) was more than 30 (maximum 50) for each titration. If we designate m absorption spectra that will be measured at n wavelengths, the individual absorbance readings thus can be arranged in a $m \times n$ matrix **R**; the m spectra form the rows of **R** and the columns consist of the n response curves gathered at the different wavelengths. According to Beer's law, for a system with N absorbing components, **R** can be decomposed into the product of a concentration matrix **C** ($m \times N$) and a matrix of the molar absorptivities **S** ($N \times n$). However, because of the inherent noise in the measured data, the decomposition does not represent **R** exactly. The matrix **T** of the residuals is given by the difference between **CS** and **R**.

$$\mathbf{T} = \mathbf{CS} - \mathbf{R} \qquad (7)$$

In the fitting procedure, the matrices **C** and **S** are determined which best represent the original matrix **R**. The task of the fitting procedure is to optimize the matrix **T** of the residuals, Eq. 6, according to the least-squares criterion. In Eq. 7, U is the sum of the squares of all elements of **T**. It is the task of nonlinear least-squares fitting to find the set of values that result in a minimum of U.

$$U = \sum_{i=1}^{m}\sum_{j=1}^{n}\mathrm{T}(i,j)^2 = \text{minimize} \qquad (8)$$

The software allows calculation of the different protonation constants; these were determined and are listed in Table 1 for various water–organic solvents mixtures. The solutions are stable and the absorption values did not change with time. The given protonation constants in aqueous solution agree well with those reported elsewhere [25, 26].

Table 1 Average values of protonation constants of salicylic acid and the KAT solvatochromic parameters of different water–DMSO mixtures at 25 °C and at constant ionic strength (0.1 mol dm^{-3} $\mathrm{NaClO_4}$)

Organic solvent (% v/v)	pK_a	π^{*a}	β^a	α^a	ε_r^b	Ref.
0.0	2.853 ± 0.009	1.09	0.47	1.17	78.36	This work
5	2.857 ± 0.021	1.10	0.46	1.11	78.00	This work
10	2.861 ± 0.010	1.10	0.47	1.05	77.73	This work
15	2.880 ± 0.013	1.11	0.48	0.99	77.45	This work
20	2.906 ± 0.011	1.11	0.51	0.94	77.17	This work
25	2.941 ± 0.016	1.12	0.53	0.88	76.87	This work
30	2.983 ± 0.007	1.12	0.56	0.82	76.53	This work
35	3.027 ± 0.030	1.12	0.58	0.76	76.15	This work
40	3.072 ± 0.010	1.12	0.60	0.70	75.70	This work
45	3.119 ± 0.011	1.12	0.61	0.64	75.14	This work
50	3.159 ± 0.005	1.12	0.62	0.59	74.43	This work
0.0	2.81					[25]
0.0	2.842					[26]

[a] The KAT solvatochromic parameters were taken from Ref. [27]

[b] The dielectric constants were taken from Ref. [28]

Effect of the solvent on the protonation constants of salicylic acid

As shown in Fig. 1, when an alkaline solution was added to the acidic solution of salicylic acid the absorption spectrum shifted to substantially lower wavelength. The protonation constants of salicylic acid in water–DMSO mixed solvents decreased as the solvent became enriched in the organic component (Fig. 2).

In general, as shown in Table 1, increasing the amount of DMSO reduces the dielectric constant of the mixture, and, in accordance with the Born equation, Eq. 9, protonated species (HA) are expected to be more stable in media with low dielectric constants; ionic species (A^-) are, on the other hand, more stable and better solvated in media with high dielectric constants [29]. When electrostatic effects predominate, the plot of log K versus the reciprocal dielectric constant of the media, ε_r, should be linear.

$$\Delta\log K = (121.6n/r)(1/(\varepsilon_r - 0.0128)) \qquad (9)$$

where r is the common radius of the ions and n is the squared summation of the charges involved in the protonation equilibria. In this work, the correlation between pK_a with the reciprocal of the dielectric constant of water–DMSO mixtures was linear, with a correlation coefficient of 0.98, and the following expression was obtained:

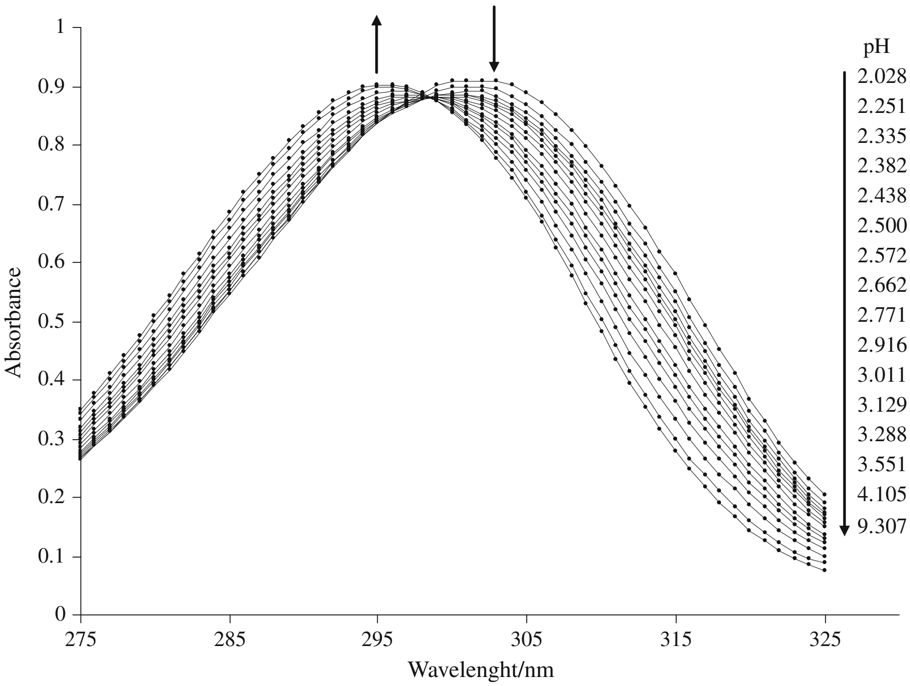

Fig. 1 Absorption spectra of salicylic acid (2.5×10^{-4} mol dm^{-3}) at 25 °C and ionic strength 0.1 mol dm^{-3} ($NaClO_4$) in pure aqueous solution without DMSO

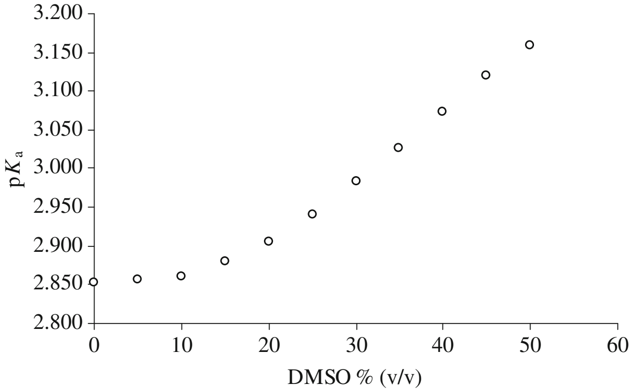

Fig. 2 Protonation constants of salicylic acid for different water–DMSO mixtures at 25 °C and ionic strength 0.1 mol dm^{-3} ($NaClO_4$)

$$\mathrm{p}K_a = -3.802(0.345) + 519.080(26.461)1/\varepsilon_r \tag{10}$$

The values in parentheses are the standard deviations of corresponding coefficients. This indicates that the protonation constants depend on the electrostatic forces and can be explained on the basis of Born's equation. However for a better evaluation of the solute–solvent interaction and to examine the correlation of protonation constants of salicylic acid with polarity and hydrogen bond properties, the most significant KAT parameters were used. Therefore, a multiparametric equation was proposed to evaluate specific and nonspecific interactions through LSER. The number of parameters in the equation depends on the significance of the solute–solvent interactions. However the general equation for LSER is usually expressed as:

$$\mathrm{p}K_a = A_0 + a\alpha + b\beta + p\pi^* \tag{11}$$

where A_0, a, b, and p are independent coefficients characteristic of the process and indicative of its sensitivity to the accompanying solvent properties. This equation can include additional terms or some of its terms can become equal to zero, depending on the property of the solute to be described [17, 30]. In order to explain the obtained pK_a values on the basis of the KAT solvent parameters, the protonation constants were correlated with solvent properties by means of single, dual, and multiple regression analysis by multiple linear regressions using the software Microsoft EXCEL [34]. Using the above regression analysis, the following single, dual, and multiple equations including r^2 coefficient and standard deviations of any coefficients (shown in parentheses) were obtained.

$$\mathrm{p}K_a = -5.406(2.257) + 7.529(2.029)\pi^* \quad r^2 = 0.605 \tag{12}$$

$$\mathrm{p}K_a = 2.010(0.057) + 1.787(0.106)\beta \quad r^2 = 0.969 \tag{13}$$

$$\mathrm{p}K_a = 3.454(0.040) - 0.554(0.044)\alpha \quad r^2 = 0.945 \tag{14}$$

$$\mathrm{p}K_a = 4.193(0.888) + 2.126(0.162)\beta - 2.126(0.863)\pi^* \quad r^2 = 0.982 \tag{15}$$

$$\mathrm{p}K_a = 2.255(0.465) + 1.487(0.576)\beta - 0.096(0.181)\alpha \quad r^2 = 0.970 \tag{16}$$

$$\mathrm{p}K_a = 8.924(0.817) - 0.803(0.041)\alpha - 4.720(0.705)\pi^* \quad r^2 = 0.992 \tag{17}$$

$$\mathrm{p}K_\mathrm{a} = 7.376(0.239) - 0.491(0.029)\alpha - 4.004(0.181)\pi^* + 0.890(0.078)\beta \quad r^2 = 1.000 \tag{18}$$

The results show that none of the single-parameter correlations of pK_a values individually with π* give good results. However, correlation analysis of pK_a values with dual-parameter and multi-parameter equations indicates significant improvement compared with the single-parameter models. Comparison of the results shows that the dual-parameter KAT equation including α and π* terms is the best, because it yields the lowest standard deviation and has an acceptable correlation coefficient.

The coefficients of α and π* in the correlation analysis of the dual-parameter KAT equation are negative in all cases. The negative π* values indicate that a decrease in the polarity of the mixed solvents reduces the pK_a values. Thus, an increase in the polarity increases the solvation of the species, and therefore makes protonation equilibrium more likely. Moreover, the negative α terms indicate an increase in the hydrogen bond donor acidity capability of the solvent and an increase in the solvation tendency of the produced anions. Consequently, the protonation constants increase with decreasing α. However, correlation analysis of pK_a values with the single-parameter model of the KAT equation including the β term is the best and yields the lowest standard deviation in both solvent systems. In a similar study, the same results were obtained for other aqueous solvent mixtures [31].

Thermodynamic protonation constant of salicylic acid in aqueous solution

The thermodynamic protonation constant of salicylic acid, pK_a^0, was estimated by applying a Debye–Hückel equation. Let us consider Eq. 1. The thermodynamic dissociation constant is expressed by the extended Debye–Hückel equation (Eq. 19):

$$\mathrm{p}K_\mathrm{a}^0 = \mathrm{p}K_\mathrm{a} + AZI^{0.5}/\left(1 + \mathrm{a}BI^{0.5}\right) \tag{19}$$

where $A = 0.5112$ (mol$^{-0.5}$ l$^{0.5}$ K$^{1.5}$), a$B = 1.5$ (mol$^{-0.5}$ m^{-1} l$^{0.5}$ K$^{0.5}$ 10^{10}) for aqueous solutions at 25 °C, and $Z = \sum\left(\text{charge}^2_\text{products}\right) - \sum\left(\text{charge}^2_\text{reactant}\right)$. According to Eq. 19, the value estimated for the thermodynamic protonation constant at an ionic strength of 0.1 M sodium perchlorate and at 25 °C is p$K_\mathrm{a}^0 = 3.072$. On the other hand, the SPARC online calculator program [32] was also used to compute the aqueous pK_a and the results were compared with estimated thermodynamic dissociation constants. The SPARC online calculator program includes algorithms based on chemical structure theory which combines the principles of quantitative structure–activity relationships, linear free energy relationships, and perturbation theory from quantum chemistry. This program estimates the pK_a of any organic compound solely from its chemical structure [32, 33]. For salicylic acid the value calculated at 25 °C is p$K_\mathrm{a}^0 = 3.059$. This is indicative of good agreement between values found experimentally and theoretically.

Conclusion

The protonation constants of salicylic acid in water and in water–DMSO mixtures containing 0–50% (v/v) DMSO were successfully determined by spectrophotometric and potentiometric methods at 25 °C and an ionic strength of 0.1 M sodium perchlorate. Generally, it was observed that the pK_a values of salicylic acid increase with increasing volume fraction of DMSO. The high correlation coefficients between the pK_a values and the physicochemical properties of the binary mixtures demonstrate the existence of a linear relationship between these magnitudes in these media.

Experimental

Reagents

Salicylic acid (99%) was obtained from Sigma–Aldrich. DMSO of the highest available purity was obtained from Merck and used without further purification. Sodium perchlorate was from Merck and was dried under vacuum at room temperature for at least 72 h before use. NaOH solution was prepared from a titrisol solution (Merck) and its concentration was determined by several titrations with a standard HCl solution. Perchloric acid was from Merck and was used as supplied. All dilute solutions were prepared from double-distilled water with a conductivity of 1.3 ± 0.1 μΩ^{-1}.

Instrumentation

The electromotive force was measured using a Metrohm model 781 pH ion-meter. The combined glass-pH electrode (model 6.0258.000) was modified by replacing its aqueous KCl solution with 0.1 mol dm^{-3} and with 0.01 mol dm^{-3} NaCl + 0.09 mol dm^{-3} $\mathrm{NaClO_4}$ saturated with AgCl in appropriate solvent. The electrode was soaked for 15–20 min in the water–organic solvent mixture before potentiometric measurements. All titrations were carried out in a 50 cm^3 thermostatted double-walled glass vessel.

Spectrophotometric measurements were performed on a Shimadzu 2100 UV–vis spectrophotometer with a Pentium 4 computer and using thermostatted matched 10 mm quartz cells. The measurement cell was of the flow type. A peristaltic pump allowed circulation of the solution under study from the potentiometric cell to the spectrophotometric cell, so the absorbance and the emf of the solution could be measured simultaneously. To exclude carbon dioxide from the system, a stream of purified nitrogen was passed through a sodium hydroxide solution and then bubbled slowly through the reaction solution.

Acknowledgments The authors gratefully acknowledge financial support form the Research Council of Islamic Azad University Jouybar branch.

References

1. Andrasi M, Buglyo P, Zekany L, Gaspar A (2007) J Pharm Biomed Anal 44:1040
2. Holmes O (1993) Human acid-base physiology: a student text. Chapman and Hall Medical, London
3. Martell AE, Smith RM (1974) Critical stability constants. Plenum, New York
4. Sahoo SK, Kanungo BK, Baral M (2009) Monatsh Chem 140:139
5. Farajtabar A, Gharib F, Jamaat P, Safari N (2008) J Chem Eng Data 53:350
6. Gharib F, Jabbari M, Farajtabar A (2009) J Mol Liq 144:5
7. Gharib F, Farajtabar A (2009) Rev Inorg Chem 29:37
8. Catalan J, Dıaz D, Garcıa-Blanco F (2001) J Org Chem 66:5846
9. Luzar A, Stefan J (1990) J Mol Liq 46:221
10. Mancera RL, Chalaris M, Refsonc K, Samios J (2004) Phys Chem Chem Phys 6:94
11. Shashkov SN, Kiselev MA, Tioutiounnikov SN, Kiselev AM, Lesieur P (1999) Physica B 271:184
12. Habibi-Yangjeh A (2004) Bull Korean Chem Soc 25:1165
13. Mancini PM, Vottero LR (2006) J Phys Org Chem 19:34
14. Kamlet MJ, Taft RW (1976) J Am Chem Soc 98:377
15. Taft RW, Kamlet MJ (1976) J Am Chem Soc 98:2886
16. Kamlet MJ, Abboud J-LM, Taft RW (1977) J Am Chem Soc 99:6027
17. Reichardt C (2004) Solvents and solvent effects in organic chemistry. Wiley-VCH, Weinheim
18. Gharib F, Jabbari M, Farajtabar A, Shamel A (2008) J Chem Eng Data 53:1772
19. Gharib F, Shamel A (2009) J Chem Eng Data 54:993
20. Gran G (1950) Acta Chem Scand 4:559
21. Gran G (1952) Analyst 77:661
22. Gameiro P, Reis S, Lima JLFC, de Castro B (2000) Anal Chim Acta 405:167
23. Jaime Ferrer JS, Couallier E, Rakib M, Durand G (2007) Electrochim Acta 52:5773
24. Beltran JL, Codony R, Prat MD (1993) Anal Chim Acta 276:441
25. Martell AE, Motekaitis RJ, Smith RM (1990) Polyhedron 9:171
26. Tauler R, Marques I, Casassas E (1998) J Chemometr 12:55
27. Migron Y, Marcus Y (1991) J Chem Soc Faraday Trans 87:1339
28. Kaatze U, Pottel R, Schafer M (1989) J Phys Chem 93:5623
29. Barbosa J, Barron D, Beltran JL, Buti S (1998) Talanta 45:817
30. Barron D, Buti S, Ruiz M, Barbosa J (1999) Polyhedron 18:3281
31. Farajtabar A, Gharib F (2010) J Sol Chem. doi:10.1007/s10953-010-9496-y
32. Hilal SH, Karickhoff SW, Carreira LA (2003) Prediction of chemical reactivity parameters and physical properties of organic compounds from molecular structure using SPARC, National Exposure Research Laboratory, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, NC
33. Hilal SH, Karicckhoff SW, Carreira LA (2004) QSAR Comb Sci 23:709
34. Microsoft Excel, Microsoft Corporation (2002) California