Conductometric study of diclofenac salts in water at different temperatures

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ABSTRACT

The conductivity of diclofenac alkali metal salts in water in the temperature range between 293.15 and 318.15 K has been obtained experimentally. The values of the limiting molar conductivity of salts were calculated using the Lee–Wheaton equation in the version, introduced by Pethybridge. The limiting molar conductivity of the diclofenac anion was estimated, and the hydration number of diclofenac was calculated based on its values. The analysis of the activation energy of conductivity shows that the ion transport process in the systems under study is carried out mainly by the ion migration mechanism.

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1. Introduction

A large number of drugs are weak acids or bases which are used as salts for improving their solubility. Diclofenac, which relates to such compounds, is a nonsteroidal anti-inflammatory drug and has a very low solubility in water (17.8 mg/l) [1]. The high hydrophobicity of diclofenac is partially retained even when the drug is in salt form. It is well known, that the ionic mobility in aqueous solutions of bases and acids occurs mainly by the Grotthuss-type mechanism [2] while the mobility of cations and anions in salt solutions occurs by the migration-type mechanism [3]. The important indicator of salts in solutions is the values of their degree of dissociation, that's possible to obtain by the conductometric method. Also the diffusion coefficient of an ion can be calculated on the basis of the ionic conductivity data using the Nernst–Einstein equation. All these data are very important to identify the therapeutic efficacy of drugs [4,5].

There is a lack of papers regarding determination of conductometric parameters of diclofenac in the literature [6,7]. The electrical conductivity of aqueous solutions of diclofenac sodium and potassium in the temperature range between 278.15 K and 313.15 K, and the conductivity of MeDic (Me = Li, Na, K) in a water–ethanol mixture at 298.15 K were studied by M. Bester-Rogac [6] and Y. Maitani et al. [7], respectively. It should be noted that the experiment described by M. Bester-Rogac [6] was performed more correctly, compared to the work presented by Y. Maitani et al. [7], namely bidistilled water was used instead of distilled one; the accuracy of temperature control was much higher.

In the present study, we investigated the conductivity of dilute aqueous solutions of alkali metals of diclofenac (Me = Li, Na, K, Rb, Cs) for a temperature range between 293.15 K and 318.15 K. This range of

temperatures has been chosen because it covers all the physiologically important temperatures. The description of the data was obtained on the basis of equations that have been carried out; the mobility of diclofenac and the characteristics of ion solvation were discussed.

2. Experiment

2.1. Chemicals

Diclofenac sodium salt (2-[(2,6-dichlorophenyl)amino]benzeneacetic acid sodium salt, >99.7%, "Aldrich") (NaDic) and diclofenac potassium salt (2-[(2,6-dichlorophenyl)amino]benzeneacetic acid potassium salt, >99.7%, "Aldrich") (KDic) were used without additional treatment. Diclofenac lithium salt (2-[(2,6-dichlorophenyl)amino]benzeneacetic acid lithium salt) (LiDic), diclofenac rubidium salt (2-[(2,6-dichlorophenyl)amino]benzeneacetic acid rubidium salt) and diclofenac cesium salt (2-[(2,6-dichlorophenyl)amino]benzeneacetic acid cesium salt) were gifts from Prof. A. Fini (Bologna, Italy) and were prepared in accordance with the method described in [8].

LiDic was dried under vacuum at 353.15 K and RbDic and CsDic at a range of temperature from 373.15 to 380.15 K for 6 h till reaching constant weight.

The freshly prepared bidistilled water was used as the solvent with the conductivity of less than 1.2×10^{-6} S/cm, which further was degassed in a quartz flask.

2.2. Preparation of solutions

Solutions were prepared by dilution. The concentrated solution was prepared as follows. Salt was placed in a thin-walled glass ampoule, which was closed tightly by a silicone rubber stopper in a dry box over P_2O_5. Weighing was carried out on scales produced by Sartorius

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Genius Series (Germany) with an accuracy of $\pm 1 \times 10^{-5}$ g. The soldered ampoule with precisely known weight of salt was transferred to a specially made glass stoppered flask with a small appendage to the vacuum hose, where the ampoule was broken by shaking the flask, and after that the solvent was poured into the flask. After complete dissolution of the salt, the solution was transferred to another flask through a fine glass filter (for removal of glass chips) which is also under vacuum, where the dilution was carried further. The difference between molar concentration, calculated from the densities of NaDic solutions, measured by us (determined by the vibrating-tube Anton Paar DMA 4500 densitometer with an uncertainty of $\pm 10^{-5}$ g/ml), and pure solvent within the studied concentration range was less than 0.05%. This difference leads to the contribution to the error of determining conductance of less than 0.004%; therefore the molar concentration (mol/l) of all salts at each temperature was calculated taking into account the density of the pure solvent (Table 1).

2.3. Conductivity measurement

The conductivities of the solutions were determined with the help of a three-electrode measuring cell with plane-parallel platinum electrodes with platinum black coating. The cell was calibrated by the conductometric standard potassium chloride solution (RADELKIS). The conductance of the solution was independently measured by means of three conductance cells with cell constants of 0.04368, 0.04449 and 0.04218 cm^{-1} at 298.15 K. The temperature dependence of cell constants was described by Eqs. (1) and (2) [11]

$$K_T = K_{298}\left[1 + \left(\frac{1}{K_{298}}\right)\left(\frac{dK_{298}}{dT}\right)(T-298.15)\right] \tag{1}$$

$$\left(\frac{1}{K_{298}}\right)\left(\frac{dK_{298}}{dT}\right) = \alpha_{gl} - 2\alpha_{Pt} = -15 \times 10^{-6}\left(K^{-1}\right), \tag{2}$$

where K_{298} is the cell constant at 298.15 K, and α_{gl} and α_{Pt} are the thermal expansion coefficients of glass and platinum respectively.

The resistance of solutions was determined by the electrochemical impedance method with Solartron 1260A (UK) in the frequency range between 0.1 Hz and 1 MHz with signal amplitude of 10 mV and measurement error of <0.2%. The resistance values were determined from a high-frequency cutoff corresponding to the solution volume resistance. Temperature was controlled by the HAAKE DC50-K35 thermostat with accuracy of 0.01 °C. Resistance of water was taken into account, while calculating the molar conductivity (Λ).

Thus obtained values of the molar conductivity of salts in water at the appropriate concentrations are shown in Table 2.

3. Results and discussion

Preliminary analysis of the results of the present study and the available literature data [6] showed that for all studied salts the ionic association in water is negligible. Indeed, it has been shown by Fini et al. [1], that among the cations of alkali metals, only Li$^+$ exhibits the ability to form ion pairs with an anion in the diclofenac concentration range between 0.025 and 0.1 mol/l. According to the work published by M. Bester-Rogac [6], the association constant (K_A) of diclofenac

Table 1
Densities, viscosities, and dielectric constants of pure water.

T (K)	ρ^0 (g/ml) [9]	η^0 (cP) [9]	ε^0 [10]
293.15	0.99819	1.00160	80.20
298.15	0.99704	0.89008	78.41
303.15	0.99564	0.79735	76.60
308.15	0.99401	0.71932	74.89
313.15	0.99219	0.65298	73.17
318.15	0.99019	0.59607	71.51

potassium and sodium in the temperature range of 278.15–313.15 K is in the range between 0.1 and 0.4 l/mol.

Our preliminary calculations using several equations (Fuoss–Justice–Chen [12], Pitts [13], Fuoss–Hsia [14], Quint–Viallard [15], Lee–Wheaton [16–18], Lee–Wheaton–Pethybridge [19]) also demonstrated, that the value of salt association constant doesn't exceed 0.5 l/mol. It should be noted that for such low values of K_A, calculated from conductometric data the relative statistical error is very large, thus the discussion of obtained data is not correct. For such low values of K_A one can assume that the electrolyte is completely dissociated. Therefore, in this paper the calculation of the limiting molar conductivity was performed without an accounting of the association in accordance with the Lee–Wheaton equation in the form introduced by Pethybridge [19] (Eq. (3)):

$$\Lambda_i = \Lambda^0\left[1 + C_1\beta\kappa + C_2(\beta\kappa)^2 + C_3(\beta\kappa)^3\right]$$
$$- \frac{\rho\kappa}{1+\kappa R}\left[1 + C_4\beta\kappa + C_5(\beta\kappa)^2 + \frac{\kappa R}{12}\right] \tag{3}$$

where C_1–C_5 are complex functions of (κR), $\beta = \frac{(ze)^2}{\varepsilon kT}$, and $\kappa = \left[\frac{8\pi N(ze)^2 c}{1000\varepsilon kT}\right]^{1/2}$.

It was shown in [20] that the choice of the value of R slightly affects the limiting molar conductivity. In this work, R was assumed to be equal to the Bjerrum distance ($q = \beta/2$).

The coefficients of Eq. (3) have been calculated by functional (see Eq. (4)) minimization using the nonlinear least-squares method.

$$\sigma(\Lambda) = \sum_{i=1}^{n}\frac{\omega_i\left(\Lambda_i^{calc.} - \Lambda_i^{obs.}\right)^2}{n-m-1} \tag{4}$$

The average dispersion within minimization was lower than 1×10^{-5}. The term ω_i is a weighting coefficient, n is the number of experimental points, and m is the number of fitting parameters. The ω_i values were calculated from the relation $\omega_i = nc_i^{1/2}/\sum_{i=1}^{n}c_i^{1/2}$.

The obtained values of the limiting molar conductivity of salts in water are shown in Table 3. Results were compared with literature data for NaDic and KDic and showed that the differences between the values of Λ^0 generally do not exceed about 0.2%.

As one can see from Table 3, the limiting molar conductivity of salt increases with increasing temperature, which first of all, may be connected with the decreasing of viscosity. The dominating role of viscosity in the value of conductivity of the diclofenac salt solutions leads to the fact that the product $\Lambda^0\eta^0$ weakly depends on the temperature (Fig. 1).

In order to calculate the limiting ionic conductivity of diclofenac, we used the value λ^0 of alkali metal ions at 298.15 K and their temperature dependence, taken from Erdey-Gruz's book [21]:

$$\lambda_i^0 = \lambda_{298}^0 + a(T-298.15) + b(T-298.15)^2 + c(T-298.15)^3, \tag{5}$$

where λ^0 and λ_{298}^0 are the limit values of electrical conductivity (S cm^2/mol) at temperature T and 298.15 K, respectively; a, b, and c do not depend on the temperature parameters. The values of the coefficients are given in Table 4.

Using the following relation: $\Lambda^0 = \lambda_+^0 + \lambda_-^0$, the values of the limiting ionic conductivity of anion Dic$^-$ were calculated. The values of λ^0 (Dic$^-$), obtained for different salts, are in good agreement. Thus, at 298.15 K the value of λ^0 (Dic$^-$), obtained for LiDic, equals to 20.05, for NaDic 20.09, for KDic 20.14, for RbDic 20.11, and for CsDic 20.19. Table 4 shows the average value of λ^0 (Dic$^-$) at 298.15 K. The obtained value is in good agreement with published data, and calculated one for NaDic and KDic (Table 4). For other temperatures, the mean values of