Scientific paper

Nonsteroidal Anti-Inflammatory Drugs Ion Mobility: A Conductometric Study of Salicylate, Naproxen, Diclofenac and Ibuprofen Dilute Aqueous Solutions

Marija Bešter-Rogač

Faculty of Chemistry and Chemical Technology, University of Ljubljana, SI-1000 Ljubljana, Slovenia

** Corresponding author: E-mail: marija.bester@fkkt.uni-lj.si*
Phone: +386 1 2419 410; fax: +386 1 2419 425

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Dedicated to Professor Josef Barthel on the occasion of his 80th birthday

Abstract

The electric conductivities of aqueous solutions of nonsteroidal anti-inflammatory drugs salicylate, naproxen, ibuprofen sodium and diclofenac sodium salts and diclofenac potassium salt were measured in the temperature range from 278.15 K to 313.15 K (in steps of 5 K) and in the concentration range $3 \times 10^{-4} < c(\text{mol/dm}^{-3}) < 0.007$. Data analysis based on the low concentration chemical model of electrolyte solutions yielded the limiting molar conductivity, Λ^{∞}, and the association constant, K_A. Using the known data of the limiting conductivities of sodium and potassium ions the limiting conductivities of the salicylate, naproxen, diclofenac and ibuprofen anions were evaluated, and the radii of anions in water were estimated. Total dissociation of the investigated salts in water is evident and the considerable differences in the anion mobilities are observed. They are discussed in terms of possible hydration and hydrophobic interactions.

Keywords: Electrolyte conductivity, electrolyte solution, sodium salicylate, naproxen sodium salt, diclofenac sodium salt, diclofenac potassium salt, ibuprofen sodium salt, chemical model

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed categories of drugs worldwide in the treatment of pain, inflammation and some of them even fever in many conditions. Their mechanism for action likely relates to the inhibition of prostaglandin synthesis[1] Although they are now used widely in therapeutics, physicochemical information about them are rather scarce.

However, the effects of a drug in a biological system is the ultimate consequence of physicochemical interactions between a drug and functionally important molecules in the living organism. The dominant fluid media in the biological systems through which the drugs are transported and in which they interact are water and lipids. The drugs usually undergo a number of complicated interactions in solution which may cause not only structural changes of biological fluids but also metabolic and structural changes of drugs. Therefore drug-drug and drug-solvent interactions may be of great importance to understand their physiological action.

The temperature and concentration dependence of the electrolyte conductance has been proved as one of the most appropriate methods for studying ion-ion, ion-solvent and solvent-solvent interactions in solutions.[2]

Recently a conductivity study of some drugs in acetonitrile at 298.15 K has been carried out[3] but there is no literature data on the drug ion mobility in water so far. In the present work electrical conductivity measurements of aqueous solutions of some NSAIDs: sodium salicylate (NaSal), naproxen sodium salt (NaNap), diclofenac sodium salt (NaDic), diclofenac potassium salt (KDic), and ibuprofen sodium salt (NaIbu) at the temperatures from 278.15 K to 313.15 K (in steps of 5 K) in the concentration range $3 \times 10^{-4} < c\ (\text{mol/dm}^{-3}) < 0.007$ were carried out. Data analysis is done in the framework of the low concentration chemical model (lcCM)[4] giving the information on the ion association and mobility of ions in aqueous solutions.

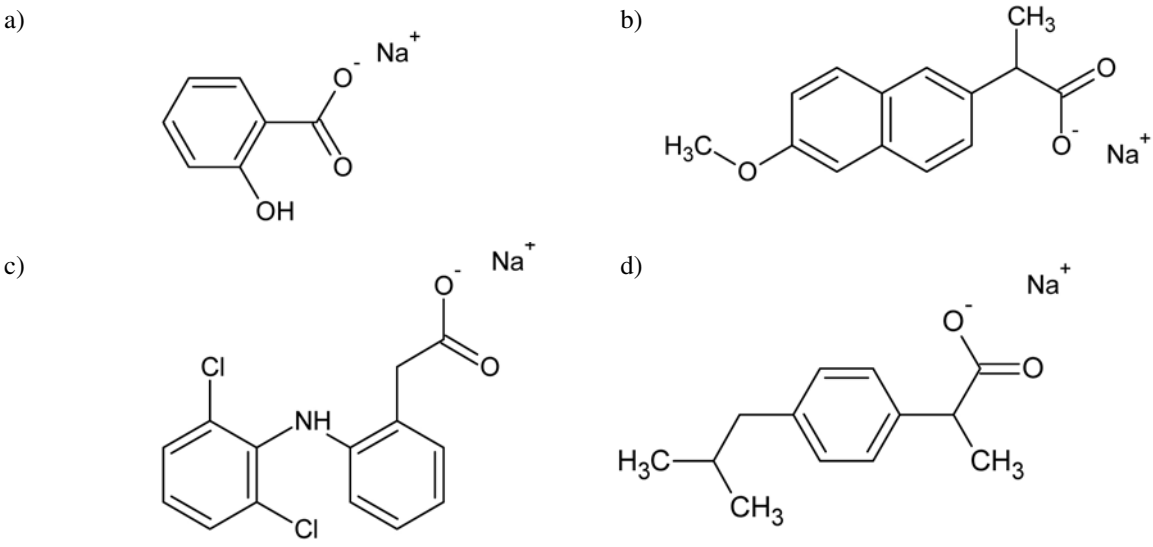

Figure 1. The structures of investigated drugs: a) salicylate, b) naproxen, c) diclofenac and d) ibuprofen sodium salt.

2. Experimetal

2. 1. Materials

Sodium salicylate (2-Hydroxybenzoic acid sodium salt, HOC_6H_4COONa, puriss. p.a., ≥99.5%, Fluka, Germany), naproxen sodium ((*S*)-6-Methoxy-α-methyl-2-naphthaleneacetic acid sodium salt, $C_{14}H_{13}NaO_3$, ≥98% , Sigma-Aldrich, Germany), diclofenac sodium (2-[(2,6-Dichlorophenyl)amino]benzeneacetic acid sodium salt, $C_{14}H_{10}Cl_2NNaO_2$, > 99.7%, Titan Pharma, India) diclofenac potassium salt (2-[(2,6-Dichlorophenyl)amino]benzeneacetic acid potassium salt, $C_{14}H_{10}Cl_2NKO_2$, > 99.7%, Titan Pharma, India), and ibuprofen sodium salt (α-Methyl-4-(isobutyl)phenylacetic acid, $C_{13}H_{17}O_2Na$, Sigma, Germany) were stored in a desiccator over P_2O_5 and used without further purification. Stock solutions were prepared by weighing pure compounds and demineralized distilled water.

Demineralized water was distilled two times in a quartz bidistillation apparatus (Destamat Bi 18E, Heraeus). The final product with specific conductivity < 6 × 10^{-7} S cm^{-1} was distilled into a flask permitting storage under an atmosphere of nitrogen.

2. 2. Conductivity Measurement

The conductivities of solutions were determined with the help of a three-electrode measuring cell, described elsewhere.[2] The cell was calibrated with dilute potassium chloride solutions[5] and immersed in the high precision thermostat described previously[6] The temperature dependence of the cell constant was taken into account.[5]

The oil bath can be set to each temperature of a temperature program with a reproducibility within 0.005 K. The temperature in the precision thermostat bath was additionally checked with calibrated Pt100 resistance thermometer (MPMI 1004/300 Merz) in connection with a HP 3458 A. The resistance measurements of solutions in the cell were performed using a precision LCR Meter Agilent 4284 A.

At the beginning of every measuring cycle the cell was filled with a weighed amount (~660 g) of water. After the measurement of the solvent conductivity at all temperatures of the program a weighed amount of a stock solution was added using a gas-tight syringe. After every addition the temperature program was run and all measured data (frequency dependent resistance, temperature) were stored by the computer and partially shown on a display to track the measuring process.[6] The measuring procedure, including corrections and the extrapolation of the sample conductivity to infinite frequency, is described in the literature.[5,6]

Table 1. Densities, viscosities and dielectric constants of pure water and limiting ionic conductivities of sodium and potassium ions in water.[a]

T/K	d_s[b]	$10^3 \cdot \eta$[c]	ε[d]	$\lambda^\infty (Na^+)$[e]	$\lambda^\infty (K^+)$[e]
278.15	0.99997	1.5192	85.897	30.30	46.72
283.15	0.99970	1.3069	83.945	34.88	53.03
288.15	0.99910	1.1382	82.039	39.72	59.61
293.15	0.99821	1.002	80.176	44.81	66.44
298.15	0.99704	0.8903	78.358	50.15	73.50
303.15	0.99565	0.7975	76.581	55.72	80.76
308.15	0.99404	0.7195	74.846	61.53	88.20
313.15	0.99222	0.6530	73.157	67.55	95.79

[a] Units: *T,* K; d_s, kg · dm^{-3}; η, *Pa · s;* λ^∞, S · cm^2 · mol^{-1}
[b] Ref.[7]; [c] Ref.[8]; [d] Ref.[9]; [e] Ref.[10]

From the weights and the corresponding solution densities *d* the molar concentrations *c* were determined. A linear change of *d* with increasing salt content for diluted solutions was assumed, $d = d_s + b\tilde{m}$, where d_s is the density of water, given in Table 1, and $\tilde{m}$ is the molonity of

Table 2. Experimental molar conductivities of the investigated drugs in water[a].

				T				
	278,15	**283.15**	**288.15**	**293.15**	**298.15**	**303.15**	**308.15**	**313.15**
$10^3 \cdot \tilde{m}$				***Λ***				
				NaSal, b = 0.067				
0.77992	49.253	56.908	65.027	73.586	82.537	91.902	101.590	111.597
1.22321	48.905	56.523	64.585	73.083	81.988	91.275	100.902	110.859
1.76798	48.587	56.152	64.163	72.605	81.432	90.671	100.228	110.114
2.39229	48.312	55.832	63.793	72.175	80.958	90.134	99.691	109.468
3.15281	48.025	55.504	63.432	71.761	80.490	89.603	99.056	108.813
3.95367	47.768	55.192	63.064	71.357	80.030	89.087	98.491	108.212
4.65674	47.557	54.962	62.785	71.030	79.664	88.676	98.033	107.711
5.50706	47.344	54.699	62.492	70.697	79.279	88.258	97.556	107.161
6.24124	47.177	54.501	62.268	70.442	78.996	87.930	97.197	106.770
7.01312	47.002	54.298	62.042	70.180	78.704	87.615	96.845	106.375
				NaNap, *b* = 0.079				
0.26893	43.613	50.395	57.599	65.208	73.190	81.549	90.268	99.274
0.52218	43.345	50.145	57.353	64.948	72.914	81.251	89.912	98.855
0.78955	43.103	49.863	57.034	64.593	72.513	80.817	89.437	98.355
1.0766	42.900	49.730	56.776	64.311	72.201	80.464	89.050	97.932
1.38111	42.721	49.414	56.525	64.022	71.891	80.120	88.672	97.523
1.76852	42.509	49.181	56.262	63.731	71.552	79.745	88.259	97.100
2.28148	42.279	48.920	55.965	63.396	71.181	79.342	87.809	96.572
2.78946	42.086	48.694	55.714	63.108	70.865	78.982	87.412	96.153
3.45331	41.891	48.466	55.447	62.791	70.504	78.579	86.964	95.675
4.39937	41.628	48.165	55.103	62.429	70.092	78.102	86.433	95.042
				NaDic, *b* = 0.122				
0.42170	40.651	47.105	54.008	61.212	68.761	76.657	84.877	93.378
0.76619	40.409	46.843	53.684	60.882	68.386	76.258	84.439	92.864
1.12796	40.164	46.542	53.344	60.480	67.931	75.766	83.905	92.323
1.54946	39.962	46.349	53.078	60.189	67.582	75.352	83.466	91.984
1.92452	39.801	46.117	52.875	59.924	67.357	75.073	83.138	91.650
2.3694	39.646	46.001	52.602	59.672	67.053	74.770	82.800	91.273
2.8900	39.483	45.746	52.454	59.437	66.770	74.457	82.458	90.846
3.5492	39.303	45.539	52.170	59.157	66.472	74.107	82.063	90.530
4.3967	39.100	45.300	51.909	58.839	66.114	73.718	81.631	89.997
				KDic, *b* = 0.128				
0.38303	56.714	65.022	73.736	82.708	92.011	101.605	111.521	121.689
0.75913	56.487	64.687	73.294	82.260	91.519	101.140	111.036	121.048
1.1398	56.247	64.413	72.942	81.874	91.137	100.641	110.422	120.607
1.5130	56.013	64.176	72.706	81.533	90.749	100.246	110.067	120.152
1.9805	55.877	63.984	72.428	81.242	90.488	99.947	109.743	119.763
2.4831	55.658	63.714	72.194	81.048	90.149	99.621	109.274	119.302
3.0674	55.533	63.536	72.010	80.756	89.827	99.260	108.945	118.833
3.7672	55.241	63.278	71.678	80.402	89.423	98.831	108.485	118.353
4.4672	55.101	63.064	71.421	80.114	89.117	98.459	108.094	117.938
5.2400	54.896	62.818	71.136	79.796	88.752	98.033	107.614	117.401
				NaIbu, b = 0.043				
0.73682	36.744	42.442	48.544	55.024	61.816	68.803	76.325	83.961
0.92933	36.581	42.271	48.373	54.825	61.605	68.604	76.092	83.753
1.1335	36.438	42.129	48.226	54.664	61.483	68.474	75.881	83.508
1.3552	36.310	41.986	48.064	54.486	61.252	68.256	75.650	83.301
1.5799	36.202	41.872	47.931	54.348	61.104	68.091	75.460	83.102
1.8264	36.094	41.745	47.801	54.207	60.932	67.909	75.251	82.871
2.0501	35.998	41.647	47.694	54.085	60.797	67.762	75.089	82.690
2.3416	35.894	41.537	47.578	53.948	60.639	67.590	74.881	82.472
2.6734	35.766	41.391	47.409	53.772	60.452	67.374	74.655	82.207
3.0726	35.649	41.261	47.254	53.593	60.256	67.170	74.406	81.900

[a] Units: $\tilde{m}$, mol · kg^{-1}; *T*, K; *Λ, S* · cm^2 · mol^{-1}*; b,* kg^2 · dm^{-3} · mol^{-1}

the electrolyte (moles of electrolyte per kilogram of solution). The densities of the solutions were determined by the method of Kratky et al.[11] using a Paar densimeter (DMA 60, DMA 601 HT) at 298.15 K combined with a precision thermostat. As usual the density gradient b is considered to be independent of temperature, see Table 2.

The measured conductivity data of all investigated salts are given in Table 2 as a function of the temperature independent molonities. They can be converted to the temperature-dependent molarities by using the relationship $c = \tilde{m}d$.

Taking into account the sources of error (calibration, measurements, impurities) the molar conductivities are accurate to within 0.1%.

3. Data Analysis

The analysis of the conductivity data in the framework of the low concentration chemical model (lcCM) given in Ref.[4] and the literature cited there, uses the set of equations

$$\frac{\Lambda}{\alpha} = \Lambda^{\infty} - S\sqrt{\alpha c} + E\alpha c \ln(\alpha c) + J_1 \alpha c - J_2 (\alpha c)^{\frac{3}{2}} \quad (1)$$

$$K_A = \frac{1-\alpha}{c\alpha^2 y'^2_{\pm}}; \quad y'_{\pm} = exp\left(-\frac{\kappa q}{1+\kappa R}\right); \quad (2a\text{–}b)$$

$$\kappa^2 = 16\pi N_A q \alpha c; \qquad q = \frac{e_o^2}{8\pi\varepsilon\varepsilon_o kT} \quad (3)$$

where Λ and Λ^{∞} are the molar conductivities at molarity c and in the infinite dilution, respectively, $(1–\alpha)$ is the fraction of oppositely charged ions acting as ion pairs, and K_A is the equilibrium constant of the lcCM with upper association limit R; $y'_{\pm}$ is the corresponding activity coefficient of the free ions, $(y'_{\pm})^2 = y'_{+} y'_{-}$, κ is the Debye parameter, e_0 is the proton charge, ε is the relative permittivity of the solvent, ε_o is the permittivity of vacuum and T the absolute temperature. The other symbols have their usual meaning. W^* is a step function for the potential of mean force between cation and anion due to non-Coulombic interactions.

The coefficients of Eq. (1) are given in Ref .[4] The limiting slope S and the parameter E are completely calculable when the solvent data are available (Table 1). The coefficients J_1 and J_2 are also functions of the distance parameter R, representing the distance to which oppositely charged ions can approach as freely moving particles in solution.

Analysis of the conductivity data of associated electrolytes are carried out by setting the coefficients S, E and J_1 of Eq. (1) to their calculated values[4] and then usually using three-parameter fits to obtain the limiting values of molar conductivity Λ^{∞}, the association K_A and the coefficient J_2 by non-linear least squares iterations. A three-parameter evaluation is reduced to a two-parameter procedure for nonassociating electrolytes,[2] where usually coefficient J_2 is also fixed. The input data for the calculation of the coefficients are the known solvent properties (Table 1) and the distance parameter R. The lower limit a of the association integral is the distance of closest approach of cation and anion (contact distance), $a = a_+ + a_-$. It was calculated from the ionic radii of the cations;[4] $a_+ = 0.098$ nm for Na^+ and 0.133 nm for K^+. Organic anions such as carboxylates, sulfonates, etc., bear their negative charge in an oxygen atom on the surface of the ionic molecule. The "radius" of such ions may be taken to be the effective van der Waals radius of the carboxylate or sulfonate group.[4] We used the value $a_- = 0.162$ nm which was estimated for formic acid[4] assuming that the radicals in the anions of the investigated drugs do not change the interionic distance between the cation and the basic oxygen atom in their structure.

From extended investigations of electrolyte solutions in amphiprotic hydroxylic solvents (water, alcohols) it is known that the upper limit of association is given by an expression of the type $R = a + ns$, where s is the length of an oriented solvent molecule, n is an integer, $n = 0, 1, 2, \ldots$ Here, s is the length of an OH-group, d_{OH}, and $s = d_{OH} = 0.28$ nm. In this study we fixed the distance parameter R at $R = 0.820$ nm for sodium and 0.855 nm for potassium salts, allowing thus three types of ion pairs in the solutions: contact ion pairs, solvent-shared and solvent-separated ion pairs.

4. Results and Discussion

Figure 2 shows a comparison of the experimental data for molar conductivities, Λ, of the NaNap aqueous

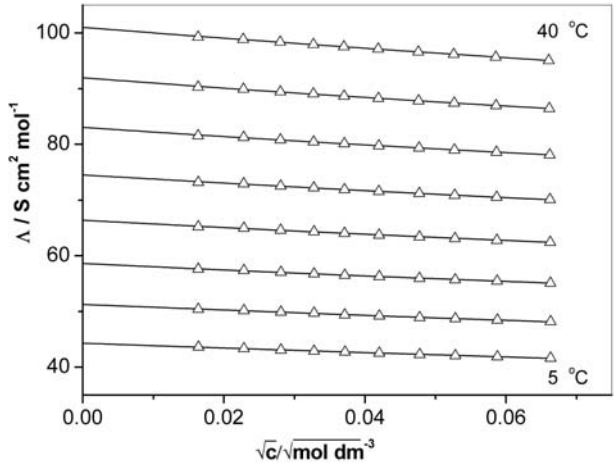

Figure 2. Molar conductivities, Λ, of aqueous NaNap solutions from 278.15 to 318.15 K (steps of 5 K). (Δ) experiment, full line: lcCM calculations.

Table 3.: Limiting molar conductivities Λ^∞ and association constants K_A of investigated salts in water.[a]

T	KDic		NaDic		NaNap		NaSal		NaIbu	
	Λ^∞	K_A	Λ^∞	K_A	Λ^∞	K_A	Λ^∞	K_A	Λ^∞	K_A
278.15	57.66 ± 0.03	0.1 ± 0.2	41.51 ± 0.01	0.1 ±	44.31 ± 0.01	1.948 ± 0.17	50.44 ± 0.02	1.720 ± 0.09	37.83 ± 0.02	2.02 ± 0.26
283.15	66.09 ± 0.02	0.1 ± 0.1	48.12 ± 0.02	0.3 ± 0.2	51.27 ± 0.02	1.806 ± 0.26	58.30 ± 0.02	1.738 ± 0.08	43.70 ± 0.01	0.94 ± 0.16
288.15	74.89 ± 0.02	0.1 ± 0.1	55.16 ± 0.02	0.4 ± 0.2	58.61 ± 0.02	1.447 ± 0.18	66.63 ± 0.02	1.726 ± 0.08	49.97 ± 0.01	0.1 ± 0.12
293.15	84.07 ± 0.03	0.1 ± 0.2	62.55 ± 0.02	0.4 ± 0.1	66.38 ± 0.02	1.266 ± 0.20	75.42 ± 0.02	1.757 ± 0.08	56.65 ± 0.03	0.1 ± 0.28
298.15	93.60 ± 0.03	0.3 ± 0.1	70.26 ± 0.02	0.1 ± 0.2	74.52 ± 0.03	1.135 ± 0.21	84.61 ± 0.02	1.779 ± 0.08	63.67 ± 0.05	0.1 ± 0.53
303.15	103.40 ± 0.05	0.1 ± 0.2	78.35 ± 0.02	0.1 ± 0.2	83.05 ± 0.03	1.062 ± 0.23	94.22 ± 0.02	1.796 ± 0.08	70.87 ± 0.14	0.1 ± 1.25
308.15	113.52 ± 0.06	0.1 ± 0.2	86.77 ± 0.03	0.1 ± 0.1	91.93 ± 0.03	1.003 ± 0.20	104.19 ± 0.02	1.795 ± 0.07	78.63 ± 0.09	0.1 ± 0.68
313.15	123.88 ± 0.06	0.1 ± 0.2	95.33 ± 0.04	0.1 ± 0.2	100.99 ± 0.03	1.604 ± 0.17	114.32 ± 0.03	2.205 ± 0.08	86.42 ± 0.05	0.1 ± 0.35

[a] Units: T, K; Λ^∞, $S \cdot cm^2 \cdot mol^{-1}$; K_A, $dm^3 \cdot mol^{-1}$

solutions given in Table 2 and the results of the lcCM calculations executed using Eqs. (1–3). All other investigated systems show similar dependence.

In Figure 3 the conductivity data for sodium salts (salicylate, naproxen, ibuprofen, diclofenac) and potassium diclofenac at 298.15 K are presented. For NaIbu solutions the experiment was performed in the same concentration range as for other salts but for unknown reason the experimental data can only be satisfactorily fitted over a narrow range of concentration.

Table 3 gives a comparison of the calculated lcCM data for all investigated salts. The limiting conductivities are dependent on the structure of the anions, as can be expected. The values of the association constants are very low and all the investigated salts could be regarded as completely dissociated in water solutions ("strong-electrolytes"). The values of K_A for NaCl aqueous solutions obtained from precise conductance measurements by using the lcCM, are in the range $0.6 < K_A < 2.6$ in the temperature range between 278.15 and 303.15 K.[12] Whereas the temperature coefficient dK_A/dT is usually positive for the alkali salt water solutions, no reliable evidence for the temperature dependence of the association process of aqueous solutions of the discussed drugs was found except at NaSal and NaIbu where slightly higher ion association at lower temperatures can be assumed.

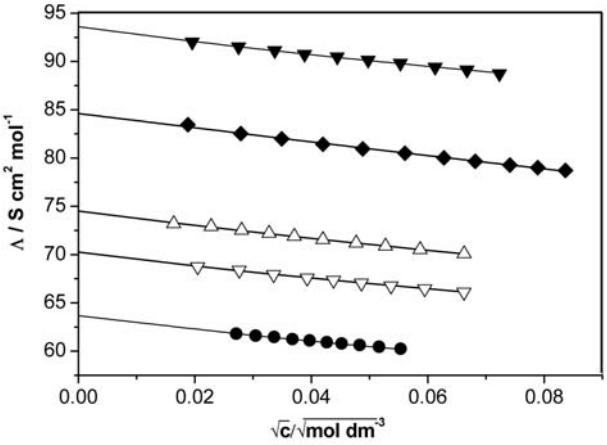

Figure 3. Molar conductivities of KDic (▼), NaSal (◆), NaNap (△), NaDic (▽) and NaIbu (●) in water at 25 °C.

Combining the limiting conductivities Λ^∞ of Table 3 and the known limiting values of cations $\lambda^\infty(M^+)$, $M^+ = Na^+, K^+$ (Table 1)

$$\lambda^\infty(T, A^-) = \Lambda^\infty(T, MA) - \lambda^\infty(T, M^+) \quad (4)$$

yields the limiting anion conductivities $\lambda^\infty(A^-)$ and their temperature dependence; see Table 4.

Table 4. Limiting conductance of anions of investigated drugs in water as a function of temperature[a]

T	λ^∞ (Dic$^-$)		λ^∞ (Sal$^-$)	λ^∞ (Nap$^-$)	$\bar{\lambda}^\infty$ (Dic$^-$)	λ^∞ (Ibu$^-$)
	NaDic	KDic				
278.15	11.19	10.93	20.14	14.01	11.06	7.53
283.15	13.20	13.06	23.42	16.39	13.13	8.82
288.15	15.40	15.28	26.91	18.89	15.34	10.25
293.15	17.69	17.63	30.61	21.56	17.66	11.84
298.15	20.09	20.10	34.46	24.37	20.09	13.52
303.15	22.61	22.64	38.50	27.33	22.63	15.15
308.15	25.23	25.32	42.66	30.40	25.28	17.10
313.15	27.78	28.08	46.77	33.45	27.93	18.87

[a] Units: *T*, K; λ^∞, $S \cdot cm^2 \cdot mol^{-1}$

From the Walden rule[4]

$$\lambda^\infty(T)\eta(T) = \frac{Fe|z|}{6\pi a_i^{(\eta)}} \quad (5)$$

the solvent dependent ionic radii $a_i^{(\eta)}$ were estimated (*F* is the Faraday constant and *z* the ionic charge). In water $a_i^{(\eta)}$ are usually called hydrodynamic radii, r_h. Values for the hydrodynamic radii of the ions of investigated salts are collected in Table 5. It is well known that comparison of the values of the hydrodynamic radii and the crystal radii of cations show large difference for Na^+ ions, whereas the ion size parameter of K^+ are close together.

Table 5. Hydrodynamic radii, r_h, of the investigated salts in water from Walden rule as a function of temperature

	r_h					
T	Na^+	K^+	Sal$^-$	Nap$^-$	Dic$^-$	Ibu$^-$
278.15	0.178	0.115	0.268	0.385	0.487	0.716
283.15	0.180	0.118	0.267	0.382	0.477	0.710
288.15	0.181	0.121	0.267	0.381	0.469	0.702
293.15	0.182	0.123	0.267	0.379	0.463	0.690
298.15	0.183	0.125	0.267	0.377	0.458	0.680
303.15	0.184	0.127	0.267	0.376	0.454	0.678
308.15	0.185	0.129	0.267	0.374	0.450	0.666
313.15	0.186	0.131	0.268	0.375	0.449	0.665

[a] Units: *T*, K; r_h, *nm*

Sodium ion is relatively small and has, therefore, an exceptionally high charge to radius ratio (charge density) and tends to orient the water molecules in its vicinity. Contrarily, its hydrated radius is much larger than similar ions and the large solvation shell around the ion also causes its low mobility and low limiting conductivities λ^∞ in solution.

The potassium ion has low charge densities and consequently ions are surrounded by water molecules which are more mobile. For the sodium ion the hydration number, *h*, obtained from transport process measurements, is reported in the literature as *h* (Na^+, 298.15 K) = 5.

The obtained hydrodynamic radii for the anions are ranked in Sal$^-$ < Nap$^-$ < Dic$^-$ < Ibu$^-$ what is not expected from their molar van der Waals volumes, V_{vdw}, calculated from the optimized geometries using the Winmostar program[13] and summarized in Table 6.

Table 6. Van der Waals volumes, V_{vdw}, van der Waals radii, r_{vdw}, of the anions and the ratio between van der Waals radii and the hydrodynamic radii at 298.15 K.[a]

	V_{vdw}	r_{vdw}	r_{vdw}/r_h
Sal$^-$	67.9	0.300	1.123
Nap$^-$	125.1	0.367	0.973
Dic$^-$	137.4	0.379	0.828
Ibu$^-$	119.2	0.362	0.532

[a] Units: V_{vdw}, $cm^3 \cdot mol^{-1}$; r_{vdw}, nm

The van der Waals radii, r_{vdw}, were calculated assuming spherical shapes of anions and Walden rule treats the ionic migration as a movement of a rigid spherical ion through viscous continuum also. The structures of the investigated ions (Figure 1) hardly express the spherical symmetry. Therefore values listed in Tables 5 and 6 can be discussed only as the rough estimation of real dimensions of the drug's anions in water. Nevertheless, values of r_h and r_{vdw} for Sal$^-$ and Nap$^-$ are close together. It appears that no explicit hydration of these anions can be assumed.

Larger differences between r_h and r_{vdw} for Dic$^-$ and Ibu$^-$ may lead to the assumption that here the hydration is more pronounced. Despite the fact that chlorine and nitrogen atoms reduce the hydrophobicity of the radical in Dic$^-$ anion the hydration can be predicted hardly even here. For Ibu$^-$ possessing higly hydrophobic alkyl chain bound to the aromatic ring this is even less likely. Rather it can be assumed that the anions are more extended and the assumption of the spherical symmetry is far from more realistic dimensions obtained by Walden rule.

From Table 5 it is evident that r_h of Sal$^-$ is almost temperature insensitive whereas at all other anions r_h is decreasing perceivably with increasing temperature. This again may lead to the conclusion that hydration – which

is more pronounced at lower temperatures – may take place.

Finally, the hydrodynamic radii of Sal^- and Nap^- ions have been found to be smaller than 0.4 nm, a common pore size of membranes so that the direct passage of the drug through the pores of the membranes is possible. The opposite is true for the Dic^- and Ibu^- and these drugs probably penetrate by partition mechanism.

For Dic^- anion in acetontrile the value of $a_i^{(\eta)}$ = 0.521 nm at 298.15 K has been found recently[3] showing completely different interactions of this anion with the solvent. It is known that solvents forming three-dimensional networks (water, alcohols) surround hydrophobic organic ions in clathrate-like structures[4] and therefore here the radii of complex organic anions are significantly different from that in organic solvents. Moreover, for the complex hydrophobic organic anions in aqueous solutions coiled configuration can be assumed.

The temperature-dependence of limiting conductivity yields Eyring's enthalpy of activation of charge transport[14]

$$ln\,\lambda^{\infty} + \frac{2}{3} ln\, d_s = -\frac{\Delta H^*}{RT} + \mathrm{B}, \qquad (6)$$

where B is the integration constant.

Values ΔH^* = 16.50, 14.72, 17.40, 17.94, 19.02 and 19.03 kJ/mol for Na^+, K^+, Sal^-, Nap^-, $Dic^-$and Ibu^-, respectively, were obtained (Figure 4).

It has been shown that the ionic migration in a non-structures solvent is very much a solvent property and that the difference in the mobilities of ions is simply the result of different ion sizes.[14,15] The observed order of the molar ionic enthalpies of activation, ΔH^*, for the cations $Na^+ > K^+$ could be explained by the energy needed for the desolvation and rearrangement of water molecules in the vicinity of the ion. Thus values of ΔH^* may depend on the expressed hydration.

Differences in the Eyring's enthalpy of activation of charge transport of the investigated anions are ranked as $Sal^- < Nap^- < Dic^- \approx Ibu^-$. They could not be ascribed to the differences in the ion sizes only ($r_h(Dic^-) < r_h(Ibu^-)$) but also to the specific interaction anions with water.

In water additional strong – hydrophobic – interactions are presented, resulting not only in the size parameters. Therefore it could be assumed that for the jump of the, for example, Ibu^- anion to a prepared vacancy in the solvent – or to produce such a vacancy – higher energy is required than for the Sal^- anion (and Nap^-) or cations investigated in this work.

This could be explained by the repulsion of water molecules by the hydrophobic site of the anions and this part is larger at Dic^- and Ibu^- than at Sal^- and Nap^-. The hydroxyl and ether group in the structure of Sal^- and Nap^-, respectively, reduce the hydrophobicity of these anions obviously .

Assuming substantial hydration of Dic^- the relatively high value of ΔH^* can be explained by the desolvation and rearrangement of water around the moving ion, whereas at Ibu^- the hydrophobicity is crucial.

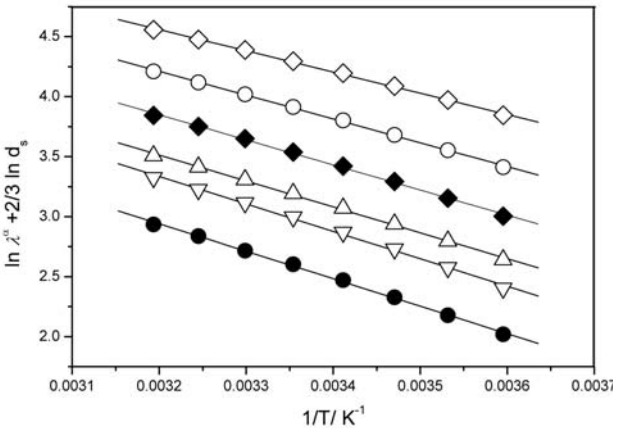

Figure 4. Plot of $ln\lambda^{\infty}$ + 2/3 lnd_s as a function of 1/T for K^+(◇), Na^+(○), Sal^- (◆), Nap^- (△), Dic^- (▽) and Ibu^- (●) in water at 298.15 K. From the slope the activation energy of the ionic movement, ΔH*, is obtained.

4. Conclusion

Nonsteroidal anti-inflammatory drugs sodium salicylate, naproxen sodium salt, diclofenac sodium salt, diclofenac potassium salt and ibuprofen sodium salt are completely dissociated in aqueous solutions. Their anions are weakly hydrated due to its hydrophobicity, whereas the hydration of cations depends on their charge densities.

From the Eyring's enthalpy of activation it could be assumed that the repulsion of water molecules by the hydrophobic site of the anion at Ibu^- is more pronounced than at Sal^- and Nap^-, where hydroxyl group and/or ether group reduce the hydrophobicity of the anions. At Dic^- the hydration could also play an important role.

Despite the fact, that the mechanism of action of NSAIDs is not completely understood,[1] it could be expected that the observed differences should have an influence on their potency, duration of action and the way in which they are eliminated from the body. However, more investigations are needed to enlighten the correlation of their transport behaviour with their pharmacological properties.

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6. References

1. J. A. Mitchell, T. D. Warner, *Nat. Rev. Drug Disc.* **2006**, *5*, 75–86.
2. J. Barthel, R. Wachter, H.-J. Gores, Temperature dependence of electrolyte conductance in non-aqueous solutions, in: B. E. Conway, J. O'M. Bockris (Eds.), Modern Aspects of Electrochemistry, New York: Plenum Press, **1979**, p.1–78.
3. R. Mandal, J. Gangopadhyay, S. C. Lahiri, *Z. Phys. Chem.* **2004**, *218*, 551–561.
4. J. Barthel, H. Krienke, W. Kunz, Physical Chemistry of Electrolyte Solutions-Modern Aspects, Steinkopf/Darmstadt, Springer/New York, **1998**.
5. J. Barthel, F. Feuerlein, R. Neueder, R. Wachter, *J. Solution Chem.* **1980**, *9*, 209–219.
6. M. Bešter-Rogač, D. Habe, *Acta Chim. Slov.* **2006**, *53*, 391–395.
7. E. F. G. Herington, *Pure Appl. Chem.* **1976**, *45,* 1–9.
8. L. Korson, W. Drost-Hansen, F. J. Millero, *J. Phys. Chem.* **1969,** *73*, 34–39.
9. B. B. Owen, R. C. Miller, C. E. Milner, H. L. Cogan, *J. Phys. Chem.* **1961**, *65*, 2065–2070.
10. H. S. Harned, B. B. Owen, The physical chemistry of electrolyte solutions, 3rd edn., Reinhold, New York, p. 233, **1958**.
11. O. Kratky, H. Leopold, H. Stabinger, *Z. Angew. Phys.* **1969**, *27*, 273–277.
12. M. Bešter-Rogač, R. Neueder, J. Barthel, *J. Solution Chem.* **1999**, *28*, 1071–1086.
13. N. Senda, Winmostar, version 3.75 http://winmostar.com
14. S. B. Brummer, G. J. Hills, *J. Chem. Soc. Faraday Trans.* **1961**, *57*, 1816–1837.
15. F. Barreira, G. J. Hills, *J. Chem. Soc. Faraday Trans.* **1968**, *64*, 1359–1375.

Povzetek

Izmerili smo električne prevodnosti vodnih raztopin salicilat, ibuprofen, diklofenak in naproksen natrijeve soli ter diklofenak kalijeve soli v temperaturnem območju med 278.15 K in 313.15 K v koncentracijskem obsegu $3 \times 10^{-4} < c$ (mol/dm^{-3}) < 0.007. Na osnovi kemijskega modela smo določili vrednosti molskih prevodnosti pri neskončnem razredčenju, Λ^{∞}, ter konstante asociacije ionov, K_A, v posameznem sistemu. S pomočjo znanih vrednosti limitnih prevodnosti natrijevega oz. kalijevega iona smo ocenili limitne prevodnosti ter hidrodinamične radije vseh preiskovanih anionov. Ugotovili smo, da je delež ionskih parov v raztopini zanemarljiv in preiskovanim elektrolitom v vodnih raztopinah lahko pripišemo popolno disociacijo v celotnem obravnavanem temperaturnem območju. Opazno razliko v mobilnosti anionov lahko pripišemo različni hidrataciji ter možnim hidrofobnim interakcijam.