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Mass transport techniques as a tool for a better understanding of the structure of L-Dopa in aqueous solutions

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ABSTRACT

Mutual diffusion coefficients, D, densities, ρ, and viscosities, η, are reported for aqueous solutions of L-3,4-dihydroxyphenylalanine (L-Dopa) at 298.15 K and 310.15 K at concentrations from (0.00025 to 0.0075) mol dm^{-3}. The aim of this study is to contribute to a better understanding of the structure of these systems and the thermodynamic behaviour of L-Dopa in solution. Thus, from these experimental data it was possible to estimate some parameters, such as the hydrodynamic radius, R_h, apparent molar volumes, ϕ_V, and diffusion coefficients at infinitesimal concentration, D^0, essential for a better understanding of disperse systems. From the measured diffusion coefficients, activity coefficients, γ, for aqueous L-Dopa solutions were also estimated by using Nernst–Hartley equation. The effect of the viscosity on the estimated hydrodynamic radius was also studied.

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1. Introduction

In the early 1960's, L-3,4-dihydroxyphenylalanine (levodopa, also called L-Dopa), a precursor of the neurotransmitters dopamine, was one of the most surprising neurological drugs as a result of its ability to induce a direct improvement in patients with Parkinson's disease, due to its conversion into dopamine in both the central nervous system and the peripheral nervous system (Carlsson, 2002).

However, the properties of the aqueous systems containing this drug are poorly known. For example, being usually orally administered and rapidly absorbed, the extension of the absorption and its clinical response depend on multiple factors, such as the stomach and intestine pH, and the concentrations of the inorganic salts present there. In fact, there are common adverse effects in the use of L-Dopa (Cotzias et al., 1967, 1969), from what some authors have suggest associating it with inorganic matrices that might result in delayed or controlled release, obtaining this way the better regulation of L-Dopa uptake and avoiding the side effects of this drug.

This has provided our impetus for the present study. Having in mind that we are particularly interested in data concerning diffusion and viscosity, and as far as the authors know, there are no data available, the present work intends to fill this gap.

As a consequence, we have also estimated some structural, thermodynamic and transport parameters, such as activity coefficients, apparent molar volumes, limiting diffusion coefficients and hydrodynamic radius of L-Dopa aqueous solutions. These data will contribute for the design of better matrices and appropriate conditions for the release and uptake of L-Dopa.

2. Experimental

2.1. Reagents and solutions

The 3-(3,4-dihydroxyphenyl)-L-alanina (L-Dopa, Fluka, purum ≥99%; M = 197.19 g mol^{-1}) was used as received (Table 1).

All the solutions were freshly prepared before each experiment. For diffusion studies, they were prepared by volume (concentration uncertainty less than 0.1%) and de-aerated during 30 min, approximately, before use. For the density and viscosity measurements, solutions were prepared by direct weighing both the solute and distilled water in a Mettler AE 240 balance with a precision of ±0.0001 g (the uncertainty concerning composition was less than±0.07%).

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Table 1
Sample description.

Chemical name	Source	Mass fraction purity
L-Dopa	Fluka	≥99%

2.2. Diffusion measurements

The theory of the Taylor dispersion technique is well described in the literature (Taylor, 1953; Ribeiro et al., 2010). Therefore, only some relevant points on the experimental determination of binary diffusion coefficients, D, will be indicated.

The method is based on the dispersion of small amounts of solution into a laminar carrier stream of solvent or solution of different composition, flowing through a long capillary tube ($(3.2799 \pm 0.0001)\ 10^4$ mm in length and a radius of 0.5570 ± 0.0003 mm) (Ribeiro et al., 2005, 2011a, 2011b; Valente et al., 2011).

A 6-port Teflon injection valve (Rheodyne, model 5020) was used to introduce 0.063 mL of solution into the laminar carrier stream of slightly different composition. A flow rate of 0.17 mL min^{-1} was maintained by a metering pump (Gilson model Minipuls 3) to give retention times of about 1.1×10^4 s. The dispersion tube and the injection valve were kept at (298.15 and 310.15) K ± (0.01 K) in an air thermostat.

Dispersion of the injected samples was monitored using a differential refractometer (Waters model 2410) at the outlet of the dispersion tube (Fig. 1). Detector voltages, $V(t)$, were measured at accurately 5 s intervals with a digital voltmeter (Agilent 34401 A) with an IEEE interface. Binary diffusion coefficients were evaluated by fitting the dispersion equation

$$V(t) = V_0 + V_1 t + V_{\max}(t_R/t)^{1/2} \exp[-12D(t - t_R)^2/r^2 t] \quad (1)$$

to the detector voltages. The additional fitting parameters were the mean sample retention time t_R, peak height $V_{\max}$, baseline voltage V_0, and baseline slope V_1.

Binary mutual diffusion coefficients (D) are calculated from the broadened distribution of the dispersed sample measured at the tube outlet (*e.g.* Callendar and Leaist, 2006).

In these experiments, small volumes, ΔV, of the solution, of composition $\overline{c_1} + \overline{\Delta c_1}$ and $\overline{c_2} + \overline{\Delta c_2}$ are injected into carrier solutions of composition $\bar{c}_1$ and $\bar{c}_2$ at time $t = 0$.

2.3. Density measurements

The density of these solutions was determined with an Anton Paar DMA5000 M densimeter (precision of 1×10^{-6} g cm^{-3} and accuracy of 5×10^{-6} g cm^{-3} in the ranges of 0–90 °C of temperature and 0–10 bars of pressure). This densimeter is provided with a Peltier system which allows keeping the temperature of the samples constant during the measurement within ±0.005°. They were carried out at 298.15 K and 310.15 K.

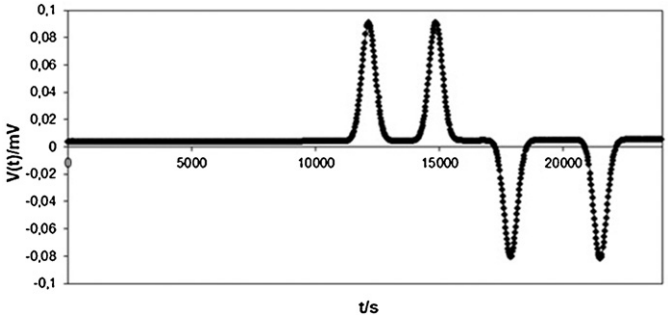


Fig. 1. Dispersion profile of a L-Dopa standard Taylor experience.

Table 2
Experimental mutual diffusion coefficients, D_{exp} for aqueous L-Dopa solutions at various concentrations, c, and temperatures.

c (mol dm^{-3})	$(D \pm S_D)$ (10^{-9} m^2 s^{-1})[a]	
	T (K) = 298.15	T (K) = 310.15
0.000250	0.635 ± 0.004	0.849 ± 0.055
0.000500	0.631 ± 0.005	0.845 ± 0.004
0.001001	0.627 ± 0.012	0.839 ± 0.011
0.001751	0.622 ± 0.015	0.837 ± 0.025
0.002501	0.612 ± 0.008	0.835 ± 0.006
0.003749	0.600 ± 0.026	0.829 ± 0.030
0.005001	0.628 ± 0.010	0.852 ± 0.007
0.006000	0.642 ± 0.018	0.856 ± 0.010
0.007001	0.661 ± 0.012	0.888 ± 0.028

[a] D and S_D are the mean diffusion coefficient for 4 experiments and the respective standard deviations of that mean.; $u(c) = 5 \times 10^{-6}$ mol dm^{-3}; $u(D) = 0.02 \times 10^{-9}$ m^2 s^{-1}; $u(T) = 0.01$ K.

The density value for each solution studied was the mean one of at least four sets of measurements. These values were reproducible within ±0.001% of uncertainty.

2.4. Viscosity measurements

Viscosity measurements were performed with an Ostwald type viscometer (capillary diameter = 0.30 mm), calibrated from water, immersed in a water-thermostat bath which temperature was controlled within ±0.02 K by using a digital thermometer. The arithmetic mean value of four sets of flow times for each solution was taken to calculate such viscosity values. The efflux time was carried out with a stopwatch with a resolution of 0.2 s. These values were reproducible within ±0.1% of uncertainty (±0.001 mPa s).

Since the efflux times were always greater than 350–400 s, the kinetic energy correction (Hagenbach correction) was considered to be not necessary and, therefore, viscosity values (in mPa s) were evaluated from the equation:

$$\eta = K\rho t \quad (2)$$

where K (equal to 0.0025314 mm^2 s^{-2} and 0.0025294 mm^2 s^{-2} at 25 and 37 °C, respectively) is the viscometer constants, ρ the density (g cm^{-3}) and t the flow time (s).

The measurements were carried out in each solution and in pure water. By applying Eq. (2) to them and combining adequately, the expression:

$$\frac{\eta}{\eta_0} = \frac{\rho t}{\rho_0 t_0} \quad (3)$$

is obtained, where η_0, ρ_0 and t_0 are referred to pure water. From this Eq. (3) the viscosity of the corresponding solution, η, was calculated. The values used for the viscosity of water were 0.8902 mPa s and 0.6925 mPa s at 25 and 37 °C, respectively (Kestin et al., 1978) and those of the density, 0.997048 g cm^{-3} and 0.993333 g cm^{-3} at 25 and 37 °C, respectively (Lide, 2007–2008).

3. Results and discussion

Diffusion coefficient values for binary systems, D, together with the standard deviations of the mean at $T = 298.15$ K and $T = 310.15$ K are summarized in Table 2. These results are, in general, the average ones from 4 independent experiments, with an uncertainty of (1–2)% (Ribeiro et al., 2012).

The concentration dependence of the measured diffusion coefficients is accurately represented by the linear equation:

$$D = D_0(1 + ac) \quad (4)$$

Table 3
Values of the parameters D^0 and a for the dependence of D with concentration in aqueous solutions of L-Dopa at 298.15 K and 310.15 K.[a]

T (K)	D^0	a	r^2
298.15	0.637 ± 0.001	−9.8 ± 0.4	0.991
310.15	0.847 ± 0.002	−13.7 ± 0.8	0.914

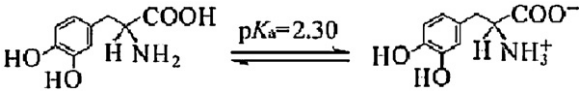
[a] These fittings were performed for $c \leq 0.00375$ mol dm^{-3} (see Table 2).

where D^0 is the diffusion coefficient at infinitesimal concentration (in m^2 s^{-1}) and a is a constant (in dm^3 mol^{-1}); both these parameters were computed by fitting the Eq. (4) to experimental data by using a least-squares procedure (Table 3).

From the binary diffusion coefficients (Table 2), we may estimate the activity coefficients for aqueous L-Dopa solutions, using the Nernst–Hartley equation (Eq. (5)) applicable to non-electrolytes (Tyrrell and Harris, 1984; Ribeiro et al., 2011c)

$$D = D_0\left(1 + \frac{d\ln\gamma}{d\ln c}\right)_{T,P} \quad (5)$$

where γ is the thermodynamic activity coefficient of that drug. Its application can be justified if we consider that in those solutions (for which the acid pH conditions promote the dissociation of the carboxylic group and the protonation of the amino one) the levodopa molecules predominantly exist as a zwitterion (Chen et al., 2004)



(6)

In addition, for dilute solutions ($c \leq 0.00375$ mol dm^{-3}) we may assume for this drug (Miyajima et al., 1983; Ribeiro et al., 2009) that

$$\ln\gamma = bc \quad (7)$$

where b (dm^3 mol^{-1}) is a constant (whose value can be determined from Eqs. 4 and 5). Combining Nernst–Hartley's equation (Eq. (5)) and Eq. (7) we obtain the values for the activity coefficients of L-Dopa (Table 4). We can observe, for both temperatures, that they decrease significantly with the increase of the concentration (<6%) and, concerning the effect of temperature, there are no appreciable differences among them (<0.2%). Despite of the limitations of this estimative method, we may interpret that variation on the basis of the increasing of the solute–solvent interactions with the increasing of the concentration (more favoured with respect to the solute–solute ones) reflecting all contributions from water molecules, including those beyond the first layer which would not be firmly enough to move as a unit with the ion.

From the extended Stokes–Einstein equation (Eq. (8)) (Erdey-Gruz, 1974), which consider the solvent as a continuum characterized by its bulk viscosity value, it is also possible to estimate the hydrodynamic radius, R_h, of L-Dopa in these solutions,

$$D = \frac{k_B T}{6\pi\eta R_h} \quad (8)$$

Table 4
Activity coefficients, γ, for L-Dopa aqueous solutions, evaluated from Eq. (5).

c (mol dm^{-3})	γ	
	T (K) = 298.15	T (K) = 310.15
0.000250	0.996	0.996
0.000500	0.992	0.992
0.001001	0.985	0.984
0.001751	0.974	0.972
0.002501	0.963	0.961
0.003749	0.944	0.942

u(c) = 5 × 10^{-6} mol dm^{-3}.

Table 5
Hydrodynamic radius, R_h, of L-Dopa in aqueous solutions at two temperatures, T.

c (mol dm^{-3})	$D\eta/T$ (10^{-15} m s^{-1} kg K^{-1})		R_h (10^{-9} m)	
	T (K) = 298.15	T (K) = 310.15	T (K) = 298.15	T (K) = 310.15
0	1.902	1.897	0.385	0.386
0.000250	1.903	1.897	0.386	0.387
0.000500	1.904	1.897	0.389	0.389
0.001001	1.904	1.898	0.393	0.393
0.001751	1.905	1.899	0.394	0.392
0.002501	1.906	1.900	0.400	0.393
0.003749	1.907	1.902	0.396	0.392
0.005001	1.908	1.904	0.390	0.384
0.006000	1.909	1.905	0.381	0.382
0.007001	1.910	1.907	0.369	0.368

u(c) = 5 × 10^{-6} mol dm^{-3}.

where k_B and η are Boltzmann's constant and the viscosity of the solvent at temperature T. Although this relation is only approximated (arising from the acceptance that the structure of both the solute kinetic species and the solvent are not considered together with the assumption of this viscosity is the only responsible of the diffusivity reduction), it can be used to estimate the radius of the moving species, since L-Dopa molecules are large enough when compared with the water molecules. Table 5 gives the ($D\eta/T$) values whose variation observed is relatively small (less than 0.5% at both temperatures) and within the imprecision of the diffusion measurements. The values calculated for the effective hydrodynamic radius R_h of L-Dopa in these solutions are also collected in Table 5. As it can be observed, the maximum variation observed in these R_h values, with respect to the limiting one at infinitesimal concentration, is around 4%.

From the R_h value at infinitesimal concentration thus determined, it is straightforward to obtain the limiting hydrodynamic molar volume of the L-Dopa, $\bar{V}^0$. These values, calculated from the approximation of spherical shape for the L-Dopa molecules, are: 144 cm^3 and 145 cm^3, at 298.15 and 310.15 K, respectively.

Table 6 shows the experimental density values of L-Dopa for both the concentration range and temperatures studied. These data were linearly fitted by using a least-squares regression method to analyse their dependence with concentration. The values obtained are summarized in Table 7. From them it can be seen that both lines are almost mutually parallels which implies that temperature has no further influence on the behaviour of this physicochemical property with concentration.

Apparent molar volumes, ϕ_V, for these L-Dopa aqueous solutions are also collected in Table 6. They were calculated by using the equation:

$$\phi_V = \frac{V - V_{H_2O}}{m} = \frac{M}{\rho} + \frac{1000}{m}\left(\frac{1}{\rho} - \frac{1}{\rho_{H_2O}}\right) \quad (9)$$

where M (=197.17 g mol^{-1}) is the molar mass of the solute, V is the volume of a solution of molality m and V_{H_2O} and ρ_{H_2O} are the volume and density of pure water, respectively. They show a good agreement with data previously published (Table II in Marriott et al., 1998).

The value at infinitesimal concentration was determined by using the Masson equation (Masson, 1929), which is applicable for dilute aqueous solutions of electrolytes:

$$\phi_V = \phi_V^0 + S_V^0\sqrt{c} \quad (10)$$

where ϕ_V^0 is the apparent partial molar volume at infinitesimal concentration (at this limiting condition $\phi_V^0 = \bar{V}_2^0$, *i.e.*, the apparent molar volume of the solute equals its partial molar volume) and S_V^0 is the experimental slope which value depends on both the nature of the solute and the temperature and has been correlated to the

Table 6
Experimental density data, ρ, and apparent molar volumes for aqueous L-Dopa solutions at various concentrations, m, and temperatures, T.

m (mol kg^{-1})	T (K) = 298.15			T (K) = 310.15		
	ρ (g cm^{-3})	$10^6\Delta$[(a)]	ϕ_V (cm^3 mol^{-1})	ρ (g cm^{-3})	$10^6\Delta$[(a)]	ϕ_V (cm^3 mol^{-1})
0.000261_7	0.997069	0.5	117.0_4	0.993357	0.8	106.3_3
0.000486_0	0.997084	1.1	123.6_6	0.993363	2.4	113.0_0
0.001009	0.997125	0.8	120.8_2	0.993408	0.4	122.9_9
0.001757	0.997175	0.8	124.9_3	0.993457	1.3	126.7_4
0.002504	0.997230	7.0	124.6_5	0.993513	0.7	125.6_5
0.004972	0.997399	0.8	126.6_7	0.993681	0.7	127.5_3
0.006990	0.997545	0.7	126.1_9	0.993826	1.1	127.0_3
0.007476	0.997588	1.1	125.0_2	0.993891	1.3	122.8_3

(a) Δ stands for standard deviation of all the measurements; u(m) = 2×10^{-6} mol kg^{-1}; u(ρ) = 5×10^{-6} g cm^{-3}; u(T) = 0.005 K.

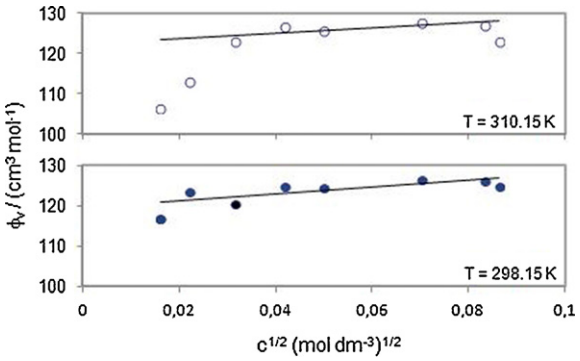


Fig. 2. Plot of ϕ_V values against $c^{1/2}$ at different temperatures (the tendency straight lines are drawn).

Table 7
Values of ρ^0 and b for the concentration dependence of D in aqueous solutions of L-Dopa at 298.15 K and 310.15 K[a].

T (K)	ρ^0 (g cm^{-3})[b]	b' (dm^3 mol^{-1})	r^2
298.15	0.997050 ± 0.000002	0.0711 ± 0.0005	0.999
310.15	0.993335 ± 0.000006	0.072 ± 0.001	0.998

[a] These linear fittings were performed from the Table 6 data, b' being the slope of the fitting.
[b] In very good agreement with literature data (Lide, 2007–2008).

solute–solute interactions taking place in solution. These limiting values are 121.6(±1.5) cm^3 mol^{-1} and 122.4(±1.9) cm^3 mol^{-1} for 298.15 and 310.15 K, respectively. They were found by disregarding the experimental points at low concentrations (Fig. 2). These limiting values agree well with that of 126.35 cm^3 mol^{-1}, independent of the temperature, previously reported in the literature (Marriott et al., 1998) by considering a linear dependence between the apparent partial molar volume and the molal concentration.

Table 8
Experimental viscosity data, η, for L-Dopa aqueous solutions at various concentrations. m. and temperatures, T.

m (mol kg^{-1})	η (mPa s)			
	T (K) = 298.15	$10^4\Delta$[a]	T (K) = 310.15	$10^4\Delta$[a]
0.000261_7	0.8907	1.5	0.6924	1.3
0.000486_0	0.8908	1.5	0.6925	2.7
0.001009	0.8910	0.1	0.6928	1.6
0.001757	0.8913	0.8	0.6932	0.9
0.002504	0.8917	2.8	0.6936	3.6
0.004972	0.8928	1.6	0.6949	2.7
0.006990	0.8937	0.9	0.6960	1.1
0.007476	0.8939	0.6	0.6963	1.0

[a] Δ stands for the standard deviation of all the measurements; u(m) = 2×10^{-6} mol kg^{-1}; u(η) = 1×10^{-3} mPa s; u(T) = 0.02 K.

Table 9
Coefficient values obtained from the analysis of the viscosity-concentration dependence for L-Dopa aqueous solutions by using the Jones–Dole equation.

T (K)	A (dm$^{3/2}$ mol$^{-1/2}$)	B (dm^3 mol^{-1})	r^2
298.15	−0.002 ± 0.002	0.52 ± 0.02	0.999
310.15	−0.001 ± 0.002	0.80 ± 0.02	0.999

In Table 8 the experimental viscosity values of L-Dopa, obtained for the concentration range and the temperatures studied, are collected. As it can be ascertained, an important decreasing of these values was obtained when the temperature increases, being the influence of the concentration very small and in the opposite sense. Moreover, the increasing of the viscosity values with the concentration of the solution is bigger for the highest temperature studied (0.55 mPa s kg mol^{-1} at 310.15 K against 0.43 mPa s kg mol^{-1} at 298.15 K).

The analysis of the concentration influence on the viscosity of the solution was performed from the well-known Jones–Dole equation, valid for solutions of electrolytes, (although L-Dopa is not an electrolyte it has a zwitterion structure)

$$\frac{\eta}{\eta_0} = 1 + Ac^{1/2} + Bc + Dc^2 \quad (11)$$

where η_0 and η are the viscosities of the pure solvent and the solution, respectively, and the A and B coefficients are depending on both the solute and the solvent, as well as on the temperature and pressure (Table 9). This B-coefficient reflects the effect of the solute–solvent interactions occurring in the solution and it is used as a criterion of measuring the *structure-making* and *structure-breaking* capacity of the solute on the solution structure. The A-coefficient has been related to the solute–solute interactions taking place in the solution. The D-coefficient depends on both the solute–solute and solute–solvent interactions and it becomes important only at high solute concentration (>0.5 mol dm^{-3}) (Donald et al., 1995) and, therefore, it was disregarded for this analysis in Eq. (11).

The large and positive values of the B-coefficient strengthened by the temperature increasing (dB/dT = 0.02) suggest that this drug has *structure-making* capacity which means that L-Dopa possesses the ability to increase water structure in the solution. This fact is in agreement with that derived from the analysis of the activity coefficients (see Table 4).

4. Conclusions

It was possible to determine experimental mutual diffusion coefficients, densities and viscosities of binary aqueous solutions of L-Dopa at 298.15 K and 310.15 K. Regarding the results obtained for the diffusion coefficient, possible electrostatic interactions can be present, resulting in a decrease in the diffusion coefficient values. From these data it is still possible to conclude that the increase in

the temperature contributes to an increase in the average velocity of the ions and, consequently, to a raise of the diffusion coefficient.

Both the density and the viscosity of these solutions show a linear dependence with the concentration. From the viscosity *A* and *B*-coefficient values found it can be concluded that solute–solvent interactions are predominant and became more important when the temperature increases.

These results became more significant when the pharmaceutical applications of this drug and its behaviour at physiological temperature are having in mind. This fact provides the usefulness of the transport data to model the diffusion for *in vivo* applications.

Acknowledgments

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References

Callendar, R., Leaist, D.G., 2006. Diffusion coefficients for binary, ternary and polydisperse solutions from peak-width analysis of Taylor dispersion profiles. J. Solut. Chem. 35, 353–379.

Carlsson, A., 2002. Treatment of Parkinson's with L-Dopa. The early discovery phase and a comment on current problems. J. Neural Transm. 109, 777–787.

Chen, X., Xie, J., Li, C., Hu, Z., Chen, X., 2004. Investigation of the factors that induce analyte peak splitting in capillary electrophoresis. J. Sep. Sci. 27, 1005–1010.

Cotzias, G.C., Van Woert, M.H., Schiffer, L.M., 1967. Aromatic amino acids and modification of parkinsonism. N. Eng. J. Med. 276, 374–379.

Cotzias, G.C., Papavasiliou, P.S., Gellene, R., 1969. Modification of parkinsonism: chronic treatment with L-Dopa. N. Eng. J. Med. 280, 337–345.

Donald, H., Jenkins, B., Marcus, Y., 1995. Viscosity B-coefficients of ions in solution. Chem. Rev. 95, 2695–2724.

Erdey-Gruz, T., 1974. Transport phenomena in aqueous solutions, 2nd ed. Adam Hilger, London, p. 151.

Kestin, J., Sokolov, M., Wakerham, W.A., 1978. Viscosity of liquid water in the range −8 °C to 150 °C. J. Phys. Chem. Ref. Data 7, 941–948.

Lide, D.R. (Ed.), 2007–2008. Handbook of Chemistry and Physics. , 88th ed. CRC Press, Boca Raton, USA, p. 6–6.

Marriott, R.A., Hakin, A.W., Liu, J.L., 1998. Modeling of thermodynamic properties of amino acids and peptides using additivity and HKF theory. J. Solut. Chem. 27, 771–802.

Masson, D.O., 1929. Solute molecular volumes in relation to solvation and ionization. Phil. Mag. 8, 218–235.

Miyajima, K., Sawada, M., Nakagaki, M., 1983. Viscosity B-coefficients, apparent molar volumes, and activity coefficients for alpha-cyclodextrin in aqueous solutions. Bull. Chem. Soc. Jpn. 56, 3556–3560.

Ribeiro, A.C.F., Lobo, V.M.M., Leaist, D.G., Natividade, J.J.S., Verissimo, L.P., Barros, M.C.F., Cabral, A.M.T.D.P.V., 2005. Binary diffusion coefficients for aqueous solutions of lactic acid. J. Solut. Chem 34, 1009–1016.

Ribeiro, A.C.F., Santos, A.C.G., Lobo, V.M.M., Veiga, F.J.B., Cabral, A.M.T.D.P.V., Esteso, M.A., Ortona, O., 2009. Binary mutual diffusion coefficients of isoniazid aqueous solutions at (298.15 and 310.15) K. J. Chem. Eng. Data 54, 3235–3237.

Ribeiro, A.C.F., Barros, M.C.F., Lobo, V.M.M., Quintanilla, G., Esteso, M.A., 2010. Diffusion coefficients of the ternary system calcium chloride–caffeine–water at (25 and 37) °C. J. Chem. Eng. Data 55, 897–900.

Ribeiro, A.C.F., Barros, M.C.F., Lobo, V.M.M., Sobral, A.J.F.N., Fangaia, S.I.G., Nicolau, P.M.G., Guerra, F.A.D.R.A., Esteso, M.A., 2011a. Interaction between calcium chloride and some carbohydrates as seen by mutual diffusion at 25° C and 37° C. Food Chem. 124, 842–849.

Ribeiro, A.C.F., Gomes, J.C.S., Barros, M.C.F., Lobo, V.M.M., Esteso, M.A., 2011b. Diffusion coefficients of nickel chloride in aqueous solutions of lactose at T = 298.15 K and T = 310.15 K. J. Chem. Therm. 43, 270–274.

Ribeiro, A.C.F., Sobral, A.J.F.N., Simoes, S.M.N., Barros, M.C.F., Lobo, V.M.M., Cabral, A.M.T.D.P.V., Veiga, F.J.B., Santos, C.I.A.V., Esteso, M.A., 2011c. Transport properties of aqueous solutions of sodium alginate at 298 15 K. Food Chem. 125, 1213–1218.

Ribeiro, A.C.F., Barros, M.C.F., Verissimo, L.M.P., Santos, C.I.A.V., Cabral, A.M.T.D.P.V., Gaspar, G.D., Esteso, M.A., 2012. Diffusion coefficients of paracetamol in aqueous solutions. J. Chem. Therm. 54, 97–99.

Taylor, G., 1953. Dispersion of soluble matter in solvent flowing slowly through a Tube. Proc. R. Soc. London A 219, 186–203.

Tyrrell, H.J.V., Harris, K.R., 1984. Diffusion in Liquids, 2nd ed. Butterworths, London, pp. 298, 403.

Valente, A.J.M., Ribeiro, A.C.F., Rita, M.B.B.J., Carvalho, R.A., Esteso, M.A., Lobo, V.M.M., 2011. Transport properties of aqueous solutions of calcium lactate in the absence and presence of beta-cyclodextrin. J. Mol. Liq. 161, 125–131.