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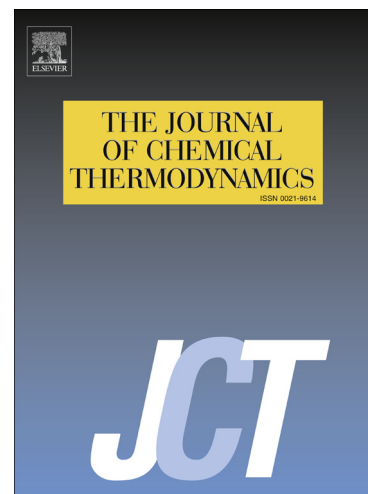Please cite this article as: M.C.F. Barros, A.C.F. Ribeiro, M.A. Esteso, V.M.M. Lobo, D.G. Leaist, Diffusion of levodopa in aqueous solutions of hydrochloric acid at 25 °C, *J. Chem. Thermodynamics* (2013), doi: http://dx.doi.org/10.1016/j.jct.2013.12.010

Diffusion of levodopa in aqueous solutions of hydrochloric acid at 25 ºC

M. C. F. Barros[a,b], A. C. F. Ribeiro[a]*, M. A. Esteso[b], V. M. M. Lobo[a] and D. G. Leaist[c]

[a]Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade de Coimbra, 3004-535 Coimbra, Portugal

[b]U.D. Química Física, Universidad de Alcalá, 28871 Alcalá de Henares, Madrid, Spain

[c]Department of Chemistry, St. Francis Xavier University, Antigonish Nova Scotia, Canada B2G 2W5

*Corresponding author:
Dra Ana Cristina Faria Ribeiro
Dept. Chemistry
University of Coimbra
3004-535 Coimbra
Portugal
Phone: +351 239854460
Fax: +351 239 827703
E-mail: anacfrib@ci.uc.pt

Abstract

Ternary mutual diffusion coefficients (D_{11}, D_{22}, D_{12} and D_{21}) measured by the Taylor dispersion method are reported for aqueous solutions of {levodopa (L-dopa) + HCl} solutions at 25 ºC and HCl concentrations up to 0.100 mol·dm^{-3}. The coupled diffusion of L-dopa (1) and HCl (2) is significant, as indicated by large negative cross-diffusion coefficients. D_{21}, for example, reaches values that are larger than D_{11}, the main coefficient of L-dopa. Combined Fick and Nernst-Plank equations are used to analyse the proton coupled diffusion of L-dopa and HCl in terms of the binding of H$^+$ ions to L-dopa and ion migration in the electric field generated by L-dopa and HCl concentration gradients.

[[]]

2

1. Introduction

L-3,4-dihydroxyphenylalanine (L-dopa) is one of the most important drugs for the treatment of Parkinson disease [1]. It is usually administered orally and is rapidly absorbed. However, the extent and rate of absorption and the resulting clinical response depend on multiple factors, including the stomach and intestine pH. Diffusion coefficients provide a direct measure of molecular mobility, an important factor in deciding rates of absorption. Moreover, the coupled diffusion of different solution components (including proton-coupled transport) and changes in the solution pH can be responsible for significant variations in the solubility and rate of absorption of drugs. A few diffusion coefficients for binary aqueous solutions of L-dopa [2] (or hydrochloric acid [3,4] at 25 ℃ have been reported, but no data are available for the coupled diffusion of L-dopa in aqueous solutions. In this study, we report ternary mutual diffusion coefficients (D_{ik}) measured by Taylor dispersion for aqueous solutions of L-dopa (1) + hydrochloric acid (2) at 25 ℃. Cross-diffusion coefficients D_{12} and D_{21} are used to estimate the number of moles of each component transported per mole of the other component by coupled diffusion. Coupled diffusion of L-dopa and HCl, indicated by cross-diffusion coefficients D_{12} and D_{21}, is analyzed in terms of H^+-ion binding to L-dopa and ion migration in the diffusion potential gradient by using combined Nernst-Planck and Fick equations [5].

2. Experimental

L-Dopa (Fluka *purum* mass fraction purity ≥ 99 %) and HCl (Sociedade Portuense de Drogas, 33.5 wt % HCl in water) were used as received. Solutions were prepared in calibrated volumetric flasks with Millipore water. See table 1.

The Taylor dispersion method for the measurement of diffusion coefficients is based on the dispersion of small amounts of solution injected into laminar carrier streams of solution of different composition flowing through a long capillary tube. The technique is described in detail in the literature [6-8]. Only a brief summary of the equipment and procedure used in the present study [9-14] is presented here.

At the start of each run, a 6-port Teflon injection valve (Rheodyne, model 5020) was used to introduce 63 mm^3 of solution into a laminar carrier stream of slightly different composition. A flow rate of 0.17 cm$^3 \cdot$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 length {32.799 ($\pm$ 0.001)} m and the injection valve were kept at 25.00 ^{o}C ($\pm$ 0.01 ^{o}C) 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. Detector voltages, $V(t)$, were measured at 5 s intervals with a digital voltmeter (Agilent 34401 A). Binary mutual diffusion coefficients D were evaluated by fitting the dispersion equation

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

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. r is the internal radius {0.5579 ($\pm$ 0.003)} mm of the dispersion tube.

Diffusion in aqueous {L-dopa (1) + HCl (2)} solutions is described by the ternary diffusion equations

$$J_1(\text{L-Dopa}) = -D_{11}\nabla C_1 - D_{12}\nabla C_2 \tag{2}$$

$$J_2(\text{HCl}) = -D_{21}\nabla C_1 - D_{22}\nabla C_2 \tag{3}$$

J_1 and J_2 are the molar fluxes of L-dopa (1) and HCl (2) driven by the concentration gradients ∇C_1 and ∇C_2 in the solutes. Main coefficients D_{11} and D_{22} give the molar fluxes of L-dopa and HCl driven by their own concentration gradients. Cross-diffusion coefficients D_{12} and D_{21} give the coupled flux of each solute driven by a concentration gradient in the other solute. A positive D_{ik} cross-coefficient ($i \neq k$) indicates co-current coupled transport of solute i from regions of higher to lower concentrations of solute k. A negative D_{ik} coefficient indicates counter-current coupled transport of solute i.

4

The Taylor technique can also be used to measure mutual diffusion coefficients (D_{ik}) for multicomponent solutions. Ternary mutual D_{ik} coefficients, defined by equations 2 and 3, were evaluated by fitting the dispersion equation

$$V(t) = V_0 + V_1 t + V_{\max} \ (t_R/t)^{1/2} \left[W_1 \exp\left(-\frac{12 D_1 (t - t_R)^2}{r^2 t} \right) + (1 - W_1) \exp\left(-\frac{12 D_2 (t - t_R)^2}{r^2 t} \right) \right] (4)$$

to two or more peaks obtained by injecting solution samples of composition $C_1 + \Delta C_1$, $C_2 + \Delta C_2$ into carrier streams of composition of composition C_1, C_2. D_1 and D_2 are the eigenvalues of the matrix of the ternary D_{ik} coefficients. W_1 and $(1 - W_1)$ are the normalized pre-exponential factors. The D_{ik} coefficients were evaluated from the fitted values of D_1, D_2, and W_1 values for each carrier-stream composition. Details of the calculations have been reported [15].

3. Results and discussion

The diffusion coefficients of the {L-Dopa (1) + HCl (2)} solutions were measured six times at each composition and averaged. The results are summarized in table 2. Main diffusion coefficients D_{11} and D_{22} were generally reproducible within $\pm\ 0.02 \times 10^{-9}\ \mathrm{m^2 \cdot s^{-1}}$. The cross-coefficients were reproducible within about $\pm 0.05 \times 10^{-9}\ \mathrm{m^2 \cdot s^{-1}}$.

The cross-coefficients are negative, indicating counter-current coupled flows of L-dopa and HCl. In general, D_{12} and D_{21} increase and decrease, respectively, with the solute fraction of L-Dopa, defined as $X_1 = C_1/(C_1 + C_2)$. The values of the ratio D_{12}/D_{22} show that a mole of diffusing HCl counter-transports up to 0.13 mol L-dopa, whereas the D_{21}/D_{11} ratio shows that a mole of diffusing L-dopa can counter-transport up to 2.5 mol HCl.

Aqueous H^+ ions and L-dopa molecules associate in aqueous solutions

$$\text{L-dopa} + H^+ = \text{L-dopa} \cdot H^+ \tag{5}$$

The equilibrium constant (K_c) for the reaction is 200 mol·dm^{-3} at 25 °C [16]. In addition to providing an association mechanism for the coupled diffusion of L-dopa and HCl, the charged L-dopa·H^+ complex will migrate in the electric field (diffusion potential gradient) generated by concentration gradients in L-dopa or HCl. To assess the possible

5

importance of these effects, Fick equations 2 and 3 for the fluxes of the total L-dopa and HCl components can be combined with the Nernst-Planck equations

$$j_s(\text{species } s) = -D_s c_s \nabla \ln(y_s c_s) + \frac{FE}{RT} z_s D_s c_s \tag{6}$$

$$J_i(\text{component } i) = \sum_s v_{is} j_s \tag{7}$$

for the fluxes of the diffusing species (L-dopa molecules and the L-dopa·H^+, H^+, and Cl^- ions). In the notation used here, the stoichiometric coefficient v_{is} gives the number of moles of solute component i transported per mole of solute species s. The molar flux, diffusion coefficient, concentration, charge, and activity coefficient of species s are denoted by j_s, D_s, c_s, z_s, and y_s. R, T, F, and E are the gas constant, temperature, Faraday constant and the electric field.

Combining the Fick and Nernst-Planck equations allows each mutual D_{ik} coefficient for the L-dopa and HCl solution components to be decomposed into the pure-diffusion contribution $D_{ik(D)}$ from the fluxes of constituent species driven by concentration gradients and the electrical contribution $D_{ik(E)}$ from the migration of constituent ionic species [17].

$$D_{ik} = D_{ik(D)} + D_{ik(E)} \tag{8}$$

$$D_{ik(D)} = \sum_s v_{is} c_s D_s \left(\frac{\partial \ln(y_s c_s)}{\partial C_k} \right)_{Cm \neq k} \tag{9}$$

$$D_{ik(E)} = \sum_s \sum_q v_{is} \frac{t_s}{z_s} z_q D_q \left(\frac{\partial \ln(y_q c_q)}{\partial C_k} \right)_{Cm \neq k} \tag{10}$$

in the electric field

$$E = \frac{RT}{F} \sum_q \frac{t_q}{z_q} \frac{\partial \ln(y_q c_q)}{\partial C_k} \tag{11}$$

6

The transference number (t_q) and activity coefficient of ionic species q are calculated from the equations

$$t_q = \frac{z_q^2 c_q D_q}{\sum_s z_s^2 c_s D_s} \tag{12}$$

$$\ln y_q = -1.17 \frac{\sqrt{I}}{1+\sqrt{I}} \tag{13}$$

where $I = C_2$ is the ionic strength. The s summations run over all of the solute species. Only the ionic species (H^+, Cl^-, L-dopa·H^+) are included in the q summations. The diffusion coefficients of those species, D_s, used to calculate ternary diffusion coefficients D_{ik}, $D_{ik(D)}$ and $D_{ik(E)}$ from Eqs. 8 to 10 are indicated in table 3.

The main features of coupled mutual diffusion in aqueous L-dopa + HCl solutions are illustrated in figures 1 and 2 by plotting the measured diffusion coefficients against the solute fraction of L-dopa ($X_1 = C_1/(C_1 + C_2)$) for the solutions containing $C_1 + C_2 = 0.0050$ mol dm^{-3} total solute. The predicted values of D_{ik}, $D_{ik(D)}$ and $D_{ik(E)}$ from Eqs. 8 to 10 are also plotted.

D_{11} and D_{21} give the fluxes of L-dopa and HCl, respectively, produced by L-dopa concentration gradients. As X_1 increases from 0.00 to 1.00, D_{11} changes from the tracer diffusion coefficient of L-dopa in HCl solutions to the binary diffusion coefficient of aqueous L-dopa solutions. D_{11} passes through a weak maximum over this composition range. According to the Nernst-Planck analysis, this maximum is due to the small electrostatic contribution $D_{11(E)}$ to D_{11}. As a consequence of the L-dopa protonation equilibrium, an increase in the L-dopa concentration reduces the concentration of free H^+ ions (at fixed HCl concentration), causing H^+ ions to diffuse "up" L-dopa concentration gradients to replace the H^+ ions lost by association to the L-dopa molecules. The electric field generated to slow down the highly mobile H^+ ions to maintain electro-neutrality drives the charged L-dopa·H^+ species down the L-dopa concentration gradient. This proton-coupled transport mechanism for L-dopa is indicated by the positive $D_{11(E)}$ values plotted in figure 1.

The cross-coefficient D_{21} gives the coupled flux of HCl produced by L-dopa concentration gradients. The diffusion of free H^+ ions up L-dopa concentration gradients and the slowing down of these ions by the diffusion-induced electric field are reflected by the positive and negative values of $D_{21(D)}$ and $D_{21(E)}$, respectively. The pure-diffusion contribution $D_{21(D)}$ is dominant, leading to large negative values of D_{21}. In fact, the ratio D_{21}/D_{11} reaches values as large as -2.5, indicating that each mole of the diffusing L-dopa component counter transports up to 2.5 moles of the HCl component. In the limit $X_1 \rightarrow 1$ (binary solutions of L-dopa), however, D_{21} drops to zero because an L-dopa concentration gradient cannot produce a coupled flow of HCl in an HCl-free solution.

Cross-coefficient D_{12} gives the coupled flux of L-dopa produced by HCl concentration gradients. A gradient in HCl concentration produces concentration gradients in L-dopa molecules and L-dopa·H^+ ions of equal magnitude, but opposite sign. Because the L-dopa and L-dopa·H^+ species have nearly identical diffusion coefficients, the pure-diffusion fluxes of L-dopa in molecular and ionic form effectively cancel, and the contribution $D_{12(D)}$ to D_{12} is essentially zero (see figure 1). However, the migration of L-dopa·H^+ ions in the electric field generated by HCl concentrations is significant, with each mole of HCl counter-transporting up to 0.13 mol L-dopa.

Main coefficient D_{22} gives the flux of HCl produced by its own concentration gradient. The pure-diffusion and electrostatic contributions to D_{22} are positive and negative, respectively. As the solute fraction of L-dopa increases, the conversion of H^+ ions to less mobile L-dopa·H^+ species reduces D_{22}.

4. Conclusions

The effect of added hydrochloric acid on the diffusion of L-dopa has been investigated by measuring ternary mutual diffusion coefficients for aqueous solutions of L-dopa + HCl. The measured D_{ik} coefficients have been compared with values calculated from Nernst-Planck equations. This approach provides detailed information about the composition dependence of the D_{ik} coefficients and mechanisms for the coupled diffusion of the L-dopa and HCl components.

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TABLE 1 Provenance and mass fraction purity of the compounds studied

Compound	CAS number	Supplier	Mass fraction purity	Water content mass fraction
L-Dopa	59-92-7	Fluka	≥ 0.99	-
HCl	7647-01-0	Sociedade Portuense de Drogas	-	0.335

11

Table 2 Ternary mutual diffusion coefficients of aqueous {L-Dopa (1) + HCl (2)} solutions at 25 ºC [a,b,c]

C_1/ mol·dm^{-3}	C_2/ mol·dm^{-3}	X_1	D_{11}/ 10^{-9} m^2·s^{-1}	D_{12}/ 10^{-9} m^2·s^{-1}	D_{21}/ 10^{-9} m^2·s^{-1}	D_{22}/ 10^{-9} m^2·s^{-1}
0.0000	0.0050	0.0000	0.61 (0.62) ± 0.01	−0.07 (0.00) ± 0.02	−0.16 (−0.78) ± 0.08	2.99 (3.27) ± 0.02
0.0010	0.0040	0.2000	0.64 (0.64) ± 0.001	−0.11 (−0.04) ± 0.02	−0.28 (−0.66) ± 0.02	2.99 (3.18) ± 0.03
0.0020	0.0030	0.4000	0.66 (0.65) ± 0.01	−0.13 (−0.08) ± 0.01	−0.28 (-0.50) ± 0.06	3.01 (3.16) ± 0.02
0.0030	0.0020	0.6000	0.65 (0.65) ± 0.005	−0.20 (−0.11) ± 0.01	−0.16 (−0.32) ± 0.04	3.01 (3.09) ± 0.02
0.0040	0.0010	0.8000	0.65 (0.64) ± 0.01	−0.20 (−0.13) ± 0.01	−0.11 (−0.14) ± 0.01	2.96 (3.03) ± 0.05
0.0050	0.0000	1.0000	0.62 (0.62) ± 0.01	−0.36 (−0.13) ± 0.05	−0.02 (0.00) ± 0.01	2.67 (2.88) ± 0.03
0.0000	0.1000	0.0000	0.64 (0.62) ± 0.01	−0.01 (0.00) ± 0.01	−1.60 (−1.48) ± 0.55	2.90(2.77) ± 0.02
0.0005	0.1000	0.0050	0.61 (0.62) ± 0.02	−0.01 (0.00) ± 0.003	−1.23 (−1.49) ± 0.10	2.94 (2.78) ± 0.004
0.0005	0.0200	0.0240	0.62 (0.63) ± 0.005	−0.02 (−0.01) ± 0.004	−0.10 (−1.25) ± 0.01	2.75 (3.02) ± 0.04
0.0025	0.1000	0.0240	0.63 (0.63) ± 0.001	−0.02 (−0.01) ± 0.003	−0.81 (−1.50) ± 0.12	2.94 (2.80) ± 0.01

12

0.0005	0.0100	0.048	0.64 (0.63) ± 0.01	−0.10 (−0.01) ± 0.004	−0.77 (−1.04) ± 0.07	2.98 (3.10) ± 0.01
0.0025	0.0200	0.1110	0.58 (0.66) ± 0.002	−0.09 (−0.04) ± 0.01	−0.78 (−1.29) ± 0.07	3.03 (3.08) ± 0.01
0.0025	0.0100	0.2000	0.64 (0.67) ± 0.002	−0.05 (−0.06) ± 0.01	−0.67 (−1.04) ± 0.07	3.02 (3.16) ± 0.02
0.0070	0.0200	0.2590	0.68 (0.73) ± 0.001	−0.06 (−0.12) ± 0.01	−0.20 (−1.33) ± 0.03	3.08 (3.19) ± 0.02
0.0005	0.0010	0.3330	0.66 (0.63) ± 0.01	−0.16 (−0.03) ± 0.03	−0.03 (−0.24) ± 0.02	3.04 (3.22) ± 0.02
0.0025	0.0025	0.5000	0.63 (0.65) ± 0.01	−0.12 (−0.10) ± 0.10	−0.23 (−0.41) ± 0.07	2.97 (3.13) ± 0.01
0.0025	0.0010	0.7140	0.640 (0.64) ± 0.007	−0.080 (−0.10) ± 0.010	−0.106 (−0.18) ± 0.075	3.098 (3.08) ± 0.010
0.0070	0.0010	0.8750	0.650 (0.64) ± 0.020	−0.073 (−0.14) ± 0.002	−0.100 (−0.10) ± 0.045	2.701 (2.77) ± 0.030

[a] C_1 and C_2 in units of mol·dm^{-3}.

[b] $D_{ik} \pm S_D$ in units of 10^{-9} m^2 s^{-1}. S_D represents the respective standard deviations.

[c] Predicted D_{ik} values in parenthesis.

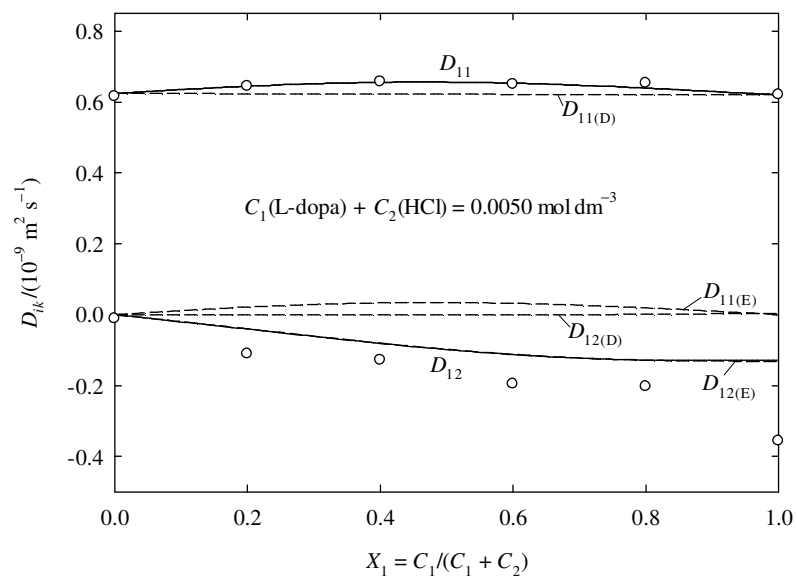**Table 3[a]   Species diffusion coefficients for (L-dopa + HCl) solutions at 25 ºC**

Species	D_s / 10^{-9} $m^2 \cdot s^{-1}$
H+	9.33[a]
Cl^-	2.03[a]
L-dopa	0.62[b]
L-dopa H^+	0.62[c]

[a]The diffusion coefficients of these species are evaluated from limiting ionic conductivities by Robinson and Stokes [18].
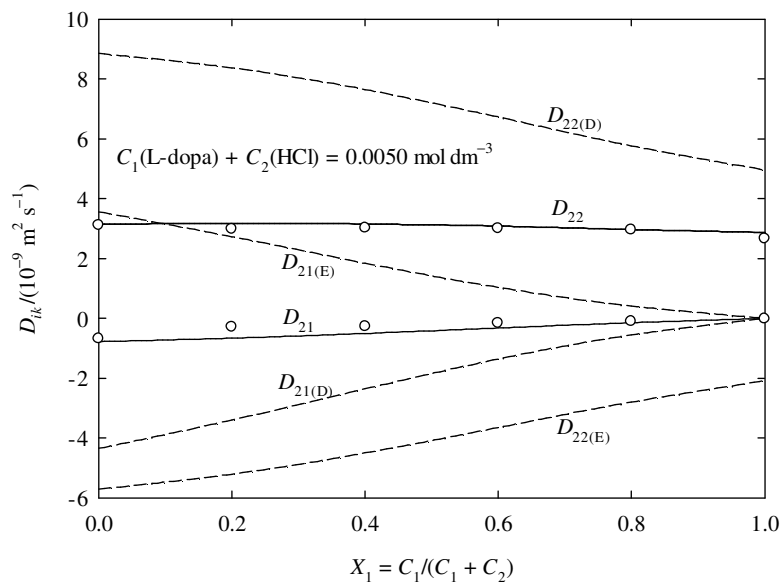
[b]We consider, as an approximation, $D_S = D_{11}$ ($X_1 = 1$) for $C_1 = 0.0050$ M.

[c]We consider, as an approximation, $D_S = D_{11}$ ($X_1 = 0$).

Figure 1. Ternary mutual diffusion coefficients of aqueous {L-dopa (1) + HCl (2)} solutions containing 0.0050 mol·dm^{-3} total solute. Measured D_{11} and D_{12} values: O. The solid and dashed curves are D_{ik} values predicted by Eqs. (8-10).

15

Figure 2. Ternary mutual diffusion coefficients of aqueous {L-dopa (1) + HCl (2)} solutions containing 0.0050 mol·dm^{-3} total solute. Measured D_{21} and D_{22} values: O. The solid and dashed curves are D_{ik} values predicted by Eqs. (8-10).

16

TABLE 1 Provenance and mass fraction purity of the compounds studied

Compound	CAS number	Supplier	Mass fraction purity	Water content mass fraction
L-Dopa	59-92-7	Fluka	≥ 0.99	-
HCl	7647-01-0	Sociedade Portuense de Drogas	-	0.335

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Table 2 Ternary mutual diffusion coefficients of aqueous {L-Dopa (1) + HCl (2)} solutions at 25 °C [a,b,c]

$C_1/$ mol·dm^{-3}	$C_2/$ mol·dm^{-3}	X_1	$D_{11}/$ 10^{-9} m^2·s^{-1}	D_{12} 10^{-9} m^2·s^{-1}	$D_{21}/$ 10^{-9} m^2·s^{-1}	$D_{22}/$ 10^{-9} m^2·s^{-1}
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0.0050	0.0000	1.0000	0.62 (0.62) ± 0.01	−0.36 (−0.13) ± 0.05	−0.02 (0.00) ± 0.01	2.67 (2.88) ± 0.03
0.0000	0.1000	0.0000	0.64 (0.62) ± 0.01	−0.01 (0.00) ± 0.01	−1.60 (−1.48) ± 0.55	2.90(2.77) ± 0.02
0.0005	0.1000	0.0050	0.61 (0.62) ± 0.02	−0.01 (0.00) ± 0.003	−1.23 (−1.49) ± 0.10	2.94 (2.78) ± 0.004
0.0005	0.0200	0.0240	0.62 (0.63) ± 0.005	−0.02 (−0.01) ± 0.004	−0.10 (−1.25) ± 0.01	2.75 (3.02) ± 0.04
0.0025	0.1000	0.0240	0.63 (0.63) ± 0.001	−0.02 (−0.01) ± 0.003	−0.81 (−1.50) ± 0.12	2.94 (2.80) ± 0.01
0.0005	0.0100	0.048	0.64 (0.63) ± 0.01	−0.10 (−0.01) ± 0.004	−0.77 (−1.04) ± 0.07	2.98 (3.10) ± 0.01
0.0025	0.0200	0.1110	0.58 (0.66) ± 0.002	−0.09 (−0.04) ± 0.01	−0.78 (−1.29) ± 0.07	3.03 (3.08) ± 0.01
0.0025	0.0100	0.2000	0.64 (0.67) ± 0.002	−0.05 (−0.06) ± 0.01	−0.67(−1.04) ± 0.07	3.02 (3.16) ± 0.02
0.0070	0.0200	0.2590	0.68 (0.73) ± 0.001	−0.06 (−0.12) ± 0.01	−0.20 (−1.33) ± 0.03	3.08 (3.19) ± 0.02
0.0005	0.0010	0.3330	0.66 (0.63) ± 0.01	−0.16 (−0.03) ± 0.03	−0.03 (−0.24) ± 0.02	3.04 (3.22) ± 0.02

18

0.0025	0.0025	0.5000	0.63 (0.65) ± 0.01	−0.12 (−0.10) ± 0.10	−0.23 (−0.41) ± 0.07	2.97 (3.13) ± 0.01
0.0025	0.0010	0.7140	0.640 (0.64) ± 0.007	−0.080 (−0.10) ± 0.010	−0.106 (−0.18) ± 0.075	3.098 (3.08) ± 0.010
0.0070	0.0010	0.8750	0.650 (0.64) ± 0.020	−0.073 (−0.14) ± 0.002	−0.100 (−0.10) ± 0.045	2.701 (2.77) ± 0.030

[a]C_1 and C_2 in units of mol dm^{-3}.

[b]$D_{ik} \pm S_D$ in units of 10^{-9} m^2 s^{-1}. S_D represents the respective standard deviations.
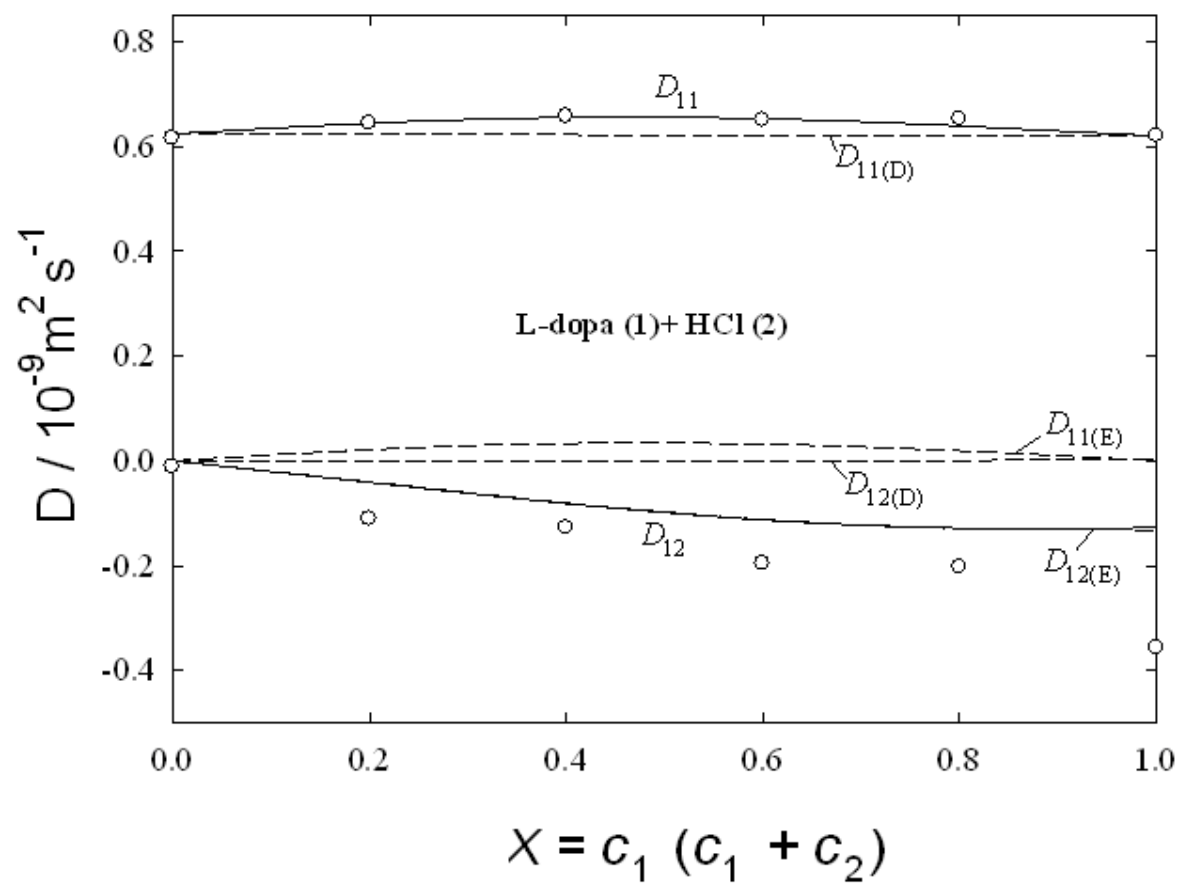
[c]Predicted D_{ik} values in parenthesis.

Table 3[a] Species diffusion coefficients for (L-dopa + HCl) solutions at 25 ºC

Species	D_s / 10^{-9} $m^2 \cdot s^{-1}$
H+	9.33[a]
Cl⁻	2.03[a]
L-dopa	0.62[b]
L-dopa H⁺	0.62[c]

[a]The diffusion coefficients of these species are evaluated from limiting ionic conductivities

by Robinson and Stokes [18].

[b] We consider, as an approximation, $D_S = D_{11}$ ($X_1 = 1$) for C_1=0.0050 M.

[c]We consider, as an approximation, $D_S = D_{11}$ ($X_1 = 0$).

20

Research Highlights

Ternary mutual diffusion coefficients of aqueous L-dopa plus hydrochloric acid at 25 ºC

Diffusion of L-dopa driven by HCl gradients.

Coupled diffusion of L-dopa and HCl