



# Diffusion of levodopa in aqueous solutions of hydrochloric acid at 25 °C



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## 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 °C and HCl concentrations up to 0.100 mol · dm<sup>-3</sup>. 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–Planck equations are used to analyze the proton coupled diffusion of L-dopa and HCl in terms of the binding of H<sup>+</sup> ions to L-dopa and ion migration in the electric field generated by L-dopa and HCl concentration gradients.

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## 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 °C 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 °C. 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<sup>+</sup>-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  $\geq 99\%$ ) and HCl (Sociedade Portuguesa 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<sup>3</sup> of solution into a laminar carrier stream of slightly different composition. A flow rate of 0.17 cm<sup>3</sup> · min<sup>-1</sup> was maintained by a metering pump (Gilson model Minipuls 3) to give retention times of about 1.1 · 10<sup>4</sup> s. The dispersion tube length {32.799 (±0.001)} m and the injection valve were kept at 25.00 °C (± 0.01 °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

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

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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 Portuguesa de Drogas		0.335

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

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

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

$J_1$  and  $J_2$  are the molar fluxes of L-dopa (1) and HCl (2) driven by the concentration gradients  $\nabla C_1$  and  $\nabla C_2$  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  $i$ .

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

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

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].

TABLE 2

Ternary mutual diffusion coefficients of aqueous {L-Dopa (1) + HCl (2)} solutions at 25 °C.<sup>a,b,c</sup>

$C_1/\text{mol} \cdot \text{dm}^{-3}$	$C_2/\text{mol} \cdot \text{dm}^{-3}$	$X_1$	$D_{11}/10^{-9} \text{m}^2 \cdot \text{s}^{-1}$	$D_{12} \cdot 10^{-9} \text{m}^2 \cdot \text{s}^{-1}$	$D_{21}/10^{-9} \text{m}^2 \cdot \text{s}^{-1}$	$D_{22}/10^{-9} \text{m}^2 \cdot \text{s}^{-1}$
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
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

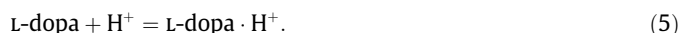
<sup>a</sup>  $C_1$  and  $C_2$  in units of  $\text{mol} \cdot \text{dm}^{-3}$ .<sup>b</sup>  $D_{ik} \pm S_D$  in units of  $10^{-9} \text{m}^2 \cdot \text{s}^{-1}$ .  $S_D$  represents the respective standard deviations.<sup>c</sup> Predicted  $D_{ik}$  values in parenthesis.

### 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  $\pm 0.02 \times 10^{-9} \text{m}^2 \cdot \text{s}^{-1}$ . The cross-coefficients were reproducible within about  $\pm 0.05 \times 10^{-9} \text{m}^2 \cdot \text{s}^{-1}$ .

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-transport 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  $\text{H}^+$  ions and L-dopa molecules associate in aqueous solutions



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

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

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

for the fluxes of the diffusing species (L-dopa molecules and the L-dopa  $\text{H}^+$ ,  $\text{H}^+$ , and  $\text{Cl}^-$  ions). In the notation used here, the stoichiometric coefficient  $v_{is}$  gives the number of moles of solute

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