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Coupled mutual diffusion in aqueous paracetamol + sodium hydroxide solutions

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ABSTRACT

Ternary mutual diffusion coefficients (D_{ik}) measured by the Taylor dispersion method are reported for aqueous paracetamol + NaOH solutions at 25.00 °C and concentrations up to 0.050 mol dm⁻³. The coupled diffusion of paracetamol (**1**) and NaOH (**2**) is significant, as indicated by the large negative crossdiffusion coefficients. In sodium hydroxide solutions, paracetamol, a weak acid, is partially converted to its sodium salt. To help interpret the results, the measured D_{ik} coefficients are compared with predictions based on Nernst and Nernst-Planck equations for mixed electrolyte solutions. The analysis shows that the diffusion of the paracetamol and sodium hydroxide components is strongly coupled by the electric field (diffusion potential) generated by the ionic concentration gradients.

Keywords: Paracetamol, NaOH, salts: diffusion, transport properties, solutions

1. Introduction

Paracetamol (PAR, N-(4-hydroxyphenyl) acetamide) belongs to the class of non-steroidal anti-inflammatory drugs due to its remarkable analgesic, anti-inflammatory and antipyretic action [**1,2**]. Besides the adverse effects on the human health provoked by a long-term consumption or overdose [**3**], paracetamol is considered an emerging pollutant with a high impact in the contamination of surface and waste waters [**4**]. This may result in hazardous consequences in the biota and in the food chain. Such relevant environmental effects have led to the development of sensors [**5**] and techniques for removal of paracetamol from surface and wastewaters. Among them, we can cite advanced

oxidation processes [6], nanofiltration [7] and the adsorption onto activated carbon [8]. For all these processes the mass transport by diffusion plays an important role.

Despite the broad range of applications, the bioavailability still remains a drawback in the paracetamol administration. This results from combination of several processes occurring in the gastro-intestinal system and generating significant losses and delays until the drug dose reaches the systemic circulation [9]. The better knowledge of these systems is, indeed, of major importance for the reliable and safe delivery of precise dosages of this drug, within the therapeutic range as well as to avoid under and over-dosage or to prevent gastric toxicity [9]. Aiming such improvement, several new ways to delivery paracetamol have been developed in recent years [10-12]. Although much of those studies report diffusion coefficients for the release of paracetamol from solid formulation matrices [13], the knowledge of the paracetamol diffusion in aqueous solution, corresponding to the limit diffusion coefficient for the release kinetics, is scarce. Blokhina et al. [14] have reported self-diffusion coefficients of paracetamol in deuterated water, at 25.00 °C, as equal to $7.12 (\pm 0.02) \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$, which after correction with viscosity [15] leads to a selfdiffusion coefficient in water as equal to $8.75 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$. Some of us [16] have reported binary mutual diffusion coefficients of paracetamol, at 25.00 °C and natural pH (ca. 5.9), by using by using the Taylor dispersion technique [17,18]. The mutual limiting diffusion coefficient for paracetamol is equal to $6.64 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ [16], in good agreement with that obtained by NMR selfdiffusion. However, no information exists on the diffusion behaviour in basic conditions, which mimetizes the pH of the intestine and colon that can reach a value of 8.5 [19]. This is relevant once the paracetamol can be considered a weak acid with a pKa equal to 9.78 [20], can react with hydroxide ions, the OH⁻ ions, producing water and the paracetamol anion A⁻. In fact, in the presence of excess of hydroxide ions and from the high value for this equilibrium constant $K = 1.66 \times 10^4$, almost all of the paracetamol molecules (HA) can be converted to the sodium paracetamol salt (NaA). In this case, the bioavailability of paracetamol tends to decrease in an alkaline media; the knowledge of the behaviour of the paracetamol conjugated base in terms of mass transport by diffusion is the main motivation of this work. Thus, we propose a comprehensive experimental and theoretical study of the diffusion of paracetamol in combination with sodium hydroxide at low concentrations.

In previous work [16], paracetamol transport was studied by using the Taylor dispersion technique [17,18] to measure the mutual diffusion of paracetamol in water. The diffusion in aqueous paracetamol solutions is described by Fick's law [18]

$$J(\text{PAR}) = -D\nabla C \quad (1)$$

a single binary mutual diffusion coefficient, D. J and ∇C are the molar flux and the gradient in the concentration of paracetamol.

Sodium hydroxide effects on paracetamol diffusion are investigated by using Taylor dispersion to measure the ternary mutual diffusion coefficients (D_{ik}) of aqueous paracetamol(C_1) + NaOH (C_2) solutions by using coupled Fick equations (Eqs. (2) and (3)) [21,22].

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

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

J_1 and J_2 are the molar fluxes of paracetamol (1) and NaOH (2) driven by the concentration gradients ∇C_1 and ∇C_2 of each solute 1 and 2, respectively. Main diffusion coefficients D_{11} and D_{22} give the flux of each solute driven by its own concentration gradient. 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 . On the other hand, a negative D_{ik} coefficient indicates counter-current coupled transport of solute i from regions of lower to higher concentration of solute k .

2. Experimental

2.1. Materials

Paracetamol and sodium hydroxide were supplied from Sigma-Aldrich and were used as received. The solutions for the diffusion measurements were prepared using Millipore-Q water (specific resistance = $1.82 \times 10^5 \Omega \text{ m}$, at 25.00 °C). All solutions were freshly prepared at 25.00 °C before each experiment.

2.2. Binary and ternary diffusion measurements

Binary and ternary mutual diffusion coefficients were measured by the Taylor dispersion technique [17]. At the start of each run, a 6-port Teflon injection valve (Rheodyne, model 5020) was used to introduce 0.063 cm³ of solution into a laminar carrier stream of slightly different composition. A flow rate of 0.23 cm³ 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 3048.0 (± 0.1) cm, and internal radius $0.03220 \pm (0.00003)$ cm and the injection valve were kept at 25.00 (± 0.01) oC in an air thermostat. A differential refractometer (Waters model 2410) placed at the outlet of the dispersion tube monitors the dispersion profile of the injected samples. Detector voltages, $V(t)$, were measured at 5 s intervals with a digital voltmeter (Agilent 34,401 A).

Samples of solution containing paracetamol (or NaOH) at concentration $\bar{C} + \Delta C$ were injected into laminar carrier streams of composition. Binary diffusion coefficients (D) were evaluated by fitting the dispersion equation (Eq. (4)) [17,21,22]

$$V(t) = V_0 + V_1 t + V_{\max} \sqrt{(t_R/t)} e^{[-12D(t-t_R)^2/(r^2 t)]} \quad (4)$$

to the measured detector voltages. V_0 is the baseline voltage, V_1 the baseline slope, V_{\max} the peak height, and t_R the mean sample retention time.

Ternary dispersion profiles were prepared by injecting paracetamol(1) + sodium hydroxide(2) solution samples of composition $\bar{C}_1 + \Delta C_1$, $\bar{C}_2 + \Delta C_2$ into carrier streams of composition \bar{C}_1 , \bar{C}_2 . Coupled diffusion produces ternary dispersion profiles [21,22] (Eqs. (5) and (6))

$$V = \bar{V} + V_1 + V_{\max} \sqrt{\frac{t_R}{t}} \times \frac{(a + b\alpha_1)\sqrt{D_1}e^{-12D_1(t-t_R)^2/r^2t} + (1 - a - b\alpha_1)\sqrt{D_2}e^{-12D_2(t-t_R)^2/r^2t}}{(a + b\alpha_1)\sqrt{D_1} + (1 - a - b\alpha_1)\sqrt{D_2}} \quad (5)$$

$$\alpha_1 = \frac{R_1 \Delta C_1}{R_1 \Delta C_1 + R_2 \Delta C_2} \quad (6)$$

D_1 and D_2 are the eigenvalues of the matrix of ternary D_{ik} coefficients (Eqs. **(7)** and **(8)**) and α_1 is the fraction of the initial refractive index difference due to paracetamol. R_1 and R_2 are the detector sensitivities for paracetamol(1) and NaOH(2): $R_1 = \delta V / \delta C_1$ and $R_2 = \delta V / \delta C_2$.

$$D_1 = \left\{ D_{11} + D_{22} + (D_{11} - D_{22}) \sqrt{1 + \left[4D_{12}D_{21} / (D_{11} - D_{22})^2 \right]} \right\} / 2 \quad (7)$$

$$D_2 = \left\{ D_{11} + D_{22} - (D_{11} - D_{22}) \sqrt{1 + \left[4D_{12}D_{21} / (D_{11} - D_{22})^2 \right]} \right\} / 2 \quad (8)$$

Eq. **(5)** was fitted to pairs of ternary profiles measured for $\alpha_1 \approx 0$ (initial paracetamol concentration difference) and $\alpha_1 \approx 1$ (initial NaOH concentration difference), being more complicated than Eq. **(4)** for binary profiles due to the effects of coupled diffusion. Ternary mutual diffusion coefficients were calculated from the D_1 , D_2 , a , b fitting parameters and the relative detector sensitivity R_2/R_1 using

$$D_{11} = D_1 + \frac{a(1-a-b)}{b}(D_1 - D_2) \quad (9)$$

$$D_{12} = \frac{R_2}{R_1} + \frac{a(1-a)}{b}(D_1 - D_2) \quad (10)$$

$$D_{21} = \frac{R_1}{R_2} + \frac{(a+b)(1-a-b)}{b}(D_2 - D_1) \quad (11)$$

$$D_{22} = D_2 + \frac{a(1-a-b)}{b}(D_2 - D_1) \quad (12)$$

The a and b parameters in these Eqs. (9)-(12) are given by

$$a = \frac{D_{11} - D_1 + (R_1/R_2)D_{12}}{(D_2 - D_1)} \quad (13)$$

$$b = \frac{D_{22} - D_{11} + (R_1/R_2)D_{12} - (R_2/R_1)D_{21}}{(D_2 - D_1)} \quad (14)$$

3. Results

Binary aqueous solutions of paracetamol and NaOH were used to test the reproducibility of the diffusion measurements. These systems were chosen because their diffusion coefficients are accurately known from previous studies [16].

Table 1 gives the concentrations of the test solutions that were used, the mean D values at 25.00 °C determined from four to six replicate dispersion profiles, and their relative deviations from the literature D values tabulated. Comparison of the results suggests an acceptable uncertainty of 1-3% for the binary Taylor D values reported here [16,23].

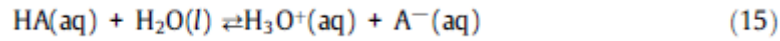
Ternary dispersion profiles were measured for paracetamol (C_1 -) + NaOH (C_2) carrier solutions containing $C_1 + C_2 = 0.0100 \text{ mol dm}^{-3}$ and $C_1 + C_2 = 0.0500 \text{ mol dm}^{-3}$ total solute at paracetamol solute fractions [$X_1 = C_1/(C_1 + C_2)$] from 0.020 to 1.00, at least six times at each carrier-stream composition. **Table 2** gives the average D_{ik} coefficients determined for each carrier-solution composition by fitting Eq. (5) to four or five replicate pairs of dispersion profiles. Main diffusion coefficients D_{11} and D_{22} were generally reproducible to within ($\pm 0.015 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$). Cross-diffusion coefficients D_{12} and D_{21} describing the coupled diffusion of paracetamol and NaOH were reproducible to within about ($\pm 0.05 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$). Coupled diffusion in the solutions is significant. For example, values of the ratio D_{12}/D_{22} indicate that a mole of diffusing NaOH counter-transport up to 0.24 mol of paracetamol, whereas values of D_{21}/D_{11} show that a mole of diffusing paracetamol counter-transport up to 0.4 mol of NaOH. D_{11} increases with the solute fraction of paracetamol. The D_{22} values are considerably larger than the D_{11} values and increase dramatically with the solute fraction of NaOH. Also, cross-coefficient D_{12} becomes very large and negative with increasing solute fraction of paracetamol. In the limit $X_1 \rightarrow 0$, D_{12} is zero because NaOH concentration gradients cannot drive coupled flows of paracetamol in solutions that do not contain paracetamol. Similarly, D_{21} is zero in the limit $X_1 \rightarrow 1$. In this case, D_{22} is the tracer diffusion coefficient of NaOH in supporting paracetamol solutions, and D_{11} is the binary mutual diffusion coefficient of aqueous paracetamol.

3.1. Interpretation of the diffusion coefficients

3.1.1. Limiting diffusion coefficients from Nernst equations

Although accurate prediction of D_{ik} coefficients is not possible, helpful information can be obtained by using Nernst equations to estimate D°_{ik} values at infinite dilution for comparison with measured D_{ik} coefficients. In this limit, the solutions become ideal and the thermodynamic factors are unity. We present Nernst equations [24] for the limiting diffusion coefficients of aqueous paracetamol (C_1) + NaOH(C_2) solutions for three different relative concentrations of paracetamol and NaOH: 1) molar excess of paracetamol ($C_1 > C_2$); 2) molar excess of NaOH ($C_2 > C_1$); and 3) equimolar paracetamol and NaOH ($C_1 = C_2$).

Aqueous paracetamol (abbreviated HA) is a weak acid ($pK_a = 9.78$) [25],



$$K_a = \frac{C_{\text{H}^+} C_{\text{A}^-}}{C_{\text{HA}}} = 10^{-9.78} \quad (16)$$

Table 1 Comparison of the mean diffusion coefficients, D, at 25.00 OC measured by Taylor dispersion for 0.0100 mol dm⁻³ NaOH and paracetamol solutions and the previous literature values [16,23].

Solution	ΔC^a /mol dm ⁻³	$D / 10^{-9} \text{ m}^2 \text{ s}^{-1}$	$D_{\text{Lit}} / 10^{-9} \text{ m}^2 \text{ s}^{-1}$	$\Delta D/D \%$
NaOH	0.010	2.019	2.030 ^{b)}	-0.5
paracetamol	0.010	0.660	0.650 ^{c)}	1.5

a) ΔC represents the difference between the flow and injection solutions, respectively.

b) D_{Lit} represents the literature diffusion coefficients values [23].

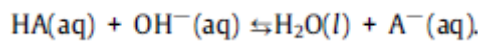
c) D_{Lit} represents the literature diffusion coefficients values [16]. $\Delta D/D$ represents the relative deviations between our data and the literature diffusion coefficients values [16,23].

Table 2 Ternary mutual diffusion coefficients of aqueous paracetamol(C_1) + NaOH(C_2) solutions at 25.00 oC (predicted D_{ik} values from Nernst-Planck Eqs. (59)-(67) in parentheses).^a

C_1	C_2	X_1	D_{11}	D_{12}	D_{21}	D_{22}
0.0000	0.0100	0.000	0.700 (0.690)	-0.080 (0.000)	-0.805 (-0.920)	1.960 (2.130)
0.0025	0.0075	0.250	1.005 (0.891)	-0.160 (-0.174)	-1.890 (-1.179)	2.166 (2.359)
0.0045	0.0055	0.450	1.500 (1.353)	-0.748 (-0.582)	-1.986 (-1.646)	3.088 (2.779)
0.0055	0.0045	0.550	0.775 (0.883)	0.0100 (-0.059)	-0.013 (-0.391)	1.090 (1.453)
0.0100	0.0000	1.000	0.757 (0.690)	0.205 (0.206)	-0.002 (0.000)	0.910 (0.933)
0.0000	0.0500	0.000	0.690 (0.690)	0.036 (0.000)	-0.668 (-0.925)	2.043 (2.130)
0.001	0.0490	0.020	0.715 (0.700)	-0.136 (-0.008)	-0.884 (-0.938)	2.088 (2.141)
0.0490	0.001	0.980	0.763 (0.690)	0.100 (0.217)	-0.055 (0.000)	0.955 (0.915)
0.0500	0.000	1.000	0.600 (0.690)	0.050 (0.217)	0.023 (0.000)	0.998 (0.914)

^a concentrations in units of mol dm⁻³, diffusion coefficients in units of 10⁻⁹ m² s⁻¹.

If sodium hydroxide is added to paracetamol solutions, the OH⁻ ions react with the paracetamol molecules, producing water and the paracetamol anion:



The equilibrium constant for this neutralization reaction is

$$K = \frac{K_a}{K_w} = \frac{C_{\text{A}^-}}{C_{\text{HACOH}^-}} = 10^{-9.78+14.0} \quad (17)$$

At 25 °C, the value of equilibrium constant K is 1.66 x 10⁴. Fick's equations, however, give the fluxes of the total (reacted plus unreacted) paracetamol(1) and sodium hydroxide(2) solution components.

$$J_1(\text{total paracetamol}) = -D_{11}\nabla C_1 - D_{12}\nabla C_2 \quad (18)$$

$$J_1(\text{total NaOH}) = -D_{21}\nabla C_1 - D_{22}\nabla C_2 \quad (19)$$

To interpret the measured D_{ik} coefficients, it is necessary to relate the fluxes of the components (total paracetamol and total NaOH) to the fluxes of the actual diffusing species (HA, A⁻, Na⁺ and OH⁻).

Table 3 gives estimates of the diffusion coefficients of the solution species. D_{Na^+} and D_{OH^-} were evaluated from limiting ionic conductivities [18]. For molecular paracetamol, we will use $D_{HA} = 0.69 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$, the binary diffusion coefficient of paracetamol in solution at infinite dilution, measured in this work, and adopt the same diffusion coefficient value for the structurally-similar paracetamol anion.

The diffusion coefficient of OH⁻ ions is significantly larger than the diffusion coefficients of the other species due to anomalous transport by proton-hopping in aqueous solutions.

3.11.1. Strong-acid approximation for paracetamol (1) + NaOH (2) diffusion.

Case I: Molar Excess of Paracetamol ($C_1 > C_2$)

If paracetamol is present in excess, then almost all of the OH⁻ ions from NaOH are consumed by the HA + OH⁻ ⇌ H₂O + A⁻ neutralization reaction. At these compositions, it is physically more reasonable to describe diffusion in terms of HA + NaA components instead of HA + NaOH components.

For the dilute solutions considered here, Nernst's equation [18]

$$D_{Na^+A^-} = \frac{2D_{Na^+}D_{A^-}}{D_{Na^+} + D_{A^-}} \quad (20)$$

can be used to estimate the main diffusion coefficient of the sodium paracetamol salt. Also, it is a good approximation to assume uncharged HA molecules diffuse independently of the NaA salt.

Fick's equations for the fluxes of molecular paracetamol (HA) and paracetamol salt (Na⁺ + A⁻ ions) components can therefore be written as

$$\begin{aligned} J'_1(\text{unreacted paracetamol}) &= -D'_{11}\nabla C'_1 - D'_{12}\nabla C'_2 \\ &= D_{HA}\nabla C'_1 \end{aligned} \quad (21)$$

$$J'_2(\text{NaA}) = -D'_{21}\nabla C'_1 - D'_{22}\nabla C'_2 = -D_{Na^+A^-}\nabla C'_2 \quad (22)$$

Table 3 Species diffusion coefficients, D_s , at 25.00 °C.

species	$D_s / (10^{-9} \text{ m}^2 \text{ s}^{-1})$
molecular paracetamol (HA)	0.69
paracetamol anion (A^-)	0.69
Na^+	1.334
OH^-	5.280

which gives

$$D'_{11} = D_{HA} \quad (23)$$

$$D'_{12} = D'_{21} = 0 \quad (24)$$

$$D'_{22} = D_{Na+A^-} \quad (25)$$

From stoichiometry, the total paracetamol flux is the sum of the fluxes of the reacted and unreacted paracetamol.

$$J_1(\text{total paracetamol}) = J'_1(HA) + J'_2(NaA) \quad (26)$$

and the flux of total sodium hydroxide flux equals the flux of the sodium paracetamol salt.

$$J_2(\text{total NaOH}) = J'_2(NaA) \quad (27)$$

Substituting Eqs. (21) and (22) into Eqs. (28) and (29) and using

$$C_1(\text{total paracetamol}) = C'_1(HA) + C'_2(NaA) \quad (28)$$

$$C_2(\text{total NaOH}) = C'_2(NaA) \quad (29)$$

shows the ternary D_{ik} coefficients of the total paracetamol and total sodium hydroxide components are related to the D_{ik}' coefficients of unreacted paracetamol and sodium paracetamol as follows

$$D_{11} = D'_{11} + D'_{21} = D_{HA} \quad (30)$$

$$D_{12} = -D'_{11} + D'_{12} - D'_{21} + D'_{22} = D_{Na+A^-} - D_{HA} \quad (31)$$

$$D_{21} = D'_{21} = 0 \quad (32)$$

$$D_{22} = -D'_{21} + D'_{22} = D_{Na^+A^-} = 2D_{Na^+}D_{A^-} / (D_{Na^+} + D_{A^-}) \quad (33)$$

Eqs. (30) to (33) are useful because they relate the ternary D_{ik} coefficients of the paracetamol and sodium hydroxide components to the diffusion coefficients of the actual diffusing species, in this case HA molecules and the Na^+ and A^- ions.

If the concentration of the sodium hydroxide component (C_1) is increased, the neutralization reaction $HA + OH^- \rightleftharpoons H_2O + A^-$ increases the concentration of paracetamol anions (A^-) while reducing the concentration of paracetamol molecules (HA). Paracetamol anions therefore diffuse “down” the sodium hydroxide concentration gradient, together with Na^+ anions to maintain electroneutrality. Simultaneously, molecular paracetamol diffuses “up” the sodium hydroxide gradient to replace the HA molecules lost by the neutralization reaction. As a result, cross-coefficient D_{12} for the coupled flow of paracetamol caused by the sodium hydroxide concentration gradient is $D_{Na^+A^-} - D_{HA}$.

In solutions containing excess paracetamol ($C_1 > C_2$), a change in the concentration of molecular paracetamol produces negligible changes in the concentrations of the Na^+ and A^- ions, and crosscoefficient D_{21} for the coupled flow of sodium hydroxide is zero.

For a strong mixed electrolyte, such as aqueous $NaCl(1) + NaOH(2)$ solutions, the main diffusion coefficient D_{22} for the NaOH component is the tracer diffusion coefficient of the OH^- ion in the limit $C_2 \rightarrow 0$. For paracetamol(1) + NaOH(2) solutions, however, D_{22} is equals the diffusion coefficient $D_{Na^+DA^-}$ of the sodium paracetamol salt in the limit $C_2 \rightarrow 0$.

Case II: Molar excess of sodium hydroxide ($C_1 < C_2$)

In solutions with a molar excess of sodium hydroxide, almost all of the paracetamol molecules (HA) are converted to the sodium paracetamol salt (NaA). At these compositions, diffusion is conveniently described by Fick equations

$$J'_1(NaA) = -D''_{11} \nabla C''_1 - D''_{12} \nabla C''_2 \quad (34)$$

$$J'_2(NaOH) = -D''_{21} \nabla C''_1 - D''_{22} \nabla C''_2 \quad (35)$$

for the fluxes of sodium paracetamol and sodium hydroxide, a ternary mixed electrolyte.

Ternary D_{ik} coefficients for the $NaA(C_1)$ and $NaOH(C_2)$ electrolyte components can be estimated by using the limiting Nernst equations [24]

$$D''_{11} = D_{A^-} + t_{A^-}(D_{Na^+} - D_{A^-}) \quad (36)$$

$$D''_{12} = t_{A^-}(D_{Na^+} - D_{OH^-}) \quad (37)$$

$$D''_{21} = t_{OH^-}(D_{Na^+} - D_{A^-}) \quad (38)$$

$$D''_{22} = D_{OH^-} + t_{OH^-} (D_{Na^+} - D_{OH^-}) \quad (39)$$

The transference numbers

$$t_{A^-} = \frac{c_{A^-} D_{A^-}}{c_{A^-} D_{A^-} + c_{OH^-} D_{OH^-} + c_{Na^+} D_{Na^+}} \quad (40)$$

$$t_{OH^-} = \frac{c_{OH^-} D_{OH^-}}{c_{A^-} D_{A^-} + c_{OH^-} D_{OH^-} + c_{Na^+} D_{Na^+}} \quad (41)$$

give the fraction of the electric current carried by the A^- and OH^- ions in an applied electric field.

A sodium hydroxide concentration gradient generates an electric field which slows down the more mobile OH^- ions and speeds up the less-mobile ions Na^+ ions to maintain electroneutrality. The electric field has the additional effect of driving the migration of paracetamol anions “up” the sodium hydroxide concentration gradient, counter-current to the flux of NaOH, leading to negative values of cross-coefficient D''_{12} . The electrostatic mechanism for the coupled diffusion of paracetamol as the sodium paracetamol salt is emphasized by Eq (37) which shows D''_{12} is proportional to the transference number of the paracetamol anion. D''_{12} is also proportional to $D_{Na^+} - D_{OH^-}$, which in turn is proportional to the electric field generated by sodium hydroxide concentration gradients.

Similarly, cross-coefficient D''_{21} for the NaOH coupled flow is proportional to t_{OH^-} and to $D_{Na^+} - D_{A^-}$. Because the diffusion coefficient of Na^+ ion is larger than that of the bulkier paracetamol anion, the predicted D''_{21} values are positive.

From stoichiometry, the flux of the total paracetamol component equals the flux of the sodium paracetamol salt

$$J_1(\text{total paracetamol}) = J_1''(\text{NaA}) \quad (42)$$

and the flux of total (reacted plus unreacted) sodium hydroxide is

$$J_1(\text{total NaOH}) = J_1''(\text{NaA}) + J_2''(\text{NaOH}) \quad (43)$$

Substituting Eqs. (34) and (35) into Eqs. (28) and (29) and using

$$C_1(\text{total paracetamol}) = C_1''(\text{HA}) \quad (44)$$

$$C_2(\text{total NaOH}) = C_1''(\text{NaA}) + C_2''(\text{NaOH}) \quad (45)$$

gives

$$D_{11} = D''_{11} - D''_{12} = D_{A^-} + t_{A^-} (D_{OH^-} - D_{A^-}) \quad (46)$$

$$D_{12} = D''_{12} = t_{A^-} (D_{Na^+} - D_{OH^-}) \quad (47)$$

$$D_{21} = D_{11}'' - D_{12}'' + D_{21}'' - D_{22}'' = t_{A^-}(D_{A^-} - D_{OH^-}) \quad (48)$$

$$D_{22} = D_{12}'' + D_{22}'' = D_{OH^-} + (1 - t_{A^-})(D_{Na^+} - D_{OH^-}) \quad (49)$$

Eqs. (46) to (49) can be used to calculate the ternary D_{ik} coefficients of the total paracetamol and total sodium hydroxide components in terms of the diffusion coefficients of the diffusing solute species, in this case Na^+ , A^- and OH^- ions. Cross-coefficients D_{12} and D_{21} are proportional to $(D_{Na^+} - D_{OH^-})$ and $(D_{A^-} - D_{OH^-})$, respectively, which in turn are proportional to the electric field produced by paracetamol and sodium hydroxide concentration gradients. Because the diffusion coefficient of the OH^- ions is significantly larger than that of the Na^+ and A^- ions, large negative values of D_{12} and D_{21} are predicted.

Case III: Equimolar paracetamol and sodium hydroxide ($C_1 = C_2$)

Paracetamol and sodium hydroxide react completely in this case and diffuse together as the sodium paracetamol salt. At these compositions, $\nabla C_1 = \nabla C_2$, and Fick's ternary diffusion equations simplify to binary equations for the diffusion of the salt

$$J_1(\text{total paracetamol}) = -D_{11}\nabla C_1 - D_{12}\nabla C_2 = -D_{Na^+A^-}\nabla C_1 \quad (50)$$

$$J_1(\text{total NaOH}) = -D_{21}\nabla C_1 - D_{22}\nabla C_2 = -D_{Na^+A^-}\nabla C_2 \quad (51)$$

and

$$D_{11} + D_{12} = D_{21} + D_{22} = D_{Na^+A^-} \quad (52)$$

The D_{ik} coefficients predicted using the strong-acid approximation are plotted as the dashed curves in **Fig. 1**. There is a sharp break in the predicted D_{ik} values at paracetamol solute fraction 0.500, marking the transition from alkaline $NaA + NaOH$ solutions to acidic $HA + NaA$ solutions.

3.1.2. Nernst-Planck analysis of Paracetamol + NaOH diffusion

Nernst-Planck equations provide a detailed description of diffusion by expressing the flux of each solution species ($s = HA, A^-, Na^+, OH^-$) as the sum

$$J_s = J_{sD} + J_{sE} \quad (53)$$

of the pure-diffusion flux

$$j_{sD} = -D_s\nabla c_s \quad (54)$$

driven by the species concentration gradient ∇c_s and (for charged species) the ion-migration flux

$$j_{sE} = \frac{FE}{RT} z_s D_s c_s \quad (55)$$

driven by the electric field E (diffusion potential gradient)

$$E = \frac{F}{RT} \sum_s \frac{t_s}{z_s} \nabla \ln c_s \quad (56)$$

z_s and c_s are the charge and the concentration of species s . F is the Faraday constant, T the temperature and R the gas constant.

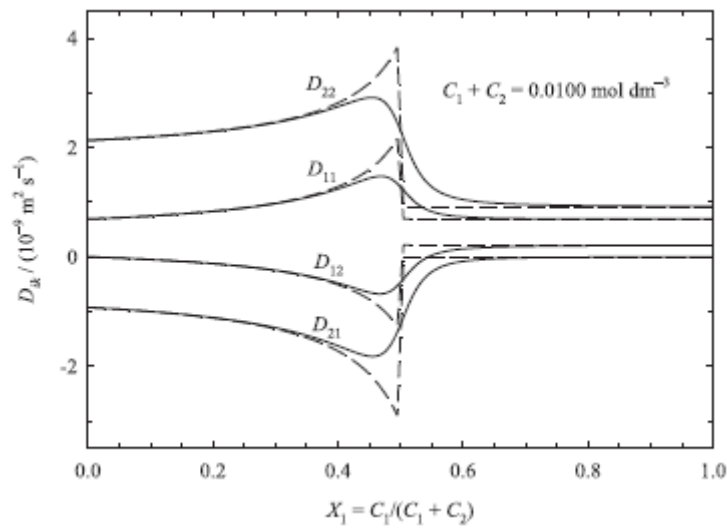


Fig. 1. Ternary diffusion coefficients of aqueous paracetamol(C_1) + NaOH(C_2) at $C_1 + C_2 = 0.0100 \text{ mol dm}^{-3}$ total solute concentration plotted against the paracetamol solute fraction. Dashed curves: the strong-acid approximation. Solid curves: Nernst-Planck calculations.

Combining the Fick equations for the fluxes of the paracetamol and NaOH components with the Nernst-Planck equations for the fluxes of the constituent species

$$J_1(\text{total paracetamol}) = j_{HA} + j_{A^-} \quad (57)$$

$$J_2(\text{total NaOH}) = j_{Na^+} \quad (58)$$

allows each ternary D_{ik} coefficient to be separated into the pure-diffusion contribution D_{ikD} and the electrostatic contribution D_{ikE} from ion migration.

$$D_{ik} = D_{ikD} + D_{ikE} \quad (59)$$

This procedure [26] gives

$$D_{11D} = D_{HA} \frac{\partial c_{HA}}{\partial C_1} + D_{A^-} \frac{\partial c_{A^-}}{\partial C_1} \quad (60)$$

$$D_{12D} = D_{HA} \frac{\partial c_{HA}}{\partial C_2} + D_{A^-} \frac{\partial c_{A^-}}{\partial C_2} = (D_{HA} - D_{A^-}) \frac{\partial c_{HA}}{\partial C_2} \approx 0 \quad (61)$$

$$D_{21D} = D_{Na^+} \frac{\partial c_{Na^+}}{\partial C_1} = 0 \quad (62)$$

$$D_{22D} = D_{Na^+} \frac{\partial c_{Na^+}}{\partial C_2} = D_{Na^+} \quad (63)$$

for the pure-diffusion contributions

The Nernst-Planck analysis suggests that pure-diffusion contributions to the coupled diffusion of paracetamol and NaOH are negligible. D_{21D} , for example, is zero. From stoichiometry, $C_1 = C_{HA} + C_A$ and therefore $\partial C_{HA}/\partial C_2 = \partial C_A/\partial C_2$. Eq (61) shows, as a result, that D_{12D} is proportional to the diffusion coefficient difference $D_{HA} - D_{A^-}$, which is assumed to zero in the present study.

The electrostatic contributions to the Dik coefficients are

$$D_{11E} = -t_{A^-} \left(D_{A^-} \frac{\partial c_{A^-}}{\partial C_1} + D_{OH^-} \frac{\partial c_{OH^-}}{\partial C_1} \right) \quad (64)$$

$$D_{12E} = -t_{Na^+} \left(D_{Na^+} - D_{A^-} \frac{\partial c_{A^-}}{\partial C_1} - D_{OH^-} \frac{\partial c_{OH^-}}{\partial C_1} \right) \quad (65)$$

$$D_{21E} = t_{Na^+} \left(D_{A^-} \frac{\partial c_{A^-}}{\partial C_1} - D_{OH^-} \frac{\partial c_{OH^-}}{\partial C_1} \right) \quad (66)$$

$$D_{22E} = -t_{Na^+} \left(D_{Na^+} - D_{A^-} \frac{\partial c_{A^-}}{\partial C_2} - D_{OH^-} \frac{\partial c_{OH^-}}{\partial C_2} \right) \quad (67)$$

The D_{ik} coefficients predicted by the Nernst-Planck equations are plotted as solid curves in **Fig. 2**. To improve the accuracy of the predictions, the strong-acid approximation was not used. Instead, Eq (17) was solved to calculate the concentrations of the HA, A and OH species.

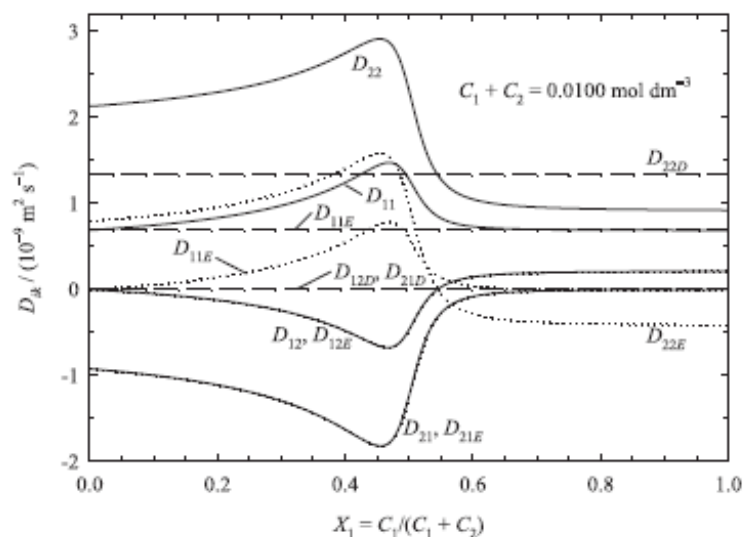


Fig. 2. Pure-diffusion and electrostatic contributions to the ternary diffusion coefficients calculated for aqueous paracetamol(C_1) + NaOH(C_2) solutions at $C_1 + C_2 = 0.0100 \text{ mol dm}^{-3}$ total solute concentration.

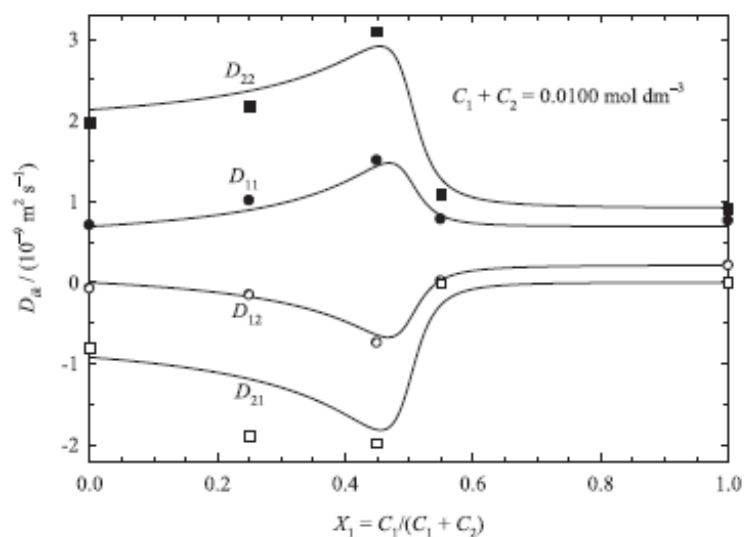


Fig. 3. Ternary diffusion coefficients of aqueous paracetamol (C_1) + NaOH(C_2) at $C_1 + C_2 = 0.0100 \text{ mol dm}^{-3}$ total solute concentration plotted against the paracetamol solute fraction. Measured values: filled circles, D_{11} ; hollow circles, D_{12} , hollow squares, D_{21} ; D_{21} filled squares. The solid curves give the Nernst-Planck predictions.

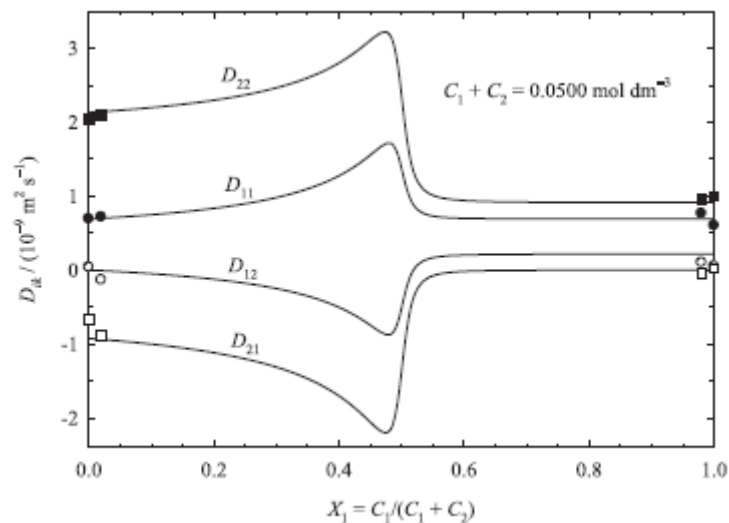


Fig. 4. Ternary diffusion coefficients of aqueous paracetamol (C_1) + NaOH(C_2) at $C_1 + C_2 = 0.0500 \text{ mol dm}^{-3}$ total concentration. Measured values: filled circles, D_{11} ; hollow circles, D_{12} , hollow squares, D_{21} ; D_{21} filled squares. The solid curves give the Nernst-Planck predictions.

The pure-diffusion and electrostatic contributions to the D_{ik} coefficients are illustrated in **Fig. 2**.

3.2. Comparison of the measured and predicted ternary diffusion coefficients

In **Figs. 3 and 4** the ternary D_{ik} coefficients measured for paracetamol + NaOH solutions with $C_1 + C_2 = 0.0100 \text{ mol dm}^{-3}$ and $0.0500 \text{ mol dm}^{-3}$ total are plotted for comparison with the predicted values. The good agreement between our data and Nernst-Planck values show us that model is useful and may be of interest to a wide range of workers interested in electrolyte transport in complex systems where coupled diffusion is present.

4. Conclusions

The effects of added sodium hydroxide on the diffusion of aqueous paracetamol have been investigated by measuring ternary mutual diffusion coefficients for aqueous solutions of paracetamol + NaOH. Because paracetamol is a weak acid ionized by NaOH,

the diffusion behaviour of systems resulting of the mixture of these components strongly depends of the ratio between the concentration of the two components. That is, while with an excess NaOH (paracetamol solute fraction $X_{\text{paracetamol}} < 0.500$), we have an aqueous system containing sodium paracetamide plus sodium hydroxide ternary mixed electrolyte, with excess paracetamol (paracetamol solute fraction $X_{\text{paracetamol}} > 0.500$) the system is constituted by paracetamol and sodium hydroxide components.

The measured D_{ik} coefficients have been compared with the limiting Nernst-Planck coefficients to help understand the composition dependence of the D_{ik} coefficients and the electrostatic mechanism for the coupled diffusion of paracetamol and NaOH. Although this model does not allow accurate prediction of mixed electrolyte diffusion coefficients, it is useful because it supplies qualitative

information about the dependence of the Dik coefficients on the system composition, helping us to understand the main features of the results, including the composition dependence of the D_{ik} coefficients and the mechanism of coupled diffusion.

In summary, depending of the concentration ratio of these components (paracetamol and NaOH) or the pH media, it is observed a significant coupled diffusion in these solutions. Given the possible pharmacological applications for this drug on biological systems, it can be concluded that the paracetamol + NaOH system provide transport data necessary to model the diffusion in pharmaceutical applications.”

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