Experimental Determinations of Diffusion Coefficients in Dilute Aqueous Solution Using the Method of Hydrodynamic Stability

Marylee Z. Southard,[1,5] Lloyd J. Dias,[2] Kenneth J. Himmelstein,[3] and Valentino J. Stella[4]

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Diffusion coefficients were experimentally determined in dilute aqueous solution at 25 ± 0.1°C, ionic strength 0.5 *M*, using Taylor's method of hydrodynamic stability. The methodology described is accurate enough to show significant differences in diffusion coefficients between the various ionic forms of the same species as a function of degree of ionization. In Taylor's method, diffusion coefficients were measured by allowing two solutions of differing solute concentration to contact in a capillary tube, forming a stable, measurable concentration gradient. The solute diffusion coefficient is a function of the gradient, the solution viscosity, the solution density, and some capillary dimensions. Viscosity was maintained constant across experiments and values of sufficient accuracy were available in the literature. Solution densities were measured with a tuning fork densimeter. Compounds studied were *o*-aminobenzoic acid, benzoate anion, the four forms of phosphate and citrate, and the zwitterionic forms of glycine, diglycine, and triglycine. Based on the results for the four forms of phosphate and citrate, experimental diffusivity values vary with the ionic state of the diffusant, presumably because of the altered state of hydration as charge varies. For the glycine series, the diffusivity showed an unexpected dependency on molecular weight (size).

KEY WORDS: diffusion coefficient; drug dissolution; capillary stability.

INTRODUCTION

Diffusion along a concentration gradient is a major transport mechanism in the dissolution of drugs from solid/liquid interfaces (1–5). Accurate estimates or measurements of diffusivities of various ionic species of the drug and buffer under the experimental conditions of the dissolution studies were required to allow any quantitative description of the physicochemical processes which govern dissolution. Diffusivity has been shown to vary with the state of ionization, presumably because of altered hydration states between species (6–9). The objective of this work, therefore, was to determine experimentally the diffusion coefficients of a number of buffer species at varying pH values and at an ionic strength of 0.5 *M* (KCl).

Solution diffusion coefficients can be determined by a number of methods (10). One of these, conductance, is the easiest for variably charged species but is limited experimentally to studies performed without the presence of other swamping electrolytes. Theoretical calculations are possible to assess diffusion coefficients under nonlimiting conditions for multiply charged species. However, these methods cannot be used actually to determine values for diffusivity under the experimental conditions employed here, i.e., diffusion in the presence of other electrolytes for application to complex dissolution systems. Other methods have various strengths and weaknesses (10). This paper describes the methodology and some improvements on a relatively new method used to determine diffusion coefficients based on the theory of capillary stability (7,8), as applied by Quinn *et al.* (11), where a stable and measurable concentration gradient is established in a capillary tube. The establishment of this gradient is used to determine diffusivity. In this study, refinements to the methodology, including temperature control and the use of a tuning fork densimeter, allowed the determination of diffusion coefficients in relatively dilute solutions in the presence of swamping electrolytes to be made.

Compounds studied included *o*-aminobenzoic acid, benzoate anion (the ionized form of benzoic acid), and the four ionic forms of phosphate and citrate, as well as the zwitterionic forms of glycine, diglycine, and triglycine. The values obtained are compared to those determined by others.

THEORETICAL

The method of determining diffusivity used in the present study is based on the occurrence of free convection of solute (not its diffusion) produced by a density gradient. Taylor (7) first related this phenomenon to the driving force behind Fickian diffusion, the concentration gradient. When two solutions of differing solute concentration are contacted, by definition, a density gradient exists. The case of interest is shown in Fig. 1, where a reservoir of a denser solution (higher concentration) is in contact with a sealed tube containing a less dense (lower concentration) solution. When the two solutions are allowed to mix, the denser solution mixes with and displaces the less dense solution as it moves. At each point in the vertical dimension, radial diffusion occurs. The concentration gradient, acting as the driving force for fluid movement, is reduced as the more dense solution moves down the tube mixing with the less dense solution. After the process has continued, a condition of pseudostability is reached. Wooding (8) first derived equations to find criteria defining this condition within the capillary tube. Building on the work of Taylor (7) and Wooding (8), Quinn *et al.* (11) applied this theory along with experimental observations to estimate the minimum contact time, t_c, to achieve this metastable condition between the two liquids. The minimum contact time is defined by Eq. (1):

$$\frac{t_c D}{R} \approx 25 \tag{1}$$

[1] Department of Chemical and Petroleum Engineering, University of Kansas, Lawrence, Kansas 66045.
[2] American Cyanamid, Pearl River, New York 10965.
[3] Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, Nebraska 68198.
[4] Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kansas 66045.
[5] To whom correspondence should be addressed.

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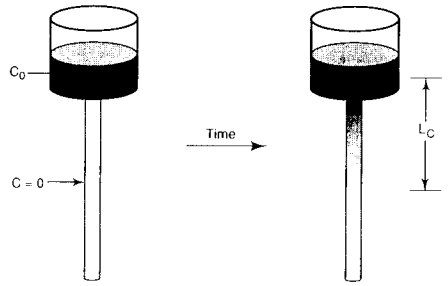

Fig. 1. Illustration of Taylor's theory of hydrodynamic stability. C_o is the concentration of diffusant in the donor phase; L_c is the penetration depth of diffusant in the capillary at a condition of stability.

Once this metastable state is established, the diffusivity can be determined from Eq. (2),

$$D = \frac{\alpha g R^4 C_o}{67.94 \mu L_c} \quad (2)$$

where D is the diffusion coefficient or diffusivity, μ is the fluid viscosity, R is the tube radius, g is the gravitational constant, C_o is the solute concentration in the donor phase, and L_c is the penetration depth, which Quinn *et al.* (11) showed can be determined from Eq. (3),

$$L_c = 2L\frac{\overline{C}}{C_o} \quad (3)$$

where L is the length of the capillary and C is the average capillary concentration which can be experimentally determined. The term α can be found if the densities of both the capillary and reservoir solution are known through Eq. (4):

$$\alpha = \frac{\rho_{cup} - \rho_o}{C_o} \quad (4)$$

where ρ_o is the density of the solute-free solution, and ρ_{cup} is the density of the solute-containing solution. The reader should refer to the work of Quinn *et al.* (11) for a more extensive discussion of the theory associated with this technique.

Because the diffusivity determination method described above is dependent on an accurate value of α, a very precise method for its measurement is required. In the present study this was especially important since diffusion coefficients were being determined in relatively dilute solutions. The accuracy with which α can be determined affects the ability to discern small differences in diffusivity between species. Quinn *et al.* (11) list this requirement as one of the major drawbacks to the capillary method. Because of accurate temperature control within runs and careful measurements using a tuning fork-type densimeter (12–15), these limitations were overcome in the present study.

MATERIALS AND METHODS

Materials. O-aminobenzoic acid (OABA), hydrazine sulfate and sodium molybdate (Aldrich Chemical Co., Milwaukee, WI), benzoic acid (J. T. Baker Chemical Co., Phillipsburg, NJ), and the glycines (Sigma Chemical Co., St. Louis, MO) were all obtained from commercial sources. Naphthalene-2,3-dicarboxaldehyde was obtained from the Chemistry Department of The University of Kansas. All materials other than benzoic acid and OABA, which were recrystallized from water, were used as received.

Equipment and Operations. The capillary apparatus (Fig. 2) consisted of three capillary tubes, each in contact with a reservoir at its open, upper end. The tubes (Ace Glass, Inc., Vineland, NJ) were 0.16-cm-I.D. precision-bore glass tubing, with a maximum bore tolerance of ±0.010 mm. Each tube was 61 cm long. The reservoir cups were 125-ml polycarbonate jars. The tube/reservoir joint was seated with white Teflon tape wrapped around the tube and sealed on the exterior with silicone. The lower end of each capillary tube was sealed, to prevent leakage of capillary solution, with a 20-gauge hypodermic needle and luer fitting permanently inserted to allow easy removal of the capillary contents.

As Quinn *et al.* (11) described, the capillary method for diffusivity determination can give accurate results provided several physical factors are controlled. These constraints include the length of time the reservoir and capillary fluids must contact each other and a very slow filling of the reservoir to minimize forced convective currents and overshoot of the penetration depth. For the experimental apparatus used here, the required residence time was 5–11 hr. The requirement for slow filling was fulfilled by using delivery cups and very small-bore delivery tubing to transfer the final 100 ml of 125 ml total to each reservoir. Each reservoir cup was filled by gravity flow through the 0.5-mm-ID capillary tubing (Dural Plastics and Engineering, Dural, New South Wales 2158, Australia). Because the tubing ends were immersed in the reservoir fluid, no dripping action disturbed the fluid. Each experiment was performed in triplicate.

Since α [used in Eq. (2) to calculate D] is highly sensitive to temperature, accurate measurement and control of the reservoir temperature were imperative. The maximum permissible variation in fluid temperature was ±0.1°C to achieve the desired accuracy in the diffusivity measured. Because of these temperature control requirements, the tube/reservoir arrangement was totally enclosed in a plywood box (manufactured at The University of Kansas), thermostatically controlled with a Thermistemp temperature controller (YSI Inc., Yellow Springs, OH; Model 71A) and probe, and a 60-W light bulb (Fig. 2). Two small fans (W. W. Grainger Inc., 1/125 hp each) were mounted as shown to pro-

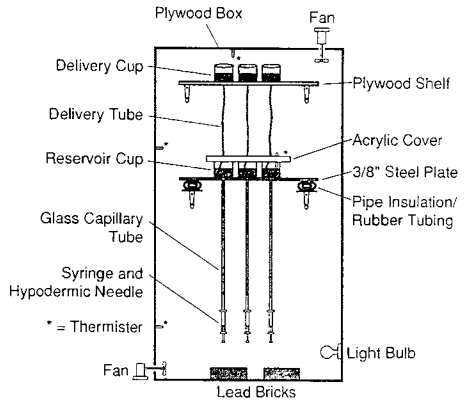

Fig. 2. Capillary apparatus for diffusion coefficient determination.

vide temperature uniformity throughout the box. Three thermistors (Newark Electronics, Chicago, IL) were mounted on the top, middle, and bottom of the box interior, and one thermistor was encased in a glass probe for insertion in one of the liquid reservoir cups. All four thermister leads were wired to a selector switch and the output read on a multimeter (Keithley, Inc., Cleveland, OH), reading resistance as ohms. Each thermistor was calibrated using a platinum resistance thermometer and a large constant-temperature bath whose temperature had been established accurately. The box closure was hinged on one side and made of Plexiglass for viewing ease.

A second critical environmental factor to control was vibration. The entire box was placed on a rubber mat in a quiet room on structural concrete away from motors and other sources of vibration. No part of either fan touched the box or its contents. Vibration was damped out on the main platform (a ⅜-in. steel plate) by allowing it to rest on two sections of 2-in. gray foam pipe insulation, each of which had a section of 1-in. rubber tubing inserted crosswise. Two lead bricks were placed in the bottom of the box for further stabilization.

Capillary Experiment Method. Donor and receptor solutions were made so that they were identical except for the presence of the diffusing component in the donor. The donor solution was 0.02 *M* in diffusing species, and enough 5 *M* sodium hydroxide or concentrated hydrochloric acid was added to obtained the desired pH. Ionic strength was maintained using 0.5 *M* potassium chloride. The receptor had an identical KCl concentration and the amount of acid or base needed to match the pH of the donor phase. Because further addition of KCl to compensate for the small ionic strength difference would create a KCl concentration gradient in the opposite direction from the diffusant of interest, the receptor solution had an ionic strength slightly under 0.5. Because diffusion coefficient values are affected by ionic strength (10), there may be some small error generated by this experimental constraint.

In each run (done in triplicate), approximately 400 ml of donor solution and 40 ml of capillary solution were filtered under vacuum. Twenty milliliters of each solution was sealed and retained for a density determination. For each capillary tube, exactly 2 ml of the KCl stock solution was put into a syringe with a 1-ml Pipetman (Rainen Instrument Co., Inc., Woburn, MA). The filled syringe was inverted and connected to the needle-tube fitting. The fluid was slowly injected into the tube until the level was seen above the tube top. Filtered donor solution was poured into each cup to a level a few millimeters below the tube end. The remaining donor solution was slowly poured into the delivery cup to a predetermined level. The total donor solution volume in each unit was at least 120 ml to satisfy the criterion that the reservoir volume be 100 times the capillary volume (11).

To allow the entire apparatus to equilibrate thermally before each experiment, the delivery tubing was raised to prevent fluid transfer to the reservoirs. Acrylic lids were laid over the delivery and reservoir cups to minimize evaporation. A thermowell containing a thermistor was inserted into one reservoir cup for temperature monitoring, and a plywood barrier was positioned between the light bulb and the capillary tubes to eliminate temperature gradients in the tubes. Both fans and the thermostat were turned on and the box door shut. The entire apparatus was left 6 hr or more to come to a uniform temperature.

Each experiment was started by lowering the delivery tubing. The flow of donor solution was initiated, if necessary, by pulling liquid into the tubing with a 25-gauge needle and syringe. The tubing was quickly inserted into each cup and the box closed again. The liquid temperature was noted at the startup time and compared to the value observed at the end of the experiment. The final temperature was taken as the stable temperature of the equilibrated solutions. If the variation in reservoir fluid temperature during an experiment varied more than 0.1°C, the experiment was aborted.

At the completion of each experiment, enough reservoir solution was withdrawn by pipette to expose the top end of the capillary tube, and a 20-ml sample was retained for analysis. The capillary solution was withdrawn into the syringe, disconnected from the tube fitting, and also retained for analysis.

Diffusion coefficients of phosphate and citrate were evaluated at various pH values. For phosphate, the pH values chosen were 1.0, 4.2, 9.0, and 13.0 to maintain a predominant single form of phosphate in each set of experiments. That is, with the pK_a values of phosphate at this ionic strength, effectively only a single ionic form of phosphate was present at each pH value. Because citrate K_a values were quite close, seven pH values between pH 2 and pH 9 were used. For glycine, diglycine and triglycine no pH adjustment was made. That is, diffusivity of only the zwitterionic forms of the three species was determined. Also, the diffusivity of *o*-aminobenzoic acid was determined in water because its value is a well-known standard (16). The diffusivity of benzoate (conjugate base of benzoic acid) in KCl also was determined to corroborate the value found by Mooney *et al.* (5) using a rotating-disk experiment.

Analytical Methods. *o*-Aminobenzoic acid and benzoic acid concentrations were determined by UV spectroscopy from standard curves, while phosphate concentration was determined by the molybdate blue method (17). Citrate concentration was determined using a standard literature procedure (18), and the glycine series concentrations were analyzed fluorimetrically using the naphalene-2,3-dicarboxaldehyde/sodium cyanide method (19).

Tuning-Fork Densimeter Measurements. To determine the α values needed for the diffusivity calculation using Eq. (2) for a given fluid, the natural oscillation period, τ, for that fluid in a SODEV densimeter was determined (12). Temperature was maintained at 25 ± 0.001°C since τ is a strong function of temperature. By determining τ for methanol and water (two solvents of known density (16), 0.5 *M* KCl (solute-free solution) and the solute-containing solution, it was possible to calculate α for the solute-containing solution from Eq. (5) without calculating actual densities

$$\alpha = \frac{(\rho_{H_2O} - \rho_{MeOH})(\tau_{cup}^2 - \tau_o^2)}{(\tau_{H_2O}^2 - \tau_{MeOH}^2)C_o} \quad (5)$$

where τ_{cup} and τ_o are the densimeter oscillation period values for the solute-containing and solute-free solutions, respectively, and τ_{H_2O} and τ_{MeOH} are the densimeter oscilla-

tion period values for water and methanol (standards), respectively. This does assume, however, that accurate values for the density of the standards, water and methanol, were known (16). The τ values for each sample and standards were then averaged over seven or more consecutive readings.

The density differences between the donor solution (solute-containing) and the capillary solution in each experiment were extremely small due to the dilute concentration of the diffusant. For example, the α value for a H_3PO_4 experiment was 0.826, and the donor solution concentration was 0.0201 *M*. From Eq. (4), the density difference was 1.63×10^{-3} g/ml. This difference was shown in a densimeter period reading of 2887.21210 and 2887.58872 for the solute-free and solute-containing phases, respectively.

Diffusion Coefficient Calculations. Calculation of the diffusion coefficients using Eq. (2) was made using experimental α and C values for each cup unit. Any temperature corrections were made according to the method of Bird *et al.* (20). Operating temperatures during any run were constant but did vary between runs in the range of 25 ± 0.2°C. Viscosity was calculated from the known literature values, correcting for slight temperature effects between runs (21). Because all experiments were performed either in pure water or in 0.5 *M* KCl with dilute concentrations of all other species present, the viscosity of donor and receptor solutions was assumed to be unchanged.

RESULTS

Diffusion coefficients of the standard compounds, the phosphates and citrates, and the glycines determined in the present study are shown in Table I. The diffusivity obtained using *o*-aminobenzoic acid, the reference compound, compares closely with the literature value. The capillary method gave a benzoate diffusivity that was very close to the value for benzoic acid determined by Mooney *et al.* (5) in 0.5 *M* KCl using the rotating-disk method (10,22) suggesting that the ionic state of benzoate/benzoic acid has little effect on the diffusion coefficient value.

The diffusion coefficients for the phosphate species vary significantly depending on the ionic form. The diffusivity of the triionized phosphate, PO_4^{3-}, is one-half the diffusivity of the unionized form, H_3PO_4. Both values are significantly different from the diffusivities of the middle two forms, $H_2PO_4^-$ and HPO_4^{2-}, as shown by the confidence range for each value. The confidence limits were determined using Student's *t* distribution (23).

The results for citrate species are shown in Fig. 3. The diffusion coefficient of citrate varies with pH, indicating that the diffusion coefficients of the various ionic forms of citric acid differ. No attempt was made to calculate the diffusion coefficients of the individual species of citrate since, because of the closeness of the pK_a values, more than one citrate specie is present at any given pH. Nevertheless, it can be seen that as the percentage of molecules having a higher ionic charge increases, the diffusion coefficient decreases. In the limit, the diffusion coefficient of the triionized citrate ion is about two-thirds that of the unionized citric acid.

Table I. Diffusion Coefficients of Several Compounds in High-Ionic Strength[a] Aqueous Solution at 25°C

Compound	$D \pm SD^b$ ($cm^2\ sec^{-1} \times 10^6$)	95% confidence limits (23)	No. of trials
OABA[c]	8.31[d] ± 0.24	8.0–8.6	5
Benzoate	9.7[e] ± 0.7	8.8–10.5	5
H_3PO_4	11.4 ± 0.4	10.8–11.9	5
$H_2PO_4^-$	9.6 ± 1.1	8.7–10.4	9
HPO_4^{2-}	8.8 ± 0.7	8.2–9.4	9
PO_4^{3-}	5.8 ± 0.5	5.3–6.3	6
Glycine	13.1 ± 2.5	10.5–15.6	6
Diglycine	8.5 ± 0.9	7.9–9.1	12
Triglycine	6.5 ± 0.5	6.2–6.8	11

[a] I = 0.5 with KCl.
[b] Standard deviation.
[c] Determined in water.
[d] Compare with literature value (Ref. 16) in H_2O at 25°C (8.4×10^{-6} $cm^2\ sec^{-1}$).
[e] Compare with value determined from Levich plot (5) (9.6×10^{-6} $cm^2\ sec^{-1}$).

DISCUSSION

The results for phosphate (Table I) and citrate (Fig. 3) show that there is, as predicted (4,6,9), an effect of ionic charge on the diffusion coefficient. One may consider the anion of interest as being surrounded by a number of water molecules [due to hydrogen bonding and other forces (10)] and coupled cations. The potassium cation would be the cation most in contact with the anion of interest in the present system due to its relatively high concentration. The effective size of the diffusing anion would increase with ionic charge, reducing the mobility of the ion and therefore its apparent diffusion coefficient. The effective change in mobility due to solvent and ionic interactions can be seen where the diffusivity of phosphate trianion, PO_4^{3-}, is half that of phosphoric acid.

Theoretical correlations are often used to approximate the size of the effective radius of diffusing ions to estimate diffusivities. The Stokes–Einstein equation (24) predicts that the diffusivity is inversely proportional to the molecular radius. Using this correlation, the effective radius of the trian-

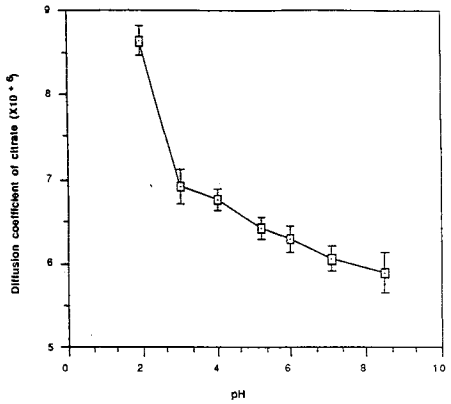

Fig. 3. Effect of pH on the diffusion coefficient of citrate in 0.5 *M* KCl at 25°C. Each point represents 8–10 readings; error bars represent the standard error of the mean.

ion would be twice the unionized phosphoric acid radius, making the effective spherical volume eight times as great. Given the complexity of ionic and solvent interactions in the system of interest, it is not likely that a hydration number can be estimated accurately.

The diffusion coefficient values determined experimentally in this study vary significantly from theoretical molecular weight (MW) predictions. As shown in Table II, neither the Stokes–Einstein equation (24) [$D = f(MW^{-1/3})$] nor the square root correlation (10) [$D = f(MW^{-1/2})$] predict the effect of ionic and solvent interactions on the diffusivity of the multiple charged species. For the glycine series where diffusivities were measured for only the zwitterionic species, molecular size should be an important correlant to diffusivity since the ionic characteristics are constant for all the glycinates. A plot of $-(\ln D)$ versus ln MW for glycine, diglycine, and triglycine should yield a straight line with slope of the proper exponent for a molecular weight correlation (Fig. 4). The slope of 0.75 indicates that results here do not follow the Stokes–Einstein or square root correlation and may suggest a linear structure for the series.

The diffusivity values determined here for the various forms of phosphate are quite different from the empirical value (8.1×10^{-6} cm^2/sec) used previously in modeling of carboxylic acid dissolution in buffered media (4). The empirical value apparently would be valid only in a mixture of H_3PO_4 and $H_2PO_4^-$ at about pH 4. The phosphate values from this study correlate qualitatively with those determined by Smidt *et al.* (6), as shown in Table III. It is unclear in what media those data were determined. A similar charge-dependent effect is observed in the diffusion coefficient data for citrate. Again, as expected, the diffusion coefficient of the trianionic form is lower than that of the unionized form.

The diffusivity values of ionized substances can be calculated from equivalent conductances, λ_i, using Eq. (6) (10):

$$D_i = \frac{2.662 \times 10^{-7}}{|Z_i|} \lambda_i \qquad (6)$$

where Z_i is the ionic charge and D_i is in cm^2/sec. Dilute solution diffusivities can be calculated from the limiting conductances, λ_i^0. Values of calculated D_i from λ_i^0 are shown in Table III and are different from most of the experimental results of this study, although they do predict the rank order

Table II. Comparison of Experimentally Determined Diffusion Coefficients[c] with Values Calculated from Molecular Theory

		D (cm^2 sec^{-1} × 10^6)		
Compound	MW	Experimental	$(MW^{-1/2})^a$	$(MW^{-1/3})^b$
Glycine	75.07	13.0	11.4	10.3
Diglycine	132.12	8.5	8.6	8.5
Triglycine	189.17	6.5	7.2	7.6
Citric acid	192.14	8.7	7.1	7.5
$Citrate^{3-}$	189.14	5.9	7.2	7.6
H_3PO_4	97.99	11.4	9.9	9.4
PO_4^{3-}	94.99	5.8	10.1	9.5

[a] Square root relationship (10).
[b] Stokes–Einstein relationship (24).
[c] I = 0.5 with KCl.

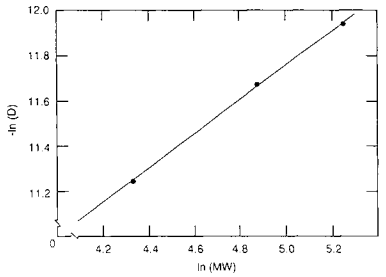

Fig. 4. ln vs −ln plot of diffusion coefficient versus molecular weight for glycine, diglycine, and triglycine.

differences. Apparently, the presence of relatively high electrolyte concentration in the medium has a significant effect. Thus, the conductance calculation does not quantitatively correlate with the experimental determinations in this system.

The usefulness of the technique explored in the present study is not limited to diffusivity determinations for small molecules. Effective diffusion coefficients of macromolecules can be determined if a larger-diameter capillary tube is used. An appropriate theoretical correlation can be used to give an initial approximate diffusivity, which is used to calculate the proper capillary tube diameter for the diffusing species of interest. The specific analytical technique required for a particular diffusant is, of course, dependent on the diffusant. Quinn *et al.* (11) show that tracers and other codiffusants may be used to ease analysis without sacrificing the accuracy of the method. Regardless of the analytical method used, only one analysis of capillary and solute-rich solutions is required per value of diffusion coefficient obtained with this technique.

One major limitation found with this method was noted when the concentration of diffusant in the donor solution is close to the solubility limit. The solubility of benzoic acid, 0.022 *M* (5), was a limitation in this study. Although the donor concentration was reduced and an effort made to solubilize all the solute, capillary results and density values

Table III. Comparison of Experimentally Determined Diffusion Coefficients[c] with Earlier Data and Calculated Values

		D (cm^2 sec^{-1} × 10^6)		
Compound	λ^0	Calculated from λ^0	Experimental (Smidt *et al.*) (6)	Experimental (this study)
$H_2PO_4^-$	36[a]	9.58	9.2	9.6
HPO_4^{2-}	57[a]	7.59	8.2	8.8
PO_4^{3-}	81[b]	7.19	7.5	5.8
PO_4^{3-}	58[c]	5.15	7.5	5.8
$Citrate^{3-}$	69[d]	6.08		5.9[e]

[a] Ref. 25.
[b] Calculated from the limiting equivalent conductance for ⅓ Na_3PO_4 (Ref. 16, Vol. VI, p. 248).
[c] Calculated from the limiting equivalent conductance for ⅓ K_3PO_4 (Ref. 16, Vol. VI, p. 252).
[d] Calculated from the limiting equivalent conductance for ⅓ $K_3C_6H_5O_4$ (Ref. 16, Vol. VI, p. 252).
[e] Read from Fig. 3, pH 8.5.

were not reproducible. Diffusivity values were imprecise; standard deviations approached 70% of the average value. To alleviate the solubility problem in this case, benzoic acid was converted to the soluble benzoate form by raising the pH. All diffusion coefficients for benzoate were consistently reproducible and compared well with the value of Mooney *et al.* (5) at the same ionic strength.

CONCLUSIONS

The method of capillary stability was used to determine accurate dilute solution diffusion coefficients of reasonably soluble solutes. It was particularly useful for complex systems containing high concentrations of electrolyte where other methods requiring pure solution or low ionic strength conditions may not be appropriate. This technique has been used in the present study to show the effect of ionic and solvent interactions on the measured diffusivity of charged species in aqueous solutions of high ionic strength, reducing the diffusion coefficient significantly. It was also used to demonstrate that a complex relationship exists between the molecular weight and the diffusivity of small linear peptides. The method appears useful for solutes having a wide range of molecular weights. The precision of the method is limited only by the requirements of strict temperature and vibration control, slow filling of the reservoir containing the diffusant, accurate methods of externally determining the densities and viscosities of the solutions used, precise analytical methodologies for the solutes, and solubility limitations of the solute.

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