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Salting Out of Aqueous Procaine Hydrochloride by Sodium Chloride at 25°C

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Aqueous procaine [2-(diethylamino)ethyl *p*-aminobenzoate hydrochloride] and its aqueous mixtures with sodium chloride have been investigated by isopiestic vapor pressure measurements and solubility measurements. Osmotic coefficients and activity coefficients were derived for aqueous procaine to concentrations of 6.5_6m (its solubility at 25°), and for its mixtures with sodium chloride up to $2m$ total concentration. Solubility measurements permitted calculation of activity coefficients in aqueous mixtures saturated with procaine. A solution saturated with both procaine and sodium chloride had a procaine solubility of only 0.03_6m.

Many organic compounds—proteins, for example—are precipitated from their saturated aqueous solutions by the addition of an inorganic salt (*3*). This salting out phenomenon is accompanied by an increase in the activity coefficient of the organic compound. Conversely, there is a decrease in the activity coefficient if the organic compound is made more soluble by salt addition. Solubility and isopiestic data for such ternary systems can both be related to activity coefficients, and recent measurements of both types have been made on aqueous mixtures of sodium chloride and urea (*1*), of potassium chloride and glycine (*2*) and also of sodium chloride and barium chloride (*8*).

Procaine (the anesthetic novocain) is a water-soluble quaternary ammonium chloride, found from preliminary experiments to be strongly salted out by sodium chloride. This system was chosen for study as part of a program designed to investigate the effect of one electrolyte on the solubility of another.

The isopiestic vapor pressure method is ideally suited to the measurement of activity coefficients of involatile solutes in aqueous solutions. Because of the way the free energy of an N-component system is altered by changes in system composition, at constant temperature and pressure $N - 1$ cross expressions of the form

$$(\partial \ln \gamma_i/\partial m_j)_{m_{i \neq j}} = (\partial \ln \gamma_j/\partial m_i)_{m_{j \neq i}} \quad (1)$$

can be defined (*4*). If the activity coefficient, γ_i, of one of the components (water in this case) can be measured as a function of composition, there are left $N - 1$ unknown activity coefficients which can be determined from the $N - 1$ cross expressions. The method is exact and depends only on the premise that the free energy is an exact differential. Although this method can in principle be applied to systems containing any number of components, the treatment of the data is difficult and it has so far been applied to solutions containing only one or two solutes.

EXPERIMENTAL

Materials. The reference salt, sodium chloride, was precipitated with hydrogen chloride and dried at 120°. The osmotic coefficients and activity coefficients of this salt were taken from the compilation by Robinson and Stokes (*9*). Reagent grade procaine was recrystallized once from water; a further recrystallization yielded material that gave the same isopiestic results as the first. Both batches, after drying at 110°, had melting points of 156° and contained 99.5 ± 0.5% of the theoretical chloride content.

Isopiestic Apparatus. The apparatus and procedure were described previously (*6*). Equilibrations were made in silver dishes 2.5 cm in diameter. Some of these dishes contained weighed mixtures of dry NaCl (A) and procaine (B) and the other dishes contained NaCl alone or procaine alone.

To start a run, the lids were removed and enough water (about 1 ml) was added to each dish to make solutions of about the desired concentration. The dishes were placed in recesses in a thick copper block which rested in a 10-cm internal diameter dry seal desiccator. The desiccator was slowly evacuated with a water aspirator and then slowly rocked back and forth in a water bath kept at 25.00°, which with the good thermal conductivity of the apparatus ensured good temperature constancy among the dishes. After equilibration for from 2 days for concentrated solutions to 7 days for the most dilute solutions, the lids were again placed on the dishes (this usually took less than 30 seconds) and the concentrations were determined by weight. Once equilibrium had been reached, there was no change in apparent concentrations of the procaine with periods in the desiccator extended up to 10 days, which indicated that the procaine was not decomposing during the equilibrations.

RESULTS AND DISCUSSION

Isopiestic Activity Coefficients. The isopiestic compositions of nine sets of comparisons are given in Table I. The first value for each set under column m is the molality of the sodium chloride reference solution; the subsequent values are total molalities in mixed solutions, with the last value referring to binary aqueous procaine. The column headed y_B gives the fraction of the procaine in the mixed solutions—that is, $m_B/(m_A + m_B)$—and the osmotic

coefficient, ϕ, is defined as $-(55.51/2\ m)$ ln a_w, where a_w, the water activity of the solutions, is constant for each set. The isopiestic compositions of four of the sets are shown in Figure 1. The average deviation of the sodium chloride molalities is 0.0008 m; that of the procaine molalities is 0.0018 m.

Binary System Water-Procaine. The osmotic coefficients for procaine at rounded molalities are shown in Table II and were interpolated from a plot of the values at $y_B = 1$ in Table I. (Another 11 sets of data with somewhat greater scatter than those in Table I gave additional intermediate points and were also used in the interpolation of osmotic coefficients for the binary system.) Assuming the literature values of ϕ_A° are not in error, and that procaine is a 1 to 1 type salt, an uncertainty of not more than 0.003 in ϕ_B° is deduced.

The mean activity coefficients for aqueous procaine are also listed in Table II and were calculated from an expression derived from Equation 1 (9).

$$-\ln \gamma_B^\circ = 1 - \phi_B^\circ + 2\int [(1 - \phi_B^\circ)/(m)^{1/2}]\, d\,(m)^{1/2} \qquad (2)$$

The graphical integration was simplified because the experimental integral argument, $2(1 - \phi_B^\circ)/(m)^{1/2}$, extrapolated to its theoretical value of 0.78 at $m = 0$. The absolute value of the integral was large, however (1.026 at 1m), and uncertainties could lead to systematic errors in γ_B° of up to 0.01 (less at high concentrations). This uncertainty is a common failing in isopiestic work and can usually be eliminated only by supplementary low concentration measurements of cell emf's or freezing point depressions.

Ternary System Water–Sodium Chloride (A)–Procaine (B). The activity coefficients for both salts were calculated from the data in Table I, using the method described by Robinson (7). The method, which depends on the cross-differentiation expression given above, is very lengthy and is not described here. The maximum concentration for which activity coefficients can be calculated is limited only by the solubility of the salts. This range can sometimes be extended by working with supersaturated solutions, but this was not possible with the two salts studied here. For the mixed salt solutions, the data required to calculate activity coefficients extended only to a total molality of just over 4 for γ_A and about 2 for γ_B. The activity coefficients of both salts are given in Table III for three values of γ_B. It follows from Equation 1 that if γ_A is increased by an increase in m_B at constant m_A, then γ_B must be increased

Table I. Compositions of Isopiestic Aqueous Mixtures of Sodium Chloride (A) and Procaine (B) at 25°[a]

m	y_B	ϕ	m	y_B	ϕ
0.1970	...	0.9246	1.9770	...	0.9820
0.2012	0.2929	0.9053	2.0768	0.1770	0.9348
0.2135	0.5758	0.8531	2.4276	0.4296	0.7997
0.2170	0.6378	0.8394	3.7478	0.8442	0.5180
0.2523	1.0	0.7219	4.8956	1.0	0.3966
0.5084	...	0.9210	2.2981	...	1.0006
0.5367	0.2753	0.8724	2.3515	0.1111	0.9779
0.5656	0.4349	0.8278	2.8770	0.4446	0.7993
0.6262	0.6225	0.7477	4.4432	0.8569	0.5175
0.9340	1.0	0.5013	5.6140	1.0	0.4096
0.6982	...	0.9257	2.5861	...	1.0184
0.8763	0.5843	0.7376	2.6286	0.0905	1.0019
0.9263	0.6526	0.6977	2.9105	0.2865	0.9049
1.1717	0.8653	0.5516	3.7715	0.6131	0.6983
1.4893	1.0	0.4340	5.1861	0.8848	0.5078
			6.2287	1.0	0.4228
0.9712	...	0.9345	2.6812	...	1.0245
0.9758	0.0784	0.9301	2.7262	0.0905	1.0076
1.1767	0.4853	0.7713	3.0217	0.2865	0.9091
1.3898	0.6758	0.6530	3.9118	0.6131	0.7022
2.3060	1.0	0.3936	5.3638	0.8848	0.5121
			6.56	1.0	0.429
1.3650	...	0.9498			
1.4403	0.2172	0.9001			
1.5944	0.3958	0.8131			
1.8507	0.5816	0.7005			
2.3319	0.7883	0.5560			
3.3800	1.0	0.3836			

[a] ϕ refers to single salt solutions at $y_B = 0$ and $y_B = 1$.

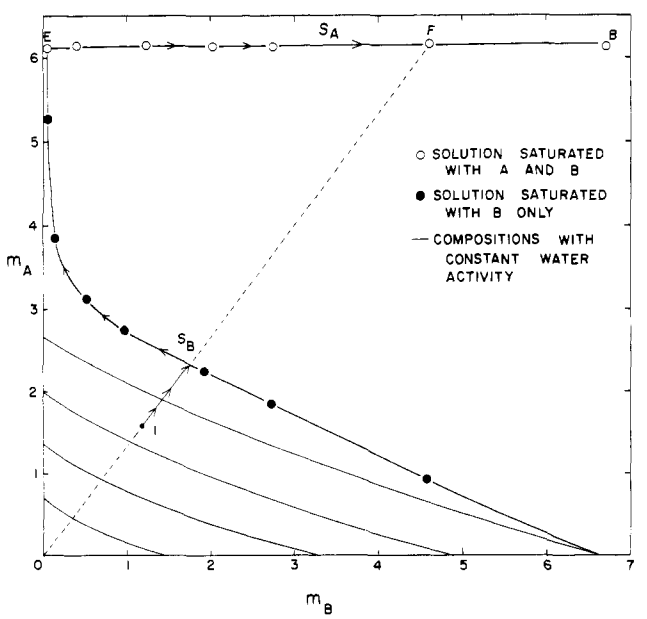

Figure 1. Compositions of aqueous mixtures of sodium chloride (m_A) and procaine (m_B)

Table II. Osmotic and Activity Coefficients of Aqueous Procaine Hydrochloride

m	ϕ_B°	γ_B°	m	ϕ_B°	γ_B°
0.1	0.84	0.645	1.5	0.433	0.163
0.2	0.756	0.517	2.0	0.403	0.134
0.3	0.690	0.433	2.5	0.390	0.116
0.4	0.638	0.373	3.0	0.384	0.103
0.5	0.595	0.328	3.5	0.382	0.0934
0.6	0.564	0.295	4.0	0.384	0.0862
0.7	0.541	0.271	4.5	0.389	0.0806
0.8	0.522	0.250	5.0	0.398	0.0764
0.9	0.503	0.232	5.5	0.407	0.0728
1.0	0.488	0.215	6.0	0.418	0.0699
			6.56	0.429	0.0674

Table III. Mean Activity Coefficients of Sodium Chloride (A) and Procaine Hydrochloride (B) in Mixed Aqueous Solution[a]

m_A	+	m_B	$-\log \gamma_A$	$-\log \gamma_B$
0.5		...	0.167	0.183
0.25	+	0.25	0.173	0.369
...		0.5	0.204	0.484
1.0		...	0.183	0.235
0.5	+	0.5	0.192	0.526
...		1.0	0.245	0.668
2.0		...	0.175	0.295
1.0	+	1.0	0.191	0.686
...		2.0	0.253	0.873
3.0		...	0.147	
1.5	+	1.5	0.174	
...		3.0	0.224	
4.0		...	0.106	
2.0	+	2.0	0.153	
...		4.0	0.186	

[a] γ values refer to single salt solutions in light places.

by an increase in m_A at constant m_B. At constant total ionic strength, however, no such restriction applies. The activity coefficients for procaine are shown in Figure 2.

Solubility Measurements. Mixed salt solutions were saturated at 25.00° with B alone or with both A and B. The total weight of both salts was obtained by evaporating aliquots to dryness, and total equivalents of chloride by titration with $AgNO_3$, thereby allowing both m_A and m_B to be calculated. The solubility of aqueous procaine determined by evaporation to dryness was 6.5m and by titration was 6.5$_6m$. This latter value of 64% by weight is in contrast with an early value of 50% (*10*). The eutonic point, E, at which the solution was saturated with both A and B had the composition of 6.09$_8m$ in A and 0.03$_6m$ in B. These solubilities are plotted in Figure 1. E was also defined by the isopiestic method described by Kirgintsev and Trushnikova (*5*). Their procedure is particularly applicable to ternary systems and is worth describing in some detail.

Several unsaturated solutions with various m_A/m_B ratios are equilibrated with one saturated solution containing a large excess of both solid A and solid B. Consider one such unsaturated solution with initial composition given by point I, in Figure 1, the solvent of which distills into the oversaturated solution. At point S_B the former solution becomes just saturated with B, which crystallizes out until the solution composition reaches point E. However, the apparent total composition of the system must lie on a projection of line OS_B (because m_A/m_B is constant) and also on horizontal line EB (because the distillation stops just as the concentration of A reaches that in the eutonic solution). Line EB is parallel to the m_B axis only because the solid procaine in equilibrium with its solutions is the anhydrous salt. (The presence and composition of a hydrate salt could be determined from a sloped line starting at E and intersecting the m_B axis.) For most ternary systems there will be a second branch line running from E parallel to the m_A axis, which corresponds to the A-rich side of the eutonic. For this particular system, however, the vapor pressure of the eutonic solution is greater than that of saturated NaCl, so that the second branch does not appear in Figure 1.

The activity coefficients of procaine in its saturated solutions can now be calculated from the solubility measurements and compared with those calculated from isopiestic measurements. At any given temperature the activity product (procaine ion activity × chloride ion activity), is a constant irrespective of what other species are present in solution.

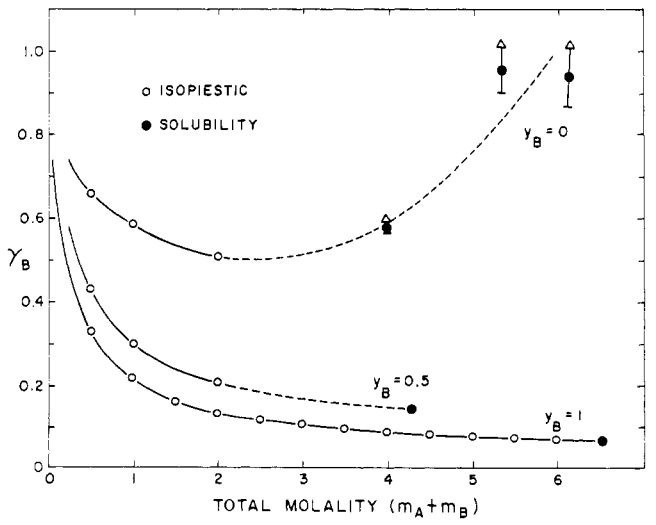

Figure 2. Mean activity coefficients of procaine in aqueous mixtures with sodium chloride

The solubility of procaine is 6.56m and from Table II γ_B° = 0.0674 at this molality. Then the activity product of procaine is $k_B = 6.56^2 \times 0.0674^2 = 0.1955$. The activity coefficient of procaine in an equimolal mixture with sodium chloride is calculated from the curve $S_B - E$ in Figure 1 for 2.14m sodium chloride in a solution of 2.14m procaine just saturated with procaine. Then $\gamma_B^2 \times 2.14 \times (2.14 + 2.14) = 0.1955$, which on solving gives $\gamma_B = 0.146$. This is plotted in Figure 2 for the curve $y_B = 0.5$; the value is not inconsistent with the lower concentration values at $y_B = 0.5$. The above procedure was repeated for the eutonic composition, which corresponds very closely to $y_B = 0$ (more exactly 0.006). At the eutonic $\gamma_B^2 \times 0.036 \times (0.036 + 6.098) = 0.1955$ so that $\gamma_B = 0.94$. Two more values corresponding to $m_A = 5.273$, $m_B = 0.040$, and $m_A = 3.835$, $m_B = 0.150$ give $\gamma_B = 0.96$ and 0.57, respectively. These latter two values also correspond to values of y_B near zero, although the approximation becomes poorer as m_B becomes greater. All three γ_B values are plotted in Figure 2; the arrows indicate that these are minimum values, because y_B is slightly greater than zero.

A comparison of the activity coefficients derived from isopiestic measurements with those from solubility measurements is difficult, because the concentrations are so different for the two types of measurements. However, it is possible to interpolate reasonable values for the intermediate concentrations.

Aqueous procaine is a considerably weaker electrolyte than most other 1 to 1 salts—for example, the activity coefficient of 1m procaine is 0.215, whereas that of 1m sodium chloride is 0.657. This weakness is also apparent in aqueous mixtures with sodium chloride containing a moderate fraction of procaine (50% or more). The most probable explanation lies in polymerization of procaine through amide hydrogen bonding.

NOMENCLATURE

- m_A = molality of sodium chloride having mean activity coefficient γ_A° and osmotic coefficient ϕ_A°
- m_B = molality of procaine hydrochloride solution in isopiestic equilibrium with m_A molal sodium chloride and having mean activity coefficient γ_B° and osmotic coefficient ϕ_B°
- m = total molality of a mixed solution of $(1 - y_B)m$ molal sodium chloride and y_Bm molal procaine hydrochloride; this solution is in isopiestic equilibrium with m_A molal NaCl. The sodium chloride in this solution has a mean activity coefficient γ_A; the procaine hydrochloride has a mean activity coefficient γ_B. The osmotic coefficient characteristic of this mixed solution is $\phi = \gamma_A^{\circ} m_A/m$. Because activity coefficients are usually made unitless, the activity product, k_B, in the discussion should, strictly speaking, have units of moles^2 kg^{-2}.

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