

The effect of urea on the solubility of methyl *p*-hydroxybenzoate in aqueous sodium chloride solution

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The effects of sodium chloride and urea, separately and together, on the solubility of methyl *p*-hydroxybenzoate in water have been studied. Sodium chloride decreases and urea increases the solubility. Observed and calculated "salting-out" parameters have been obtained for addition of sodium chloride to the benzoate-urea-water systems. Good agreement was observed between calculated and observed values, and the change in the "salting-out" parameters as the concentration of urea altered may indicate dipole-ion interaction between urea and sodium chloride.

The effect of urea on solubilities of various non-electrolytes in water has been widely studied. Although there is no conclusive evidence to support the mechanism whereby urea changes solubilities, it is generally believed that some break-up in the structure of water occurs.

Added electrolytes markedly affect the aqueous solubility of non-electrolytes, either by decreasing solubility (salting out) or, more rarely, by increasing the solubility (salting in). Surprisingly little work has been done (Wetlaufer, Malik & others, 1964; Lindstrom & Giaquinto, 1970) on the effect on non-electrolyte solubility of mixed aqueous solvents containing comparatively large quantities of non-electrolytes, e.g. urea, and electrolytes together. Such solvent systems would appear to be of some significance in biology and in pharmacy. We present some preliminary observations on the effect of urea and sodium chloride, together, on the solubility of methyl paraben (methyl *p*-hydroxybenzoate).

MATERIALS AND METHOD

Materials

Sodium chloride Analar (BDH) was used without further purification; urea (Fisons) was recrystallized from absolute ethanol and dried; methyl paraben was used without further purification.

Method

Solubilities of methyl paraben were determined in water, in 1-5 M NaCl solutions, in 1-5 M urea solutions and in 1-5 M NaCl solutions containing 1-5 M urea, respectively. Excess methyl paraben was equilibrated with the solutions at $25^\circ \pm 0.1$ for 24 h. Samples were taken, filtered, diluted with water and concentrations were determined from ultraviolet absorption plots of standard solutions determined at 256.75 nm. It had previously been found that saturation solubility is reached within 24 h.

Although urea is generally considered to be non-electrolytic, small traces of ammonium cyanate develop in aqueous solution (Bull, Breese & others, 1964) and the pH values of such urea solutions are slightly alkaline. It is possible to remove the ammonium cyanate by ion-exchange resins, but on solution of the purified urea in water the ammonium cyanate again appears rapidly as measured by conductivity changes. An alkaline pH could affect the solubility of methyl paraben since it has a phenolic OH group with a pKa of 8.5 (Sager, Schooley & others, 1945). The pH values of the equilibrated solutions ranged from 5.8 to 7.2; the highest value was for a system containing methyl paraben-5 M urea-water. It was calculated that about 1% of the total solubility of methyl paraben in this system was due to a pH effect. The effect of pH on the solubilities of methyl paraben in the other solvents would be of the same order. Consequently, since the overall experimental error is approximately $\pm 2.5\%$, it is not considered that the effect of pH would alter the findings. It would be possible to obviate the pH effect by adjusting all solutions to a known acid pH, but since it has been shown that H^+ ions affect the solubility of non-electrolytes (Lindstrom & Giaquinto, 1970), this would mean the introduction of yet another variable into an already complex system.

RESULTS AND DISCUSSION

The solubilities of methyl paraben in the various urea-NaCl-water solvents are shown in Table 1. The value for the solubility in pure water, $0.0146 \text{ kmol m}^{-3}$, agrees well with the literature value of Paruta & Sheth (1966).

Table 1. *Solubilities of methyl paraben (kmol m^{-3}) in various urea-NaCl-water systems.*

NaCl kmol m^{-3}	Urea, kmol m^{-3}					
	0	1	2	3	4	5
0	0.0146	0.0197	0.0242	0.0296	0.0354	0.0413
1	0.0093	0.0128	0.0164	0.0208	0.0258	0.0312
2	0.0062	0.0084	0.0114	0.0143	0.0187	0.0227
3	0.0038	0.0054	0.0076	0.0100	0.0129	0.0166
4	0.0023	0.0041	0.0056	0.0076	0.0099	0.0127
5	0.0016	0.0026	0.0044	0.0059	0.0080	0.0110

Two trends are obvious from the data in Table 1. The solubility of methyl paraben (i) increases with an increase in urea concentration; and (ii) decreases with an increase in NaCl concentration. The former effect, at least in salt-free solutions, has been ascribed to a breakdown of the water structure in the presence of urea (Frank & Franks, 1968). The latter effect is probably an example of "salting out". In the past, studies have focused on these phenomena separately. It is, therefore, interesting to consider a model for the combined effect.

An immediate temptation is to regard the data as the simple sum of the effect due to added urea plus the effect due to added NaCl. For example, a 5M urea solution increases the methyl paraben solubility by $0.0267 \text{ kmol m}^{-3}$, while a 5M NaCl solution

reduces the solubility by $0.0130 \text{ kmol m}^{-3}$. The net gain in solubility in a solution that is $5M$ in both urea and NaCl would then be $0.0283 \text{ kmol m}^{-3}$. This is more than double the observed value.

Perhaps, a more realistic approach would be to recognize the great potential for interaction between NaCl ions and the dipolar urea. Because of the magnitude of the urea dipole, it is quite likely that such an interaction is the principal factor in governing the eventual solution properties of these mixed solvents. Such a view implies, for example, that the degree of salting out due to the NaCl is related to the concentration of urea. This contrasts with the earlier view that salting out may be in addition to the urea effects.

A test of this hypothesis can be made by analysing the effects of added NaCl on each of six possible water and urea-water solvent systems used in this study (Columns in Table 1). If ion-urea interactions are predominant then the analysis will yield distinctive salting out effects that vary with the urea concentration. Therefore, an attempt has been made to derive values for salting out coefficients for these systems. If these values were to be urea dependent and if they agreed with the experimentally determined empirical salting out coefficients this would at least be indicative of ion-urea interactions.

The salting out phenomenon may be described by the empirical equation (Setschenow, 1889):

$$\log \frac{S_0}{S} = k C \quad \dots \quad \dots \quad \dots \quad (1)$$

where S_0 and S are the solubilities of the non-electrolytes in pure solvent and in a solution containing $C \text{ kmol m}^{-3}$ of electrolyte, respectively. The constant, k , is an empirical factor which is characteristic of the electrolyte and non-electrolyte employed. It is positive for salting out. The equation stipulates that a plot of $\log S$ vs C must be a straight line with a $\log S_0$ intercept. Fig. 1 illustrates this treatment for the data

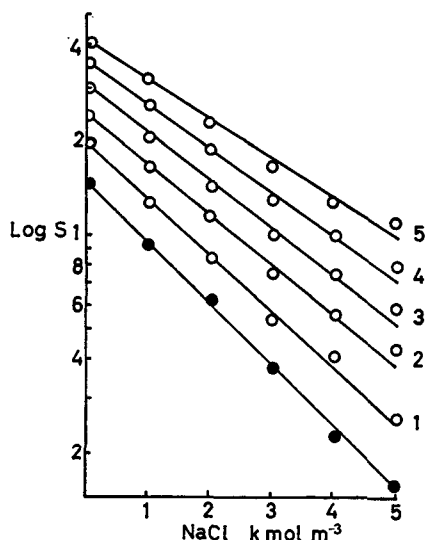


FIG. 1. Effect of various concentrations of urea on the solubility, $\log S$, of *me-p*-OH benzoate in aqueous sodium chloride solutions. Numbers give concn (kmol m^{-3}) of urea.

Table 2. *Coefficients for salting out of methyl paraben by NaCl in water and urea-water solvent systems.*

	k_0 †	k_1	k_2	k_3	k_4	k_5
Observed*	0.193	0.181	0.161	0.151	0.138	0.125
Calculated**		0.174	0.161	0.148	0.138	0.129

† Subscripts on k refer to water, 1, 2, 3, 4 and 5 kmol m^{-3} urea solutions, respectively.

* The average deviation for each value was ± 0.006 , or less.

** Equation 5.

of this study. There are six sets of data plotted, corresponding to the six columns of data in Table 1. This treatment regards water and the five urea-water mixtures as individual "pure solvents" system. The linearity of the points suggests that the salt effect is constant in each "solvent". While there is some deviation from linearity at high C , this is not especially significant in view of the added complexities which are certain to arise at high total solute concentrations.

Salting out coefficients, k , were calculated for the five points in each set of data. The average value of k for each set is given in Table 2 and serves as the slope of the straight line drawn through the corresponding data points in Fig. 1. The maximum deviation, ± 0.006 , was just slightly greater than that estimated on the basis of experimental error, ± 0.005 . It can be seen from Table 2 that k (observed) does vary with urea concentration.

The explanation of salting out phenomena used by Long & McDevit (1952) is appropriate to the present discussion. These authors assume that each non-electrolyte molecule in solution occupies an element of volume, and that the solubility of the non-electrolyte depends on the energy required to generate and maintain the necessary "hole" in the solvent system. Thus, factors which tend to increase this energy requirement will, thereby, decrease the solubility. Chief among these are the size of the molecule and the "effective pressure" of surrounding medium. Salting out is caused by the addition of a salt which increases the "effective pressure". Based on this view, McDevit & Long (1952) proposed that salting coefficients may be calculated using the expression:

$$k = \frac{\bar{V}_1^0 (V_s - \bar{V}_s^0)}{2.3 RT \beta_0} \quad \dots \quad \dots \quad \dots \quad \dots \quad (2)$$

where \bar{V}_1^0 is the partial molar volume of the non-electrolyte at infinite dilution, V_s is the molar volume of the molten salt at temperature T , \bar{V}_s^0 is the partial molar volume of the salt at infinite dilution, and β_0 is the compressibility of water. Data for \bar{V}_1^0 and V_s are generally inaccurate or lacking. As a result, absolute values of k calculated using this expression are suspect. The equation worked well, however, in predicting relative salt effects. It is this facet of equation 2 that will be employed now.

Assuming equation 1 to be essentially correct, then

$$k_0 = \frac{\bar{V}_1^0 (V_s - \bar{V}_s^0)}{2.3 RT \beta_0} \quad \dots \quad \dots \quad \dots \quad \dots \quad (3)$$

where k_0 is the coefficient determined for the effect of NaCl, s , on the solubility of methyl paraben, i , in water.

It was suggested earlier that the addition of urea leads to strong urea-ion interaction. Accordingly, of the parameters in equation 3, the expectation is that \bar{V}_s^0 should undergo the most significant change. If this is so equation 3 becomes

$$k_u = \frac{\bar{V}_1^0 [V_s - (\bar{V}_s^0 + \Delta\bar{V}_s^0)]}{2.3 RT \beta_0} \dots \dots \dots (4)$$

where k_u , is the salt coefficient in the presence of urea, and $\Delta\bar{V}_s^0$ is the change in the partial molar volume of NaCl on transfer from water to the urea-water mixture. The equation may be simplified to

$$k_u = k_0 - A \Delta\bar{V}_s^0 \dots \dots \dots (5)$$

where A is $\bar{V}_1^0/2.3 RT \beta_0$. The value of A for this system was calculated to be 15.7, using empirical expressions provided by McDevit & Long (1952), the compressibility of water, and the observed value for k_0 .

Values of $\Delta\bar{V}_s^0$ were obtained from unpublished data of apparent molar volumes of 1-1 electrolyte in urea-water mixtures. Since the molar volume study was not designed for this specific need, it was necessary to make short extrapolations to arrive at $\Delta\bar{V}_s^0$ for exactly 1, 2, 3, 4 and 5M urea solutions. These are given in Table 3.

Table 3. *The change in the limiting partial molar volume of NaCl, $\Delta\bar{V}_s^0$, on transfer from water to a urea-water solvent system[†].*

Urea, kmol m ⁻³	$\Delta\bar{V}_s^0$, m ³ kmol ⁻¹
0	0.00
1	1.22×10^{-3}
2	2.05×10^{-3}
3	2.80×10^{-3}
4	3.42×10^{-3}
5	4.05×10^{-3}

[†] Determined from unpublished data of R.E.L.

Equation 5 was then used to calculate salt coefficients for each of the five urea-water systems. The calculated values of k , thus derived, are contrasted (in Table 2) with the corresponding observed values. The agreement between the two sets of values is quite good.

The apparent success of this approach to rationalizing the events in a relatively complex solution system is useful. While it may rest, presently, on the remote possibility that a change in β_0 is exactly offset by a change in \bar{V}_1^0 in the urea-water mixture, i.e., A is constant for all systems, this limited success suggests that the above approach may be correct for urea/NaCl systems.

Alternatively, it is possible to consider the solubility changes in terms of the effects of urea and NaCl on the structuring of water. Such an approach is qualitative, and

can become indeterminate if carried too far. NaCl is known, from entropy of hydration measurements, to be a "structural breaker" and is thought to be solvated to the extent of 3.5–7 H₂O molecules (Robinson & Stokes, 1968a). Also for a 1:1 electrolyte the average separation of ions will vary from approximately 0.94 to 0.55 nm as the concentration of NaCl increases from 1–5 M (Robinson & Stokes, 1968b). Such a closely packed structure would indicate that irrespective of the mechanism by which the methyl paraben is "squeezed" out comparatively little "room" would be available for the solute.

Frank & Franks (1968) consider that urea also acts as an indirect structure-breaker when added to water, since by dissolving only in "dense" unstructured water it alters the equilibrium between "dense" water and "bulky" structured water. To re-establish the equilibrium "bulky" water would need to break down. The presence of less "bulky" water would then be more advantageous to the solution of non-electrolyte solute molecules and hence an increase in solubility would result. It seems possible that the effect of urea on the solubility of methyl paraben in NaCl/H₂O solvent systems may be explained tentatively on the same grounds, although, in this case, the equilibrium would exist between water "bound" to NaCl and free water. As the concentration of urea increases, more of the water associated with the NaCl will be stripped off and would be available for dissolving the methyl paraben. Thus, for example, although in 5 M NaCl/H₂O there are more water molecules (50 kmol m⁻³) than in 5 M urea-5 M NaCl-H₂O (38 kmol m⁻³), in the latter solvent there will be more available water than in the former, and hence an increase in solubility would be expected (Table 1).

Some insight into the energetics of the increase in solubility of methyl paraben in urea-NaCl-H₂O solvents over NaCl-H₂O systems may be obtained by calculating standard free energies of transfer (ΔG°_{tr}) from NaCl-H₂O to urea-NaCl-H₂O. These values are shown in Table 4 and are calculated from equation 6 (Nozaki & Tanford, 1963)

$$\Delta G^{\circ}_{tr} = -RT \ln \frac{S(\text{urea/NaCl})}{S(\text{NaCl})} + RT \ln \frac{N(\text{urea/NaCl})}{N(\text{NaCl})} \quad \dots \quad (6)$$

$S(\text{urea/NaCl})$ and $S(\text{NaCl})$ are concentrations (mol litre⁻¹) of methyl paraben in (urea-NaCl-H₂O) and (NaCl-H₂O) solvents respectively and $N(\text{urea/NaCl})$ and $N(\text{NaCl})$ are total numbers of mol, including H₂O, in the respective solutions. ΔG°_{tr}

Table 4. *Free energies of transfer of methyl paraben from NaCl-H₂O solvents to urea-NaCl-H₂O solvents (kJ mol⁻¹).*

Mol NaCl	Urea kmol m ⁻³				
	1	2	3	4	5
	$-\Delta G^{\circ}_{tr}$	$-\Delta G^{\circ}_{tr}$	$-\Delta G^{\circ}_{tr}$	$-\Delta G^{\circ}_{tr}$	$-\Delta G^{\circ}_{tr}$
1	0.86	1.54	2.18	2.81	3.36
2	0.86	1.69	2.34	3.10	3.65
3	0.91	1.91	2.66	3.37	4.09
4	1.47	2.32	3.08	3.90	4.57
5	1.37	2.67	3.51	4.33	5.21

is the free energy of transfer from NaCl-H₂O to urea-NaCl-H₂O at the same mol fraction, and at the limit of infinite dilution.

Inspection of ΔG^0_{tr} values shows that the process, as expected, is spontaneous and becomes more so as the concentration of urea increases. It can also be seen that for any NaCl-urea solvent system the free energy change for the transfer of methyl paraben, per mol of urea added ($\Delta G^0_{tr}/(M \text{ urea})$), decreases as the concentration of urea increases. This would indicate that the effect of urea on NaCl-H₂O is greater at lower urea concentrations, and a drastic breakdown of NaCl-H₂O structure occurs at lower urea concentrations, thus facilitating relatively large increases in the solubility of methyl paraben. Since the solvation of NaCl by water would be more pronounced at higher NaCl concentrations, the effect of urea would be expected to be more potent in solvents containing larger concentrations of NaCl. At higher urea concentrations ($\Delta G^0_{tr}/(M \text{ urea})$) is less and this may be the result of the overall decrease in the numbers of water molecules available. Unfortunately, no enthalpy or entropy of transfer values are available for these systems.

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