Influence of Copper(II) Salts on the Solubility of Caffeine in Water: Complex Formation and the Salting-out Effect

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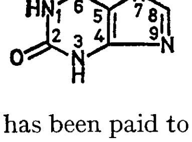
Saturation curves of caffeine monohydrate cf·H_2O and of several complex compounds in the systems H_2O–$Cu[NO_3]_2$–cf (I) and H_2O–$CuCl_2$–cf (II) have been determined at various temperatures. Solubility curves of cf·H_2O in solutions of $Cu[ClO_4]_2$ (III) and $Cu[SO_4]$ (IV) have also been examined. A regular variation in behaviour of the four systems is observed. A model is proposed and empirical expressions for (I) and (II) are calculated which take into account two different factors affecting the solubilization of caffeine by dilute solutions of copper(II) salts, *i.e.* complex-formation equilibria and the salting-out effect. A qualitatively very good agreement between the model and the experimental data is found. Thermodynamic quantities are also calculated.

THE behaviour of 1,3,7-trimethylxanthine [caffeine (cf)] as a unidentate ligand through the N^9 nitrogen atom has been pointed out and studied in our previous papers.



Particular attention has been paid to some co-ordination compounds of copper(II) which we synthesized[1,2] and investigated by means of various techniques such as *X*-ray diffraction,[3,4] single-crystal absorption spectroscopy with polarized light at 4.2 K,[5] and measurements of paramagnetic anisotropy.[6] The electronic structure of caffeine and its modification when co-ordinated has been studied theoretically by carrying out semiempirical LCAO MO calculations according to the scheme CNDO/2.[7]

We have now examined the phase diagrams of the systems H_2O–CuX_2–cf (X = NO_3 or Cl) and the influence

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[1] M. Biagini Cingi and L. Oleari, *Atti* 7 *Convegno Nazionale di Chimica Inorganica*, Pesaro, 1974, D11.

[2] M. Biagini Cingi and L. Oleari, *Atti* 8 *Convegno Nazionale di Chimica Inorganica*, Jesolo, 1975, D7.

[3] M. Biagini Cingi, A. Chiesi Villa, A. Gaetani Manfredotti, and C. Guastini, *Crystal Struct. Comm.*, 1972, **1**, 363.

[4] G. Bandoli, M. Biagini Cingi, D. A. Clemente, and G. Rizzardi, *Inorg. Chim. Acta*, 1976, **20**, 71.

[5] M. Biagini Cingi, R. Borromei, and L. Oleari, *Inorg. Chim. Acta*, 1974, **11**, 167.

[6] M. Biagini Cingi, A. Sotgiu, and E. Tondello, *Atti Accad. Peloritana*, 1974, **54**, 129.

[7] M. Biagini Cingi, G. Condorelli, I. Fragalà, and E. Tondello, *Atti Accad. Peloritana*, 1974, **54**, 113.

of other copper(II) salts on the solubility of caffeine in water. In one paper[8] it was reported that some stable compounds of general formula $MX_2 \cdot 2cf \cdot 8H_2O$ (M = Mg, Mn, Co, or Ni; X = I, ClO_4, or SCN) were prepared as crystals by evaporating aqueous solutions containing caffeine and the metal salt in the ratio 1 : 6—8. However, we have repeated the preparation in the cases of M = Mn, Co, or Ni and X = I and have obtained crystalline compounds of formula $MI_2 \cdot cf \cdot 2H_2O$, which correspond to lower contents of both caffeine and water. It has also been reported that the solubility of caffeine in water, which is rather poor,[9,10] also increases to a noticeable extent on addition of alkali-metal benzoates, citrates, salicylates, *etc.* Moreover, in some solutions containing caffeine and organic sodium salts the formation of 1 : 1 complex species has been proposed.[11]

EXPERIMENTAL AND RESULTS

The saturation curves for the systems H_2O–CuX_2–cf (X = NO_3 or Cl) were investigated at various temperatures. For each sample the composition of the different phases was determined by means of conventional analytical methods (caffeine by u.v. spectrophotometry[12] and copper by atomic absorption) after attainment of equilibrium in a thermostatted bath with continuous shaking.

The system H_2O–$Cu[NO_3]_2$–cf (I) was examined at 20.5, 34.8, and 47.4 °C. The diagram relative to 34.8 °C is given in Figure 1. For the other temperatures the saturation curve shifted but maintained the same shape. Along the line AB in Figure 1 the solution is saturated with caffeine monohydrate. The broken line between the points B and C indicates a range of rather easy supersaturation. The precipitate in this interval is slimy, light blue, and unstable. It retains water easily and is very difficult to characterize because it changes rapidly on even short exposure either to the air or to radiation. On the basis of the composition of the initial mixture and of that of the liquid phase the approximate formula $Cu[NO_3]_2 \cdot cf \cdot (8 \pm 1)H_2O$ is suggested. Also in ref. 8 it is reported that, besides stable crystalline compounds containing eight water molecules, a 'crystal slime' was obtained at higher temperatures. The slimy phase which precipitates in our preparations, already at 20.5 °C, loses water by simple exposure to the air giving the corresponding green crystalline trihydrate.

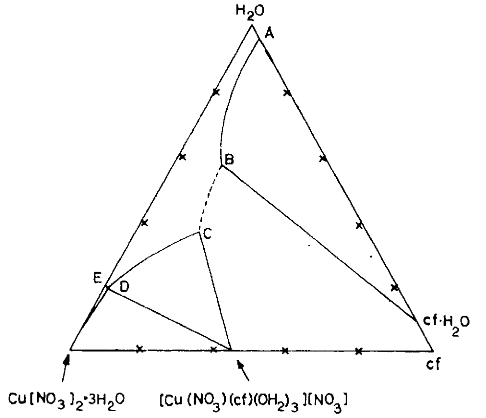

FIGURE 1 Solubility diagram for system (I) at 34.8 °C

Along the line AB the dilute solutions are light blue just like the aqueous solutions of Cu^{II}. Near point B this colour becomes turquoise and then green after point C. The precipitate is green along the curve CD, corresponding to triaqua(caffeine)nitratocopper(II) nitrate,[3] and blue along the line DE, corresponding to copper(II) nitrate hexa- or trihydrate according to whether the temperature is greater or less than 24.5 °C respectively. For the temperature range examined any saturation line can be divided into four intervals corresponding to four different solid phases:

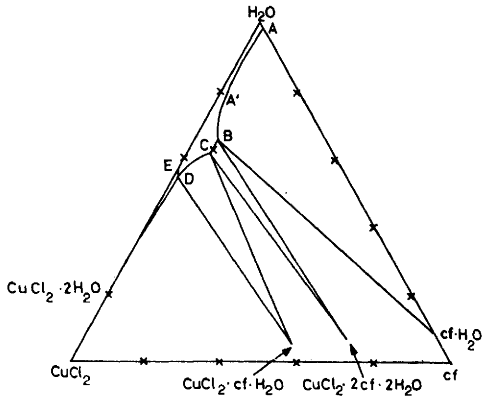

FIGURE 2 Solubility diagram for system (II) at 26.0 °C

Line	Colour of solution	Solid phase	Colour of solid phase
AB	Light blue	$cf \cdot H_2O$	White
BC	Turquoise	$Cu[NO_3]_2 \cdot cf \cdot (8 \pm 1)H_2O$	Light blue
CD	Green	$[Cu(NO_3)(cf)(OH_2)_3][NO_3]$	Green
DE	Green	$Cu[NO_3]_2 \cdot xH_2O$	Blue

The variation of the colour of the liquid phase with composition shows that several complex ions are present besides aquacopper(II) and triaqua(caffeine)nitratocopper(II). In fact, the u.v. spectra of the green solutions (range CD) cannot be expressed as a linear combination of the spectra of the above species.

The system H_2O–$CuCl_2$–cf (II) was examined at 26.0, 36.2, and 48.0 °C. The saturation line corresponding to 26.0 °C is presented in Figure 2. At the other temperatures, apart from the shift, the diagrams were practically the same. Line AB in Figure 2 corresponds to the saturation line of caffeine monohydrate. It is evident that the solubility of caffeine is nearly unchanged up to *ca.* 1.5 mol kg^{-1} of copper salt, whereas in the previous system it had already increased at very low copper salt concentrations. The colour of the liquid phase changes from light blue to green at point A′. The interval BC corresponds to the saturation line of $CuCl_2 \cdot cf \cdot H_2O$ which gives both orthorhombic and monoclinic crystals. The *X*-ray structural analysis of the orthorhombic form has been carried out.[4] Along the line CD the solution is saturated with a compound richer in caffeine having a formula $CuCl_2 \cdot 2cf \cdot 2H_2O$. *X*-Ray investigation of this compound is in progress. Finally, along the line DE the solution is saturated with copper(II)

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[8] F. Calzolari, *Gazzetta*, 1912, **42**, 15.

[9] A. Seidell, 'Solubilities of Inorganic and Organic Compounds,' 2nd edn, New York, 1919, p. 186.

[10] A. Cesàro, E. Russo, and V. Crescenzi, *J. Phys. Chem.*, 1976, **80**, 335.

[11] P. Rohdewald and M. Baumeister, *J. Pharm. Pharmacol.*, 1969, **21**, 867.

[12] H. Hadorn and K. Zürcher, *Mitt. Gibiete Hyg.*, 1965, **56**, 17.

chloride di- or mono-hydrate, according to whether the temperature is less or greater than 42.2 °C respectively.

In summary, for the temperature range investigated, we have four different intervals corresponding to four different crystalline precipitates:

Line	Colour of solution	Solid phase	Colour of solid phase
AA′	Light blue	$\mathrm{cf{\cdot}H_2O}$	White
A′B	Green	$\mathrm{cf{\cdot}H_2O}$	White
BC	Green	$\mathrm{CuCl_2{\cdot}cf{\cdot}H_2O}$	Green
CD	Green	$\mathrm{CuCl_2{\cdot}2cf{\cdot}2H_2O}$	Green
DE	Green	$\mathrm{CuCl_2{\cdot}}x\mathrm{H_2O}$	Green

The observed behaviour of the above two systems suggested the extension of the investigations to other solutions of copper(II) salts. Thus measurements were carried out in aqueous copper(II) perchlorate solutions [system (III)] at one temperature and with copper salt concentrations in the range 0—0.9 mol kg^{-1}. The results are summarized in Figure 3. It is evident that the solubility of caffeine increases with the copper salt content much more rapidly than in systems (I) and (II). Measurements were also made in aqueous copper(II) sulphate solutions [system (IV)] at one temperature and the range of the copper salt concentration was 0—1.3 mol kg^{-1}. The results are collected in Figure 3. It is evident that in this case an opposite effect occurs, *i.e.* the solubility of caffeine decreases with the copper salt content.

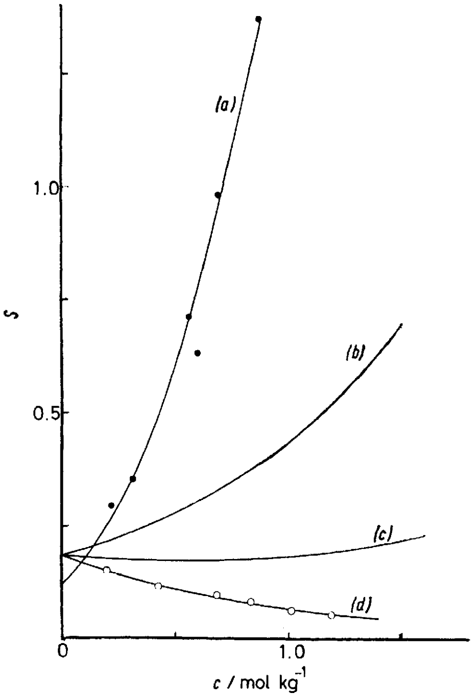

FIGURE 3 Solubility of caffeine in dilute solutions of (*a*) $\mathrm{Cu[ClO_4]_2}$ at 27.5 °C, (*b*) $\mathrm{Cu[NO_3]_2}$, (*c*) $\mathrm{CuCl_2}$, and (*d*) $\mathrm{Cu[SO_4]}$ at 36.2 °C. Curves (*b*) and (*c*) were calculated by means of equations (5) and (6)

DISCUSSION

Figures 1 and 2 show that copper(II) nitrate and copper(II) chloride give crystalline compounds containing co-ordinated caffeine. As previously pointed out, the colour variations of the liquid phases, and more specifically the absorption spectra, show clearly that several complex-formation equilibria take place in solution. It follows that, in order to interpret the solubility curves, it is necessary to take the various equilibria into account, besides the other kinds of interaction. Since the problem is rather complicated, we limit our interest to the intervals of the solubility curves where the concentrations of the different species are low. We have given particular attention to the study of the connection between caffeine solubility and copper salt concentration for solutions of low salt content, *i.e.* the lines AB in Figures 1 and 2.

On the hypothesis that the variation in caffeine solubility, for dilute solutions of the copper salt, would depend on one complex-formation equilibrium alone, according to equilibrium (1),* a linear relation would be

$$[\mathrm{Cu(OH_2)}_n]^{2+} + \mathrm{cf{\cdot}H_2O} \overset{k}{\rightleftharpoons} [\mathrm{Cu(cf)(OH_2)}_{n-m}]^{2+} + (m+1)\mathrm{H_2O};\ K = \frac{xr}{(c-x)S\gamma} \qquad (1)$$

$$S\gamma = S_0\gamma_0 \qquad (2)$$

expected between the caffeine solubility S and the copper salt concentration c according to equation (3) where

$$S = S_0 + x = S_0 + [KS_0\gamma_0/(r + KS_0\gamma_0)]c \qquad (3)$$

$x = [KS_0\gamma_0/(r + KS_0\gamma_0)]c$ is the concentration of the co-ordinated caffeine. In particular, since $\lim\limits_{c\to 0} r = 1$, and K is independent of the nature of the anion, the gradient of the caffeine solubility line $(\mathrm{d}S/\mathrm{d}c)_{c=0} = KS_0\gamma_0/(1 + KS_0\gamma_0)$ should be the same whatever the nature of the copper(II) salt. In Figure 3 it is evident that this is not the case, and other interactions have to be taken into account.

Other workers [13-15] who have studied the dependence of the solubility of organic substances on the presence of inorganic salts in aqueous solutions have introduced the term known as ' salting out ' or ' salting in ' to account for the various kinds of interactions. Salting out is rather common and corresponds to the case where the solubility of the organic substance decreases with increasing concentration of the salt. Salting in is less common and corresponds to the opposite, *i.e.* the solubility of the organic compound increases with increasing salt concentration.

Experimental data and then theoretical models [13-15] have shown that a linear relation exists between log (S_0/S) and c (the concentration of the salt) when c is low [equation (4)]:[13] k is positive in the salting-out and

$$\log (S_0/S) = kc \qquad (4)$$

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* Where $x = [\mathrm{Cu(cf)(OH_2)}_{n-m}{}^{2+}]$, $c - x = [\mathrm{Cu(OH_2)}_n{}^{2+}]$, c = copper(II) salt concentration, S and S_0 = caffeine solubilities in aqueous solution of the copper(II) salt and in pure water,† γ and γ_0 = corresponding caffeine activity coefficients, and r = ratio of the activity coefficients of $[\mathrm{Cu(cf)(OH_2)}_{n-m}]^{2+}$ and $[\mathrm{Cu(OH_2)}_n]^{2+}$.

† Values previously calculated [1] for S_0 on the basis of the solubility data of Seidell, have been recalculated using the values of Cesàro *et al.*[10] and Seidell [9] within the temperature range 20—50 °C using the relation $\log S_0 = 5.5110 - (1\,932/T)$.

[13] G. N. Lewis and M. Randall, ' Thermodynamics,' 2nd edn., McGraw-Hill, Novaro, 1965, p. 584.

[14] L. Brewer, T. R. Simonson, and L. K. J. Tong, *J. Phys. Chem.*, 1961, **65**, 420.

[15] W. F. McDevit and F. A. Long, *J. Amer. Chem. Soc.*, 1952, **74**, 1773.

negative in the salting-in effect. For a given organic substance, k depends on the nature of the salt and hence on its cation and anion. It is clear that for a given series of salts of the same cation an order of increasing salting-out or salting-in effect can be established, *e.g.*[14,15] $Na[ClO_4] < Na[NO_3] < NaCl$ (for mesityl oxide) and $Na[ClO_4] < Na[NO_3] < NaCl < Na_2[SO_4]$ (for benzene). This order generally does not change with the nature of the cation and is substantially the same as that of the hydration energies of the anions. It holds also for series of salts of the same anion and different cations. It must be pointed out that the formation of complexes in rather dilute solution corresponds to a salting-in effect with k independent of the nature of the anion.

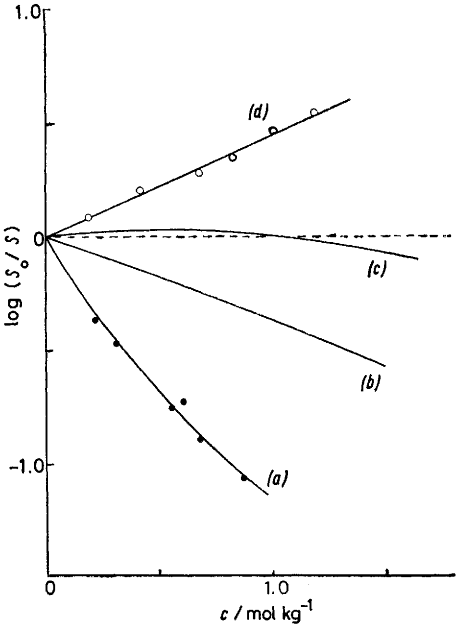

FIGURE 4 Plots of $\log(S_0/S)$ against c. See Figure 3 for details

By plotting $\log(S_0/S)$ against c (Figure 4), system (I) gives a curve approximating to a straight line of negative gradient for $c < 1.5$ mol kg^{-1}. The empirical equation (5) has been calculated by a least-squares method and

$$\log(S_0/S) = [0.7535 - (340.8/T)]c + [0.3583 - (118.2/T)]c^2 \quad (5)$$

fits the $\log(S_0/S)$ data for $c < 1.8$ mol kg^{-1} at 20.5, 34.8, and 47.4 °C with a standard deviation of 0.027. For system (II), the curve approximates to a straight line only for $c < 0.4$ mol kg^{-1} and the gradient is almost zero or slightly positive. When c increases the gradient changes and $\log(S_0/S)$ becomes negative. Here also an empirical equation has been found by the least-squares method; it fits the $\log(S_0/S)$ data for $c < 1.8$ mol kg^{-1} at 26.0, 36.2, and 48.0 °C with a standard deviation of 0.019. Finally, $\log(S_0/S)$ is always negative (salting in)

$$\log(S_0/S) = [-0.8173 + (287.3/T)]c + [0.6652 - (238.5/T)]c^2 \quad (6)$$

for system (III) and the curve has a more negative gradient than in the case of (I), whereas for (IV) both $\log(S_0/S)$ and the gradient are positive (salting out).

In Figures 3 and 4 the experimental curves for system (III) at 27.5 °C, (IV) at 36.2 °C, and (I) and (II) at 36.2 °C calculated by means of equations (5) and (6) are reported. It is evident that there is a regular variation of behaviour; the order of the effect is exactly the same as that obtained for the corresponding sodium salts with respect to mesityl oxide and benzene, as previously reported: $Cu[ClO_4]_2 < Cu[NO_3]_2 < CuCl_2 < Cu[SO_4]$. Nevertheless there are substantial differences: (*i*) in our case, at low salt concentration, a trend from a salting-in to a salting-out effect occurs; (*ii*) at higher concentrations, apart from system (IV), the salting-in effect prevails, *i.e.* the caffeine solubility is greater than that in pure water.

On the basis of these considerations and on the evidence from the absorption spectra of the presence of caffeine copper(II) complexes in solution, the behaviour of the above systems has been examined by means of a model in which a $[Cu(cf)(OH_2)_{n-m}]^{2+}$-formation equilibrium and a salting-out effect, taking other kinds of interaction into account, are considered simultaneously. Complex species $[Cu(cf)_z(OH_2)_v]$ ($z > 1$) have been neglected because, if present, their concentrations at low contents of copper(II) salt would be extremely small.

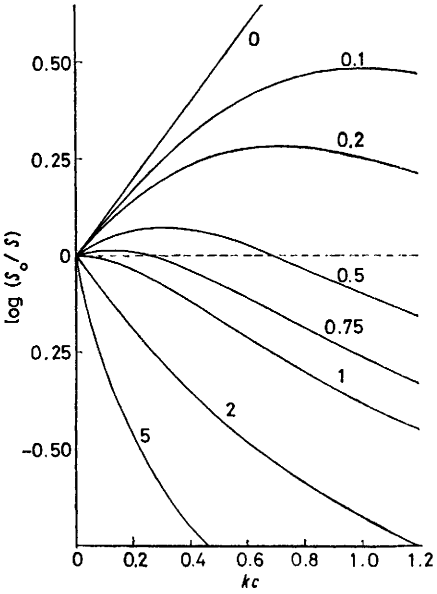

FIGURE 5 Plots of $\log(S_0/S)$ against c corresponding to several values of the quantity $\nu = K\gamma_0/[2.303\,(1 + KS_0\gamma_0)k]$

According to this model, the caffeine solubility is expressed by relation (7) which is equal to (3) but for the

$$S = S_0 10^{-kc} + x = S_0 10^{-kc} + [KS_0\gamma_0/(r + KS_0\gamma_0)]c \quad (7)$$

10^{-kc} factor which takes the salting-out effect into account, as specified above.

$$\log(S_0/S) = -\log\{10^{-kc} + [K\gamma_0/(r + KS_0\gamma_0)]c\} \quad (8)$$

Equation (7) may be rewritten as (8), and in Figure 5 a family of curves of log (S_0/S) against kc with $r = 1$ is reported which correspond to several values of the quantity $\nu = K\gamma_0/[2.303(1 + KS_0\gamma_0)k]$. We have clearly a set of behaviour types very similar to those experimentally observed. More precisely, log (S_0/S) is always negative when $\nu \geqslant 1$, *i.e.* $K\gamma_0/(1 + KS_0\gamma_0) > 2.303k$, whereas when $\nu < 1$ it is first positive for appropriately low concentrations and then negative for higher concentrations of the copper salt. Quantitatively, a check is rather difficult because we do not know how r depends on c.

Conclusions.—From the qualitative observed behaviour, on the basis of equation (7) the following order of k values can be written: $Cu[ClO_4]_2 < Cu[NO_3]_2 < CuCl_2 < Cu[SO_4]$. In particular, from the observed gradients of the curves of log (S_0/S) against c and the first derivative of equation (7) when $c = 0$ $(\lim_{c \to 0} r = 1)$, we find that (*a*), in systems (III) and (I), $k \ll \mu$, (*b*) in system (II) $k \approx \mu$, (*c*) in system (IV) $k \gg \mu$, where $\mu = K\gamma_0/[2.303(1 + KS_0\gamma_0)]$.

The above sequence can be justified by the fact that two different effects are considered in our model: complex formation and salting out. Whereas the first effect, substantially independent of the nature of the anion, is present in the various systems to the same extent, the second is remarkably affected by the nature of the anion. In fact, salting out has to be connected with the interaction between the organic solute molecules and the hydration spheres of the ions. Clearly this interaction is greater for ions having higher hydration energy. The hydration energy of spherical ions, or of those which can be considered approximately as such, is proportional to the square of the charge and inversely proportional to the radius.[16]

In the cases considered here the salting-out order depends essentially on the anions. For $[ClO_4]^-$, $[NO_3]^-$, and Cl^-, all having the same charge, the order of average radius is $[ClO_4]^- > [NO_3]^- > Cl^-$. It follows that the hydration energies and therefore the salting-out effects must have an exactly inverse order. Finally, the $[SO_4]^{2-}$ ion, which has twice the charge of the other anions, has a much higher hydration energy (four times as large for equal ionic radii); it is even higher than that of the Cl^- ion, which has a smaller radius, and consequently shows the greatest salting-out effect.

Calculations of the hydration enthalpies of the anions $[SO_4]^{2-}$, $[CrO_4]^{2-}$, $[ClO_4]^-$, and $[NO_3]^-$ are in progress at the Institute of Physical Chemistry at our University. Preliminary data give the following hydration energies: $[ClO_4]^-$, -60; $[NO_3]^-$, -74; Cl^-, -91.8;[16] and $[SO_4]^{2-}$, -271 kcal mol^{-1} (H^+, -257 kcal mol^{-1} as reference; 1 cal = 4.184 J).

From the empirical expressions (5) and (6) it is possible to comment on the thermodynamics. In fact, for solutions saturated with caffeine monohydrate, $\gamma S = \gamma_0 S_0$ holds. It follows that the salting-out expressions (5) and (6), from a thermodynamic point of view, represent the behaviour of the logarithm of the activity coefficient with respect to that in pure water [equation (9)]. Moreover,

$$\log \gamma - \log \gamma_0 = \log (S_0/S) \tag{9}$$

if $S(\partial \ln\gamma/\partial S) \ll 1$ and $S_0(\partial \ln\gamma_0/\partial S_0) \ll 1$ (likely assumptions in our case, S and S_0 being very small), from expression (9) we obtain (10) where H_{cf} is the partial

$$\frac{d \log (S_0/S)}{d\,(1/T)} \simeq \frac{\partial\,(\log \gamma - \log \gamma_0)}{\partial\,(1/T)} = \frac{H_{cf}}{2.303\,R} \tag{10}$$

molar enthalpy of caffeine with the reference state being the saturated solution in pure water at the same temperature. Therefore, from (5) and (6) we can write $H_{cf} = -1\,559c - 541c^2$ for system (I) and $1\,314c - 1\,091c^2$ cal mol^{-1} for system (II). It is evident that H_{cf} represents the partial molar enthalpy contribution relative to the effect on the caffeine of the copper salt. In particular, H_{cf} is always negative for system (I), whereas it is positive when $c < 1.2$ mol kg^{-1} and negative for higher values of c for system (II). This result agrees well with our previous considerations concerning both the hydration enthalpies of the anions and the complex-formation equilibria.

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[7/153 *Received, 31st January,* 1977]

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[16] C. S. G. Phillips and R. J. P. Williams, 'Inorganic Chemistry,' 1st edn., Clarendon Press, Oxford, 1965, pp. 160—161.