Heats of reaction and stability of caffeine complexes

It is generally considered that the solubilization of caffeine in the presence of the sodium salts of aromatic acids is associated with the formation of complexes. Little is known about the stability constants and the enthalpies of formation of these complexes.

Since caffeine is self-associated in aqueous solutions, it was necessary to determine the stoichiometric ratio of complexes in a relatively low concentration range. For these determinations the lowering of vapour pressure was measured. The apparatus used* was similar to the osmometer model manufactured by Mechrolab Inc. The galvanometer readings are proportional to the change in resistance and depend on the activities of the dissolved substances. For the determination of the stoichiometric ratio of the caffeine complexes the continuous variation method of Job (1928) was used. The changes of resistance were first determined for a number of concentrations from 0·05 to 0·2 mol litre^{-1} of caffeine or sodium salt. These values were subtracted from those obtained for mixtures of constant molarity (0·2 mol litre^{-1}) of caffeine and the sodium salts of aromatic acids.

If we assume that complexation occurs in these systems, the number of individual particles decreases and consequently the scale readings decrease. Fig. 1A shows the differences in the scale readings between the additive (theoretical) values and the values obtained from the mixtures. The differences indicated a stoichiometric ratio of 1 : 1 for these particular examples of caffeine–Na-benzoate and caffeine–Na-salicylate. The decrease in the scale readings (or the number of particles) is greater for the caffeine–Na-salicylate complex than for caffeine–Na-benzoate, which is preliminary evidence for the greater stability of the salicylate complex.

In the next part of our investigation we determined the molar enthalpy of formation of a number of caffeine complexes by a calorimetric method. The calorimetric determinations were made with the LKB 8700-calorimetry-system (described by Sunner & Wadsö, 1959) at 25°.

The osmometric measurements indicated that, for a molar ratio of 1 : 10, only a small part of the caffeine was complexed. The determination of the molar heat of formation is possible only if a well-defined amount of caffeine is completely bound in the complex. Therefore we used a caffeine–salt ratio of 1 : 1000 in the first series of experiments and a ratio of 1 : 2000 in the second series. The self-association of caffeine can be neglected in the concentration range from *ca* $5 \cdot 10^{-4}$ mol litre^{-1}.

The heat value Q, obtained after mixing a caffeine solution and a salt solution, is composed of the heat of reaction Q_1 and the heats of dilution of the caffeine solution Q_2 and the salt solution Q_3 (eqn 1).

$$Q = Q_1 - (Q_2 + Q_3) \quad .. \quad .. \quad .. \quad .. \quad (1)$$

Q_2 and Q_3 were measured when adding defined amounts of water to the caffeine and the salt solution so that the heat of reaction could be computed. The heats of reaction were then converted to the molar heats of formation by dividing by the number of moles.

In this manner the molar enthalpies of formation were determined for the caffeine–Na-benzoate complex. We found 16·65 kJ mol^{-1} for a molar ratio of 1 : 1000 and 16·40 kJ mol^{-1} for the ratio 1 : 2000. The difference is not significant. The good agreement of the values obtained for the different molar ratios demonstrates the formation of only 1 : 1 complexes in the concentration range used. The reported value of 13·8 kJ mol^{-1} of Higuchi & Zuck (1953) is in close agreement with our results.

* Dampfdruckosmometer, manufactured by Dr. ing. Knauer, West-Berlin.

In Table 1 the molar enthalpies of formation for different caffeine–Na-salts are listed. The enthalpies vary between 15–29 kJ mol^{-1}, indicating weak, but specific interactions for the different sodium salts of the aromatic acids.

The stability constant for the caffeine–salt complexes can be expressed as:

$$K_c = \frac{[\text{caffeine–salt}]}{[\text{caffeine-caffeine–salt}]\,[\text{salt-caffeine–salt}]}$$

Since the starting concentrations are known, the complexed concentrations can be determined in the following way. With the aid of the molar enthalpies of formation the concentration of the complex for any concentration ratio of the complexing compounds can be computed by measuring the heat of reaction.

Table 1. *The molar enthalpies of formation and the K_c-values for the caffeine complexes of the sodium salts of the aromatic acids*

Salt	ΔH (kJ)	ΔH (kcal)	K_c-values (25°) for the concentration ratio caffeine/salt litre mol^{-1} 1:4	1:8	1:12	1:10	1:20	1:30	Mean value
Na-benzoate	16·64a	3·974	5·1	5·2	5·4	5·2	5·3	5·2	5·2
	16·39b	3·916							
Na-*o*-hydroxybenzoate	29·25a	6·986	13·2	13·8	13·8	13·1	13·6	13·7	13·5
	29·34b	7·008							
Na-*p*-hydroxybenzoate	27·27a	6·514	7·5	7·6	7·6	7·3	7·6	7·6	7·5
	27·38b	6·540							
Na-*o*-aminobenzoate ..	20·20a	4·826	8·3	4·3	4·4				4·3
	20·45b	4·888							
Na-*p*-aminobenzoate ..	21·83a	5·214	4·3	5·3	5·3	5·0	5·4	5·4	5·2
	21·82b	5·212							
Na-*m*-nitrobenzoate ..	15·56a	3·712	5·0	8·5	8·4	8·3	8·2		8·2
	15·00b	3·584							

a = molar ratio 1:1000, b = 1:2000.

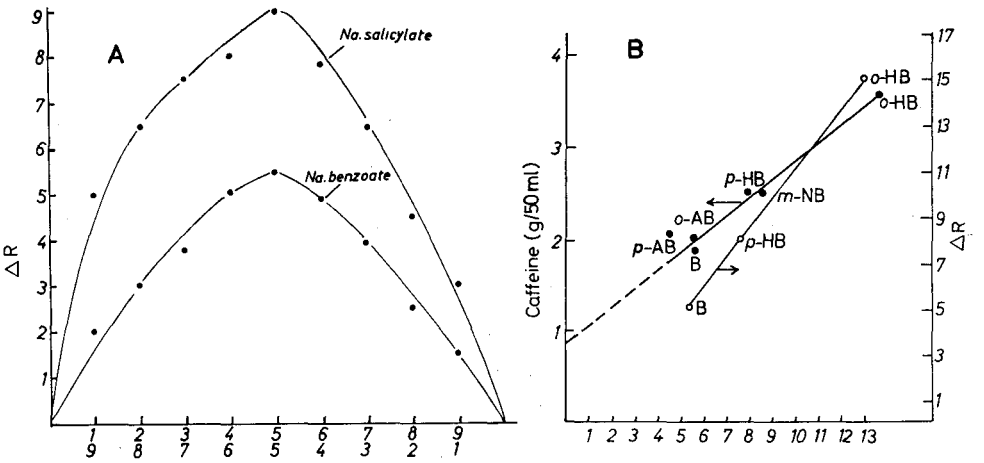

FIG. 1A. Differences in scale readings (45°) between theoretical and experimental values for caffeine-salt mixtures. Abscissa: Mol ratio salt (upper figures): caffeine (lower figures).

B. Relationship between (●—●) the ΔR values for equimolar mixtures of caffeine-salt and their K_c-values and ○—○ between the solubility of caffeine in 0·5M salt solutions (25°) and the K_c-values. Abscissa: K_c litre mol^{-1}.

A salt solution was added stepwise to a defined caffeine solution and after each addition the heat of reaction was determined. To eliminate the effect of the heats of dilution, the corrections were made as described above. In a second run the caffeine concentration was changed in order to produce a different ratio of caffeine–salt concentration.

The stability constants for the caffeine complexes (Table 1) are independent of the caffeine concentration, which is further evidence that the stoichiometric ratio 1 : 1 is correct.

The decrease in the number of free molecules detected by the isopiestic measurement for a given salt–caffeine mixture must be correlated with the stability of this complex. There is a linear relation between ΔR and the K_c-values (Fig. 1B), demonstrating the suitability of both methods for the determination of the stability of such systems.

Fig. 1B also shows that the amount of dissolved caffeine in a 0·5M salt solution is linearly dependent on the stability constants. Extrapolation to a stability constant of zero leads to the correct value of the solubility of caffeine in water. The results clearly show that the stability of the caffeine–salt complexes is the most important factor for the solubilization of caffeine by these substances.

Institut für pharmazeutische Chemie,
Westfälische Wilhelms-Universitat Münster,
Münster, BRD, Germany.

P. ROHDEWALD
M. BAUMEISTER

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Toxicity of ethanol-barbiturate mixtures

It is frequently stated that ethanol and barbiturates potentiate each other. Wiberg, Coldwell & Trenholm (1969) have published observations which they are inclined to interpret as support for this view. In our opinion, however, their data should be interpreted differently. This can be demonstrated by plotting isobols (Loewe, 1953, 1957). These are lines on a combined dose diagram connecting those dose pairs which are equi-effective in producing a defined pharmacological effect.

Fig. 1 shows Wiberg, Coldwell and Trenholm's data on acute toxicity of ethanol-barbiturate mixtures in male rats, calculated from the original mortality figures kindly provided by the authors. In each case the line indicates no more than a simple additive effect; there is no suggestion of potentiation.

Their findings on the prolongation of sleeping time might be explained by potentiation but might equally well be due to summation. The fact that two inactive doses produce a marked effect when given in combination does not necessarily indicate potentiation; summation could produce the same result, especially if the log dose-response curves were steep as they appear to be for ethanol and the barbiturates. Unfortunately, the data are insufficient to enable isobols to be constructed. The authors have used threshold or subthreshold doses of barbiturates in combination with ineffective doses of ethanol. If they had tested combinations of half these doses, or, alternatively, recorded the effects of double doses of either drug alone, summation and potentiation might have been distinguished.