Thermochimica Acta, 69 (1983) 235–252
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

Calorimetric Investigation of Aqueous Caffeine Solutions and Molecular Association of Caffeine

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Abstract

Measurements of the enthalpy of solution of β-caffeine in water as a function of concentration at four temperatures are presented. Using our measurements of the heat capacity of solid β-caffeine we obtain the partial molar heat capacity of caffeine in solution. With the aid of osmotic coefficient measurements reported by other workers, the association constant and association enthalpy of caffeine are also calculated from the data measured.

1. Introduction

Caffeine and other purines have been known since several years to undergo molecular self-association in solution ("base-stacking") [1 - 3]. Self-association is also one reason for the remarkably high, 200-fold increase in caffeine solubility between 0 and 100°C, see Fig. 1. In addition, purine compounds have a strong tendency for association with a variety of compounds.

During an investigation programme of the thermodynamic properties

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0040-6031/83/$03.00

of caffeine and aqueous caffeine solutions [4 - 9] the enthalpy of dehydration of caffeine hydrate was obtained from the enthalpies of solution of the hydrated and dehydrated forms of caffeine [5]. Remarkable differences have been found between our and literature values for the enthalpies of solution. One possible explanation for these discrepancies is the existence of different polymorphs of anhydrous caffeine [4,10,11], another may be related to the considerable concentration dependence of the solution enthalpy of caffeine in water even at low concentrations, which is due to the "base-stacking" mentioned above. The aim of the present investigation is the exact determination of the enthalpy of solution of the well defined low temperature polymorph of caffeine (β-caffeine) in water as a function of concentration and temperature. The results are used to derive data of the partial molar heat capacity of dissolved caffeine, the association constant and the association enthalpy and also give explanations for the above mentioned discrepancies.

2. Experimental

Materials:

Caffeine (DAB 7, 99.93 mol-%) was twice recrystallized from double-distilled water and desiccated to give a 99.97 mol-% product as checked by DSC [6]. Tempering under argon just below its transition temperature of 141 °C yields β-caffeine, which is the only stable polymorph up to this temperature [4,6]. The completion of phase transformation was also checked by DSC. The melting point of the purified caffeine was 236.0±0.2 °C [4,6]. The water used was double-distilled in an all quartz equipment.

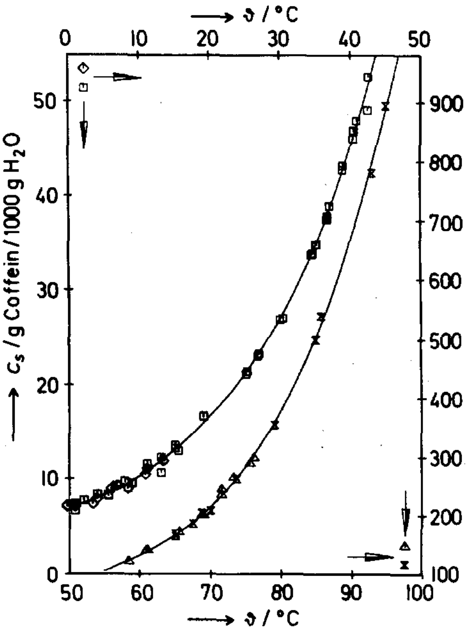
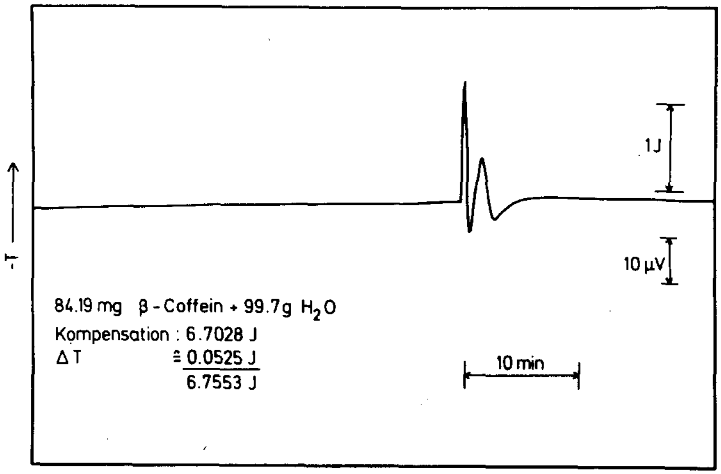


Fig. 1:

Solubility of caffeine in water [9,12]. Upper curve (caffeine hydrate) corresponds with the left and top coordinate, lower curve (β-caffeine) corresponds with the right and bottom coordinate



ig. 2: A calorimetric measurement of the dissolution of β-caffeine in water with almost complete electrical compensation of the heat of solution

Procedure:

Heats of solution were determined in an isoperibolic precision calorimeter (LKB 8700-1) with 100 cm^3 and 25 cm^3 glass reaction vessels, depending on concentration. β-caffeine samples were weighed into thin-walled, breakable 1 cm^3 glass ampoules with an accuracy of ±0.01 mg and were sealed with a small silicon rubber stopper and carbowax. The amount of water was obtained by precision pipettes to about ±0,1 %. Temperatures were controlled to within ±0.002 K (8 hours) and could be determined by the built in thermistor, calibrated against a certified mercury in glass thermometer with an uncertainty of ±0.02 K. The temperature/time curve was registrated with a resolution of 0.0001 K or better by plotting the resistance of the thermistor on a strip chart recorder. Electrical calibrations could be done with an accuracy of at least 0.01 % (current, resistance, voltage).

The experiments were run in a compensating manner: after the initial period the ampoule was crashed and the (endothermic) heat of solution was nearly balanced by appropriate amounts of electrical heating. About 98 % the temperature drop could be compensated, the residual difference was taken care of by calculation, see e. g. Fig. 2. Every experiment was preceded and followed by an electrical calibration. In this way, corrections due to heat loss of the reaction vessel or to inaccurate water filling of the vessel are negligable, but corrections for evaporation of water into the incompletely filled ampoules had to be made.

The total accuracy of the measurements is believed to be at least ±0.5 %, without regard to the special problems arising from the system caffeine/water. These are: 1. long dissolution times of caffeine (sometimes up to 10 minutes), 2. increasing uncertainties at concentrations below 5 mmol kg^{-1} due to (irreproducibly changing) heat evolved by crashing the ampoule and to variation of the heat of stirring by the broken ampoule. The measuring procedure was checked with KCl samples (Merck, SUPRAPUR) at 25.00 °C. The result $\Delta H^{\circ}_{is} = 17.52 \pm 0.06$ kJ mol^{-1} at 0.054 mol kg^{-1} falls within a range of accepted literature values (17.584 ± 0.017 kJ mol^{-1} at 0.111 mol dm^{-3} $\hat{=}$ 17.527 kJ mol^{-1} at 0.05 mol dm^{-3} [13] and 17.536 ± 0.009 kJ mol^{-1} at 0.05 mol dm^{-3} [14]).

3. Results

Measurements were carried out at 25.00, 30.00, 35.00 and 42.10 °C at concentrations in the range 2 - 62 mmol kg^{-1}. Table 1 gives the experimental integral enthalpies of solution ΔH°_{is}(exp) compared to the recalculated values ΔH°_{is}(calc), which were obtained from the following polynomials fitted to the experimental data:

$$25.00^{\circ}C:\ \Delta H^{\circ}_{is}(calc) = 16.315 - 0.11108 \cdot c/mmol \cdot kg^{-1} + 7.7874 \cdot 10^{-4}\ c^2/mmol^2 \cdot kg^{-2}$$

$$30.00^{\circ}C:\ \Delta H^{\circ}_{is}(calc) = 16.807 - 0.09204 \cdot c/mmol \cdot kg^{-1}$$

$$35.00^{\circ}C:\ \Delta H^{\circ}_{is}(calc) = 17.831 - 0.12148 \cdot c/mmol \cdot kg^{-1} + 1.0612 \cdot 10^{-3}\ c^2/mmol^2 \cdot kg^{-2}$$

$$42.10^{\circ}C:\ \Delta H^{\circ}_{is}(calc) = 18.652 - 0.09472 \cdot c/mmol \cdot kg^{-1} + 6.7236 \cdot 10^{-4}\ c^2/mmol^2 \cdot kg^{-2}$$

The polynomials were also ued to calculate the enthalpies of solution at infinite dilution ("first enthalpy of solution") and at 10 mmol kg^{-1}, see Table 2. The latter concentration was selected, because the measurements were sufficiently reproducible at this concentration. Figures 3 and 4 show the data measured together with results of other authors.

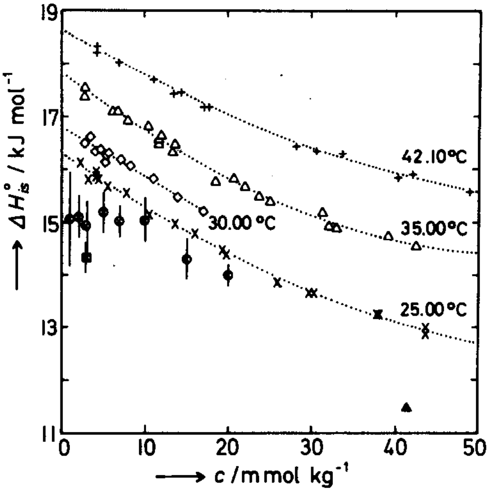


Fig. 3:

Integral enthalpies of solution of β-caffeine in water.

+ △ ◇ × our measurements.

⊗ STERN et al. at 25 °C [15]

⊠ CESÀRO et al. at 25 °C [16], ▲ MATIGNON at 12 °C [17]

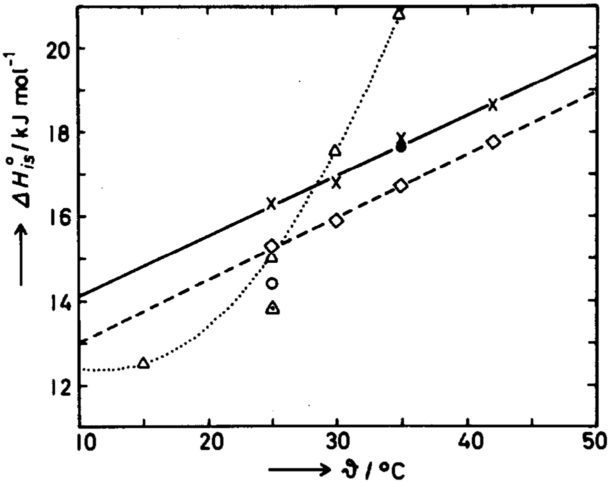


Fig. 4: Integral enthalpy of solution of β-caffeine in water as a function of temperature. × our data for infinite dilution and ◇ for 10 mmol kg^{-1}; ····△···· STERN and BEENINGA [18], ○ CESARO et al. [16], ● CESÀRO and STAREC [11], ◬ STERN and LOWE [19]

Table 1

ntegral enthalpies of solution of β-caffeine in water. ΔH°_{is}(exp) are experimental data, ΔH°_{is}(calc) - data are ecalculated from linear or quadratic regressions, see text.

ϑ = 25.00 ± 0.02 °C

1000·c ol kg^{-1}	ΔH°_{is}(exp) kJ mol^{-1}	ΔH°_{is}(calc) kJ mol^{-1}
30.37	13.68	13.66
26.01	13.88	13.95
29.66	13.68	13.71
65.64	12.34	12.38
43.49	13.01	12.96
37.70	13.26	13.23
43.63	12.92	12.95
37.91	13.24	13.22
15.91	14.78	14.74
4.44	15.85	15.84
5.55	15.69	15.72
19.23	14.48	14.47
19.80	14.40	14.42
4.13	15.88	15.87
13.50	14.97	14.96
10.41	15.16	15.24
3.20	15.84	15.97
4.14	15.96	15.87
7.69	15.57	15.51
2.27	16.12	16.07
61.62	12.46	12.43

ϑ = 35.00 ± 0.02 °C

1000·c mol kg^{-1}	ΔH°_{is}(exp) kJ mol^{-1}	ΔH°_{is}(calc) kJ mol^{-1}
11.88	16.65	16.54
31.25	15.20	15.07
2.79	17.55	17.50
2.54	17.39	17.53
39.18	14.77	14.70
11.66	16.51	16.56
13.26	16.32	16.41
6.73	17.10	17.06
7.89	16.92	16.94
10.30	16.84	16.69
6.20	17.10	17.12
11.75	16.56	16.55
13.53	16.50	16.38
18.44	15.79	15.95
20.54	15.84	15.78
32.99	14.90	14.98
25.10	15.41	15.45
32.08	14.94	15.03
42.33	14.58	14.59
23.72	15.51	15.55
21.97	15.68	15.67

ϑ = 30.00 ± 0.02 °C

1000·c ol kg^{-1}	ΔH°_{is}(exp) kJ mol^{-1}	ΔH°_{is}(calc) kJ mol^{-1}
5.44	16.29	16.31
4.66	16.39	16.38
11.04	15.85	15.79
2.86	16.52	16.54
8.32	16.09	16.04
5.61	16.30	16.29
13.88	15.50	15.53
17.04	15.23	15.24
3.41	16.62	16.49
5.36	16.15	16.31
4.08	16.37	16.43
7.27	16.18	16.14

ϑ = 42.10 ± 0.02 °C

1000·c mol kg^{-1}	ΔH°_{is}(exp) kJ mol^{-1}	ΔH°_{is}(calc kJ mol^{-1}
17.04	17.18	17.23
17.65	17.20	17.19
4.11	18.22	18.04
6.83	18.03	18.04
28.19	16.46	16.52
13.42	17.45	17.50
11.04	17.71	17.69
14.26	17.48	17.44
4.24	18.33	18.26
30.56	16.37	16.39
48.68	15.60	15.63
40.25	15.87	15.93
33.62	16.33	16.23
41.97	15.93	15.86

Table 2

Integral enthalpies of solution of caffeine in water, ΔH°_{is}(calc) in kJ mol^{-1}, at fixed concentrations

ϑ/°C	c = 0 mmol kg^{-1}	c = 10 mmol kg^{-1}
25.00	16.315	15.282
30.00	16.807	15.886
35.00	17.831	16.724
42.10	18.652	17.772

Table 3

ΔC°_p(solv) of caffeine in aqueous solution between 25 and 42.1 °C and partial molar heat capacity of caffeine in water

Authors	c	ΔC°_p	$C^\circ_{p,\,c\rightarrow 0}$(solv)
	mmol kg^{-1}	J K^{-1} mol^{-1}	
BOTHE & CAMMENGA (this work)	0	142$\pm$13	375
BOTHE & CAMMENGA (this work)	10	148$\pm$ 6	
STERN & BEENINGA [18]	2 - 6	414	661
CESÀRO & STAREC [11]	3	329	502

As seen in Fig. 3, the integral enthalpies of solution as given for 25 °C by CESARO et al. [16] and by STERN et al. [15] are considerably too low. The latter authors from their data have the wrong impression that ΔH°_{is} is independent of concentration below 10 mmol kg^{-1}. As we have found [5] and meanwhile has been confirmed by CESÀRO and STAREC [11], the discrepancies at least partly arise from the fact that other authors have not been aware of the polymorphism of caffeine. If the samples are prepared by desiccation of caffeine hydrate, by recrystallization from solution (e. g. from benzene) or by sublimation, they usually contain a considerable fraction of the high temperature α-form with a higher relative enthalpy (see dashed line in Fig. 5) and thus a lower enthalpy of solution than pure β-caffeine [5]. In addition, the rather slow dissolution rate of caffeine and the molecular self-association may also have contributed to the considerable scatter among the data of previous workers depicted in Fig. 4.

The difference in molar heat capacity between solution (0 and 10 mmol kg^{-1}) and solid β-caffeine is obtained from the slope $\frac{\partial \Delta H^{\circ}_{is}}{\partial T} = \Delta C^{\circ}_{p}$, see Fig. 4. Our data are given in Table 3 together with those obtained by other workers, whose data - as we believe - are much too high. Table 4 summarizes our and other results for the molar heat capacity $C^{\circ}_{p}(s)$ of solid β-caffeine at 25 °C and Fig. 6 shows the temperature dependence of $C^{\circ}_{p}(s)$ for β- and α-caffeine. CESÀRO and STAREC have no explanation that their data are 25 % lower than ours [20], which were obtained in good accord irrespective of method or equipment. The partial molar heat capacity of dissolved caffeine is calculated by

$$C^{\circ}_{p}(solv) = \frac{\partial \Delta H^{\circ}_{is}}{\partial T} + C^{\circ}_{p}(s) = \Delta C^{\circ}_{p} + C^{\circ}_{p}(s). \qquad (1)$$

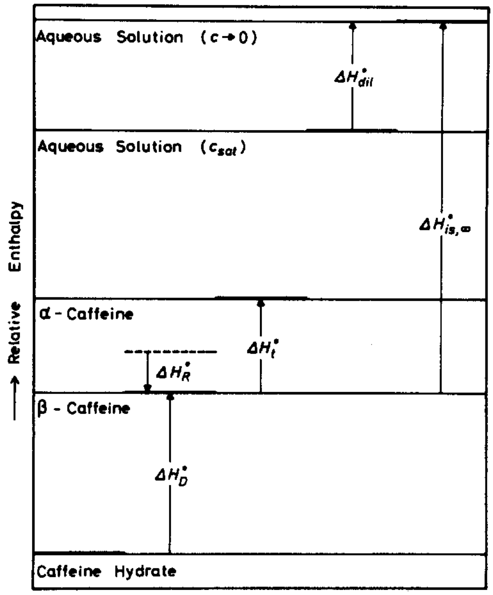


Fig. 5:

Relative enthalpies (drawn to scale) of the solid caffeine phases and caffeine solution. ΔH°_D enthalpy of dehydration, ΔH°_t enthalpy of phase transition, ΔH°_R enthalpy of recrystallization, $\Delta H^\circ_{is,\infty}$ enthalpy of solution at infinite dilution (first enthalpy of solution), ΔH°_{dil} total enthalpy of dilution

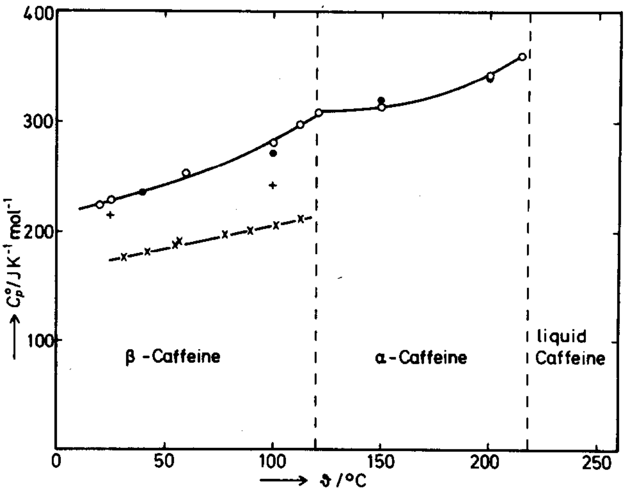


Fig. 6: Molar heat capacity of solid β- and α-caffeine.
○ dropcalorimetry, ● DSC, both our data; + GABETS et al. [21], × CESÀRO and STAREC [11]

As can be seen from Table 3 our result $C^{\circ}_{p,298}(solv) = 375\ J\ K^{-1}\ mol^{-1}$ is considerably lower than the data given by STERN and BEENINGA [18] or CESÀRO and STAREC [11], which had been derived from incorrect enthalpy of solution and heat capacity data.

We feel certain that our enthalpy of solution data using β-caffeine, which show a strong concentration dependence even at low concentration, are correct, because they are in excellent agreement with the relative molar enthalpies obtained from heat of dilution measurements reported by CESÀRO et al. [16], as can be seen in Fig. 7. Data obtained by GILL et al. [1] with a rather simple equipment are also shown in this figure; they fall a bit higher troughout. Furthermore, our results are in excellent agreement with some unpublished heat of dilution data obtained by ROHDEWALD and GALAL [22].

It is evident from what is said above that saturated aqueous solutions of purines (like caffeine) are very far from being ideal. Thus, meaningful "heats of solution" cannot be deduced from the slope of the function ln x_C versus 1/T, as e. g. has been recently done by FOKKENS et al. [23,24] in the case of theophylline (7-desmethyl-caffeine). Fig. 8 shows a corresponding plot for the solubility of caffeine in water in the range 0 - 45 °C. As with our measurements on theophylline (and in contrast to the results obtained by FOKKENS et al.) the data can be fitted much better by a polynomial of second power in 1/T than by linear regression. From the slope of the curve an "enthalpy of solution" of 36.7 kJ mol^{-1} is obtained. This, however, is far from the differential enthalpy of solution at saturation (last enthalpy of solution), which is 11,50 kJ mol^{-1}. Thus it is necessary, to determine $\partial \ln f_{oC}/\partial \ln x_C$ in the vicinity of saturation, as CESÀRO and

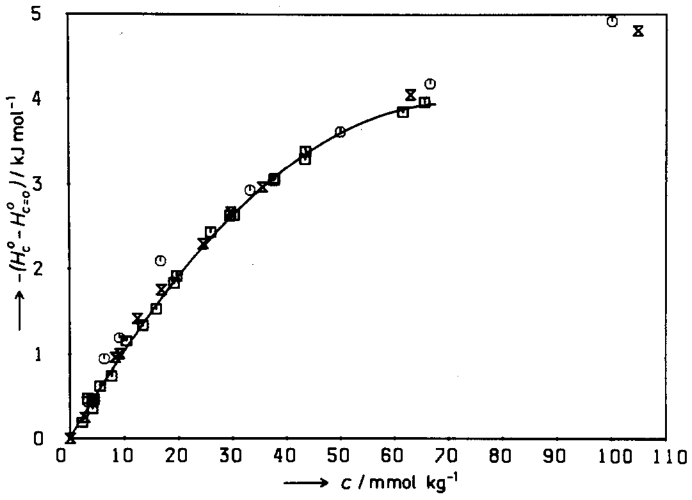


Fig. 7: Relative molar enthalpy of caffeine solutions.□ This work, ⧖ CESÀRO et al. [16], ○ GILL et al. [1]

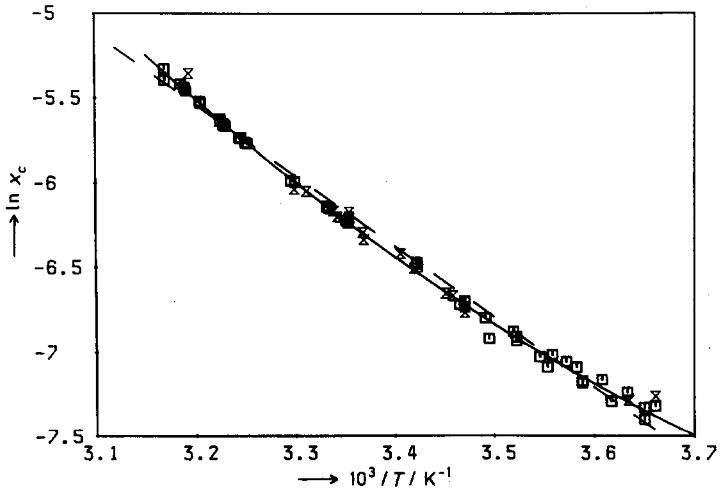


Fig. 8: Solubility of caffeine in water in the range 0 -45 °C. x_C mol fraction of caffeine.□ Our data, ⧖ literature data from various sources [6,12]. Dashed line: linear regression, full line: quadratic regression in 1/T

RUSSO have already pointed out [25].

4. Association of Caffeine in Aqueous Solution

As has been shown there is excellent agreement between the relative molar enthalpy data obtained from heat of solution and heat of dilution measurements. We have therefore used the data to calculate the molar enthalpy of self-association ΔH_A^o of caffeine. This can be derived in making the - admittedly daring - assumption that the total deviation from the behaviour of an ideal solution is due to the increasing caffeine association with concentration. If the additional assumption is made that the enthalpies of association from monomer to dimer, dimer to trimer etc. are identical, the following expression is obtained for ΔH_A^o [1]:

$$\Delta H_A^o = \frac{H_c^o - H_{c=o}^o}{c\ (1-\varphi)} = \frac{\Delta H_{is,c}^o - \Delta H_{is,\infty}^o}{c\ (1-\varphi)} , \qquad (2)$$

where $H_c^o - H_{c=o}^o$ is the relative molar enthalpy, c the total molar concentration and φ the practical osmotic coefficient. At 25 °C data for the osmotic coefficient of caffeine solutions have been taken from WESSELMANN [26,27], who had fitted a polynomial of sixth power to his own results and those of other workers. For 35 °C, we have used the data for φ reported by CESÀRO et al. [16], fitted by us with a polynomial of third power, see Fig. 9. The results for ΔH_A^o as a function of concentration are shown in Fig. 10.

In addition to ΔH_A^o, the association constant K_A of caffeine has been calculated from [1,16]

$$K_A = \frac{1-\varphi}{c \cdot \varphi^2} \qquad (3)$$

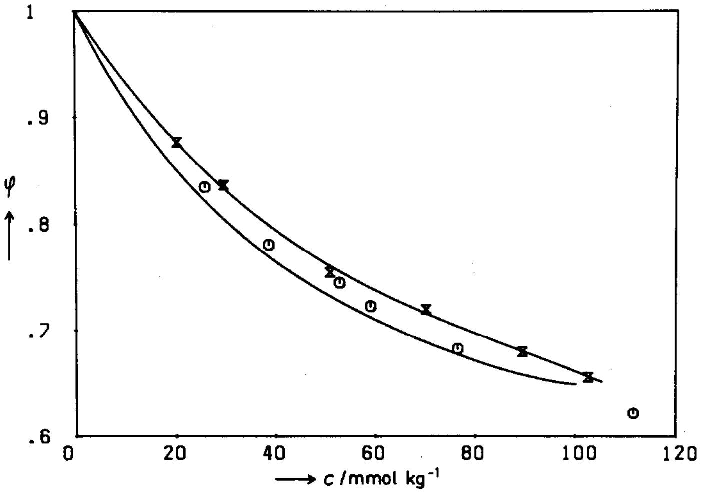


Fig. 9: Practical osmotic coefficient φ as a function of caffeine concentration in water. Upper curve fitted to ⧗, the data of CESÀRO et al. for 35 °C; ○ data of CESÀRO et al. for 29.8 °C; lower curve is the polynomial for φ (25 °C) as given by WESSELMANN [26,27]

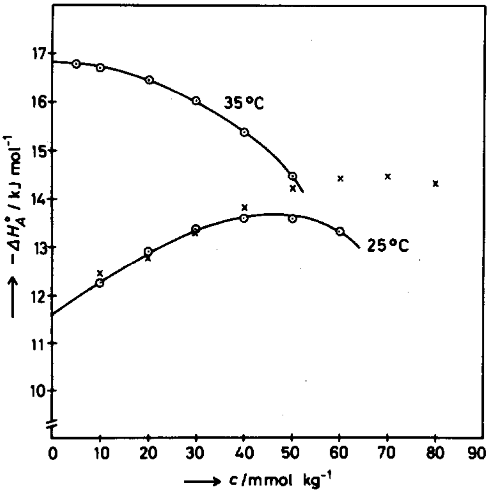


Fig. 10:

Molar association enthalpy of caffeine in water.

⊙ Our data,

× CESÀRO et al. [16]

Table 4

Heat capacity of solid β-caffeine at 25 °C.

Author(s) / method	$C_p^\circ(s)$/J K^{-1} mol^{-1}
STERN & BEENINGA [18]/estd. from KOPP's rule	254
STERN & BEENINGA [18]/estd. from C_p° of xanthine	247
BOTHE & CAMMENGA [4]/DSC (DuPont 990 TA)	232
BOTHE & CAMMENGA [12]/DSC (Mettler TA 2000)	235 (40 °C)
BOTHE & CAMMENGA [4]/Dropcalorimetry	228
CESÀRO & STAREC [11]/DSC (Perkin Elmer 1B)	173

Table 5

Association constant K_A and molar enthalpy of association ΔH_A° of caffeine in water

Author(s) / method(s)	298.15 K		308.15 K	
	K_A kg mol^{-1}	$-\Delta H_A^\circ$ kJ mol^{-1}	K_A kg mol^{-1}	$-\Delta H_A^\circ$ kJ mol^{-1}
GUTTMAN & HIGUCHI [3]/ distribution equilibrium	(14.7)			
GILL et al. [1] / heat of dilution	13±1	14±1		
CESÀRO et al. [16] / osmotic coefficient			7.9±0.2	
heat of dilution		11.8±0.5		
BOTHE & CAMMENGA heat of solution		11.6±0.5		16.9±0.5
WESSELMANN [26,27] / osmotic coefficient	10.0±0.2			

and the data for ΔH_A^o and K_A have been compiled in Table 5. The agreement between values obtained by different methods is rather satisfying. The principal source of uncertainty certainly lays in the rather poor accuracy with which the osmotic coefficients have been determined by vapour pressure osmometry. Direct measurements of the vapour pressure difference between solution and pure solvent with a precision manometer (e.g. a capacitance gauge of high resolution and zero point stability) would certainly improve the accuracy in φ [28] and in the data derived therefrom.

5. Outlook

We have meanwhile started to investigate the energetics of association between different purines. Thus, for example, the interaction between caffeine and adenosine will be studied, which, according to a hypothesis of SNYDER [29], is the starting point for the pharmacological and stimulating effectiveness of caffeine - so much appreciated with a cup of coffee or tea!

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