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CALORIMETRIC DETERMINATION OF THERMODYNAMIC DATA OF THE COMPLEXATION BETWEEN SOME DRUGS AND AROMATIC AMINO ACIDS

P. Rohdewald, G. Elmahrouk and G. Wesselmann
Institut für Pharmazeutische Chemie der Westfälischen Wilhelms-Universität Münster, Hittorfstr. 58-62

Summary

Using the method of Bolles and Drago (1) the thermodynamic properties of drug - aromatic amino acid complexes were determined calorimetrically. The comparison of K_c evaluated from vapour pressure osmometry, ORD, partition and calorimetry shows a considerable agreement, whereas the data calculated from solubility measurements differ widely from our results. Qualitatively the relationship between solubilisation through different salts and ΔJ^o for the complexation with the same salts could be demonstrated. Methylxanthines form complexes with anions and cations, the complex formation in H_2O and D_2O, determined calorimetrically, shows the greater stability of the complexes in D_2O.

Introduction

Complexation influences the solubilities and the partition coefficients of the partners in complexes, so that the solubility of caffeine is enhanced in caffeine complexes with aromatic anions or cations (6,8,16) at the other hand, the solubilities of polycyclic aromatics are increased in the presence of caffeine too(4,17). Furthermore, the complexation stabilizes esters against hydrolysis (7,9,10) and influences the absorption of drugs in vivo (5,11).

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Methods

In our intense investigations on caffeine complexes we found a stoechiometric ratio of 1 : 1 by UV-spectroscopy (13) and vapour pressure osmometry (15,18). After the determination of the activity coefficients of the substances under investigation (14) we obtained the stability constant and the enthalpy of complex formation simultaneously by application of the method of Bolles and Drago(1) with the aid of the precision calorimetry system 8701 of LKB.

In the reaction vessel - containing the solution of complex partner A - the ampoule containing the solution of B was broken after establishing the thermal equilibrium.

The heat of reaction obtained in this experiment, Q, is composed from the heats of dilution w_A and w_B and the heat of complexation w_{AB}:

$$Q = w_A + w_B + w_{AB}$$

w_A and w_B were determined in separate experiments, so that w_{AB} could be obtained from Q. The calibration procedures were performed by electrical heating.

Following the method of Bolles and Drago (1) a value for K_c^{-1} is caluculated from the activities of A and B, the total volume V of the solutions after mixing, w_{AB} and a fictive value of ΔH^o:

$$\frac{1}{K} = \frac{w_{AB}}{V} \cdot \frac{1}{\Delta H^o} + \frac{[A] \cdot [B] \cdot V}{w_{AB}} \cdot \Delta H^o - ([A] + [B])$$

With series of ΔH^o of 2,3,4 kJ more values for K_c^{-1} are calculated, these values give a straight line as a function of the fictive ΔH^o. From other experiments with other values of A and consequently new

values of w_{AB} new straight lines could be constructed. The lines cross at the true value for ΔH^{o} and K_{c}^{-1}, these intersections of the different straight lines were calculated.

Table 1: Comparison of the stability constants obtained by vapour pressure osmometry and calorimetry

complex		K (L . mol^{-1}) vapour pressure osmometry	K (L . mol^{-1}) calorimetry
Caffeine	Trypthophan . HCl	17.75	16.60
	Phenylalanine . HCl	2.43	3.20
	Tryptophan-Na	14.02	13.20
	Phenylalanine-Na	2.60	3.40
	Histidine-Na	2.84	2.40
Theophylline	Tryptophan . HCl	12.59	11.90
	Phenylalanine . HCl	1.93	2.60
	Tryptophan-Na	18.60	22.00
	Phenylalanine-Na	10.57	11.80
	Histidine-Na	20.12	20.40
Nicotinamide	Tryptophan . HCl	24.07	23.80
	Phenylalanine . HCl	57.14	53.00
Procaine . HCl	Tryptophan . HCl	18.23	21.00
	Phenylalanine . HCl	26.97	29.00

Results and discussion

By comparison of the results from the calorimetry with the stability constants- derived from our vapour pressure osmometry studies - it is obvious that the values resulting from the two independent methods are in good agreement (table 1).

In the case of complexes of caffeine with l-tryptophan and salicylamide we can compare our results for all thermodynamic data of the complexation with values given by other authors and resulting from other methods (table 2). Whereas the results derived from ORD and partition experiments (12) are in the same order of magnitude with the exception of ΔS, the values calculated from solubility experiments (3) do not agree with our results.

Table 2: Thermodynamic data for caffeine-complexes resulting from different methods

Parameter	Caffeine complexes			
	L-Tryptophan		Salicylamid	
ΔH	ORD	-16.73	Sol	-16.4
(kJ . mol^{-1})	Kal	-20.19	Kal	-31.36
K	ORD	30.0	Sol	57.9
(L . mol^{-1})	Part	26.0		
	Kal	25.53	Kal	20.13
ΔS	ORD	-28.03	Sol	-21.0
(kJ . mol^{-1} . deg^{-1})	Kal	-43.21	Kal	-80.22
ΔG	ORD	- 8.38	Sol	-10.1
(kJ . mol^{-1})	Kal	- 8.03	Kal	- 7.44

ORD (15), Sol (4), Part (15), Kal this work.

We suggest that oversimplifications inherent to the method of calculation of the stability constants from solubility measurements are the cause for these discrepancies.

However, the increase of the amount of solubilized caffeine per mol Na- or HCl-salt of aromatics with the ΔG° of complexation, derived from our calorimetric measurements, demonstrates (Fig 1)

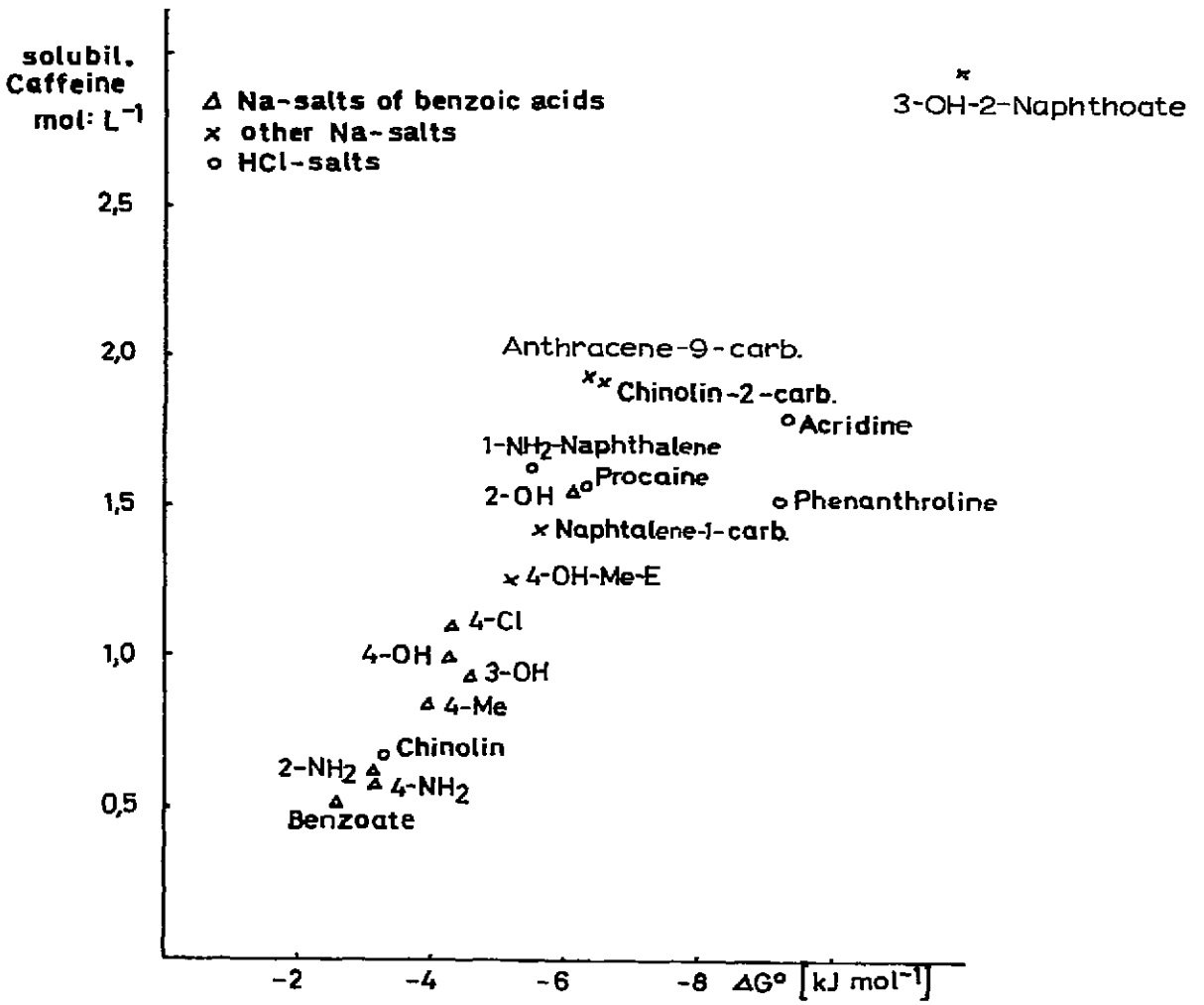

Fig 1 : The solubilisation of caffeine through hydrochlorides of aromatic amines and sodium salts of aromatic acids in relation to ΔG° complexation, determined calorimetrically (25)

that a relationship exists between the phenomenon of solubilisation or hydrotropic action and the complexation. The stability of these complexes increases with increasing size of aromatic molecules. Hydrochlorides of aromatic amines form complexes as well as sodium salts of aromatic acids.

With aromatic amino acids, complexes are formed both with the HCl- and the Na-salts (Table 3). These experiments should show, whether the protonated or unprotonated amino acids form more stable complexes.

The results indicate a weaker binding of the methylxanthines to phenylalanine compared to tryptophan, regardless of the charge of these amino acids. Histidine·Na forms a weak complex with caffeine, but with theophylline the most stable complex is formed.

Table 3 : Thermodynamic data for complexes of aromatic amino acids and methylxanthines

complexes		K_c $L.mol^{-1}$	ΔH $kJ.mol^{-1}$	ΔG $kJ.mol^{-1}$	ΔS $kJ.mol^{-1}deg^{-1}$
Tryptophan·HCl	Caffeine	17.17	- 41.03	- 7.05	- 113.95
Phenylalanine·HCl		2.43	- 20.35	- 2.20	- 60.87
Tryptophan·Na		14.02	- 42.85	- 6.54	- 121.77
Phenylalanine·Na		2.60	- 20.91	- 2.36	- 62.20
Histidine·Na		2.84	- 8.99	- 2.58	- 21.50
Tryptophan·HCl	Theophylline	12.59	- 40.13	- 6.28	- 113.54
Phenylalanine·HCl		1.93	- 22.19	- 1.63	- 68.96
Tryptophan·Na		18.60	- 33.84	- 7.24	- 89.19
Phenylalanine·Na		10.57	- 23.31	- 5.84	- 75.35
Histidine·Na		20.12	- 16.68	- 7.44	- 30.99

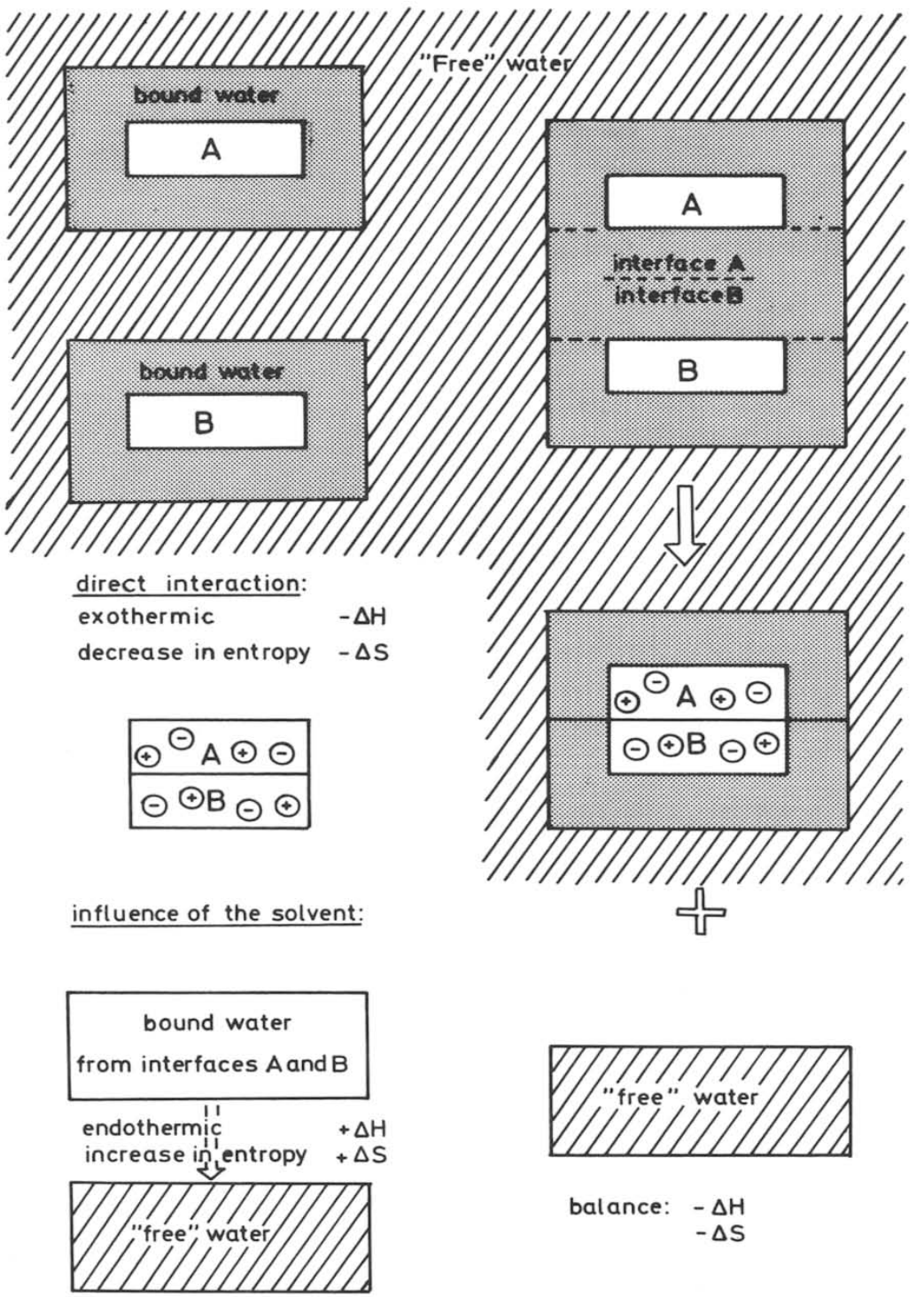

Fig 2 : Schema of the formation of caffeine complexes in water

We suggest that the complexation is caused by the stacking of the partners forming the complex. Because both planar molecules should have an ordered water layer on their surfaces, the stacking of A and B removes the part of the water molecules bound on the respective surfaces. These water molecules are converted to "free" water. This is the type of interaction according to the theory of hydrophobic interaction, the reaction should be endothermic, the entropy should increase.

In the next step the direct electrostatic interaction of the molecules should be an important factor for the complexation because the alternating negative and positive centers in the caffeine molecule give many possibilities to interact with opposite charged parts in partner molecules.

The electrostatic interaction should be exothermic and the entropy should decrease.

Both phenomena must be taken into consideration simultaneously; our results indicate only the overall effect of an exothermic reaction and a decrease of the entropy.

If water is replaced successively by ethanol or DMSO, the stability of the caffeine complexes decreases dramatically, in the pure solvents no complexation can be detected calorimetrically (19). This indicates the importance of water as solvent for the stability of these complexes.

D_2O should form stronger hydrogen bonds than H_2O (2), therefore we expect a larger amount of the hydrophobic interaction term on the overall reaction. In D_2O the stability constants of all complexes investigated are larger than in H_2O (table 4). The enthalpies of complexation are for all caffeine complexes smaller in D_2O and the entropies in D_2O are smaller too, this could indicate the more endothermic reaction in D_2O.

In the case of the complexes of procaine hydrochloride with hydrochlorides of the amino acids the stability constants are also greater in D_2O than in H_2O, but the enthalpies are much larger in D_2O. For these unexpected results we have no explanation at hand. However, the enhanced stability of all the complexes in D_2O underlines the importance of the solvent for the complex formation.

Table 4: Stability constants, ΔH^o and ΔS^o for complexes in H_2O and D_2O

complex			K_c L . mol^{-1}	ΔH^o kJ . mol^{-1}	ΔS^o kJ . mol^{-1} . Grad^{-1}
Caffeine	Na-benzoate	D_2O	5.9	-23.2	-64.1
		H_2O	2.9	-29.7	-90.7
	Na-Naphthalin-	D_2O	9.3	-41.9	-121.9
	1-carbonate	H_2O	7.1	-45.6	-136.8
	Na-Anthracen-	D_2O	15.2	-44.9	-127.9
	9-carbonate	H_2O	13.0	-46.8	-135.7
	Tryptophan . DCl	D_2O	20.4	-41.6	-114.5
	Tryptophan . HCl	H_2O	18.8	-50.2	-143.8
	Phenylalanine . DCl	D_2O	2.8	-17.7	- 50.6
	Phenylalanine . HCl	H_2O	2.0	-27.7	- 87.1
Procaine . DCl	Tryptophan . DCl	D_2O	18.4	-49.0	-140.2
Procaine . HCl	Tryptophan . HCl	H_2O	18.3	-23.6	- 55.0
Procaine . DCl	Phenylalanine . DCl	D_2O	33.9	-40.8	-107.4
Procaine . HCl	Phenylalanine . HCl	H_2O	30.6	-25.8	- 58.1

Whereas the caffeine complexes fit in the picture of the hydrophobic interaction combined with an exothermic electrostatic interaction, the complexes of procaine·HCl with the hydrochlorides of the aromatic amino acids do not follow this line.

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