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DIFFERENTIAL SCANNING CALORIMETRY OF ASPARTAME-CAFFEINE MIXTURE

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ABSTRACT

The possible interaction between aspartame and caffeine was investigated by comparing the thermal behavior, using differential scanning calorimetry, of physical mixtures of aspartame and caffeine along with mixtures, in the same molar ratios, obtained as the co-precipitate. Caffeine was found to form several complexes with aspartame. These complexes were found to be dependent on the molar ratios of aspartame to caffeine. The stoichiometry of the aspartame-caffeine complexes were determined from the enthalpy change of the DSC transitions resulting from the complex formation .

INTRODUCTION

Emery and Wright[1] studied the complexing action of caffeine with a number of compounds including sodium benzoate, sodium salicylate, citric acid, etc. Chambon et al.[2] reported a phase rule study of the caffeine-sodium benzoate-water system. They made no attempt

to obtain quantitative data relative to the stability of the complexes postulated.

Higuchi et al.[3-5] have investigated the complexing of caffeine with a number of pharmaceutical acids, esters, and salts. It was shown that these complexes were distinct molecular species capable of existing in both liquid and solid phase in fixed molecular proportions. Higuchi and Lach[6-7] further extended these caffeine complexing studies to other organic compounds. They found that the stoichiometric relationships of the complexing reaction can be calculated from phase diagrams obtained by the solubility method. In another study[8] they investigated the complexing tendencies of theophylline and theobromine with a number of organic acids and the data obtained were compared with that obtained earlier with caffeine.

Higuchi and Lachman[9] found that the rate of hydrolysis of benzocaine in aqueous solution can be substantially inhibited by addition of caffeine which had previously been shown to complex with benzocain Levy and Reuning[10] studied the effect of caffeine on the gastric absorption of salicylic acid in rats. They concluded that the absorption rate of drugs can be modified by formation of complexes which differ from the free drug mainly in size or in lipoid-water partition coefficient. Zoglio et al.[11] found that caffeine enhanced the dissolution rate of ergotamine tartrate by a factor of three at gastric pH. They found also that the partitioning rate of ergotamine tartrate from an aqueous to an organic phase was influenced by caffeine.

Kono et al.[12], using differential scanning calorimetry (DSC), polarized infrared (IR) spectroscopy and X-ray fiber photography, confirmed the formation of complexes of PEG with quanidine HCl and with phenobarbital. They discussed the structures of PEG molecules

in the complexes in comparison with a PEG-urea complex and original samples of PEG. They reported also that the formations of complexes of PEG with urea, guanidine HCl, and with phenobarbital were confirmed by DSC curves of physical mixtures of the respective original components.

The original regulation for aspartame[13] approved its use as a sugar substitute in tablet form for sweetening hot beverages, including coffee and tea, also in dry bases for beverages and instant coffee and tea. It is interesting, therefore, to investigate the possible interaction between aspartame and caffeine. This is achieved by comparing the thermal behavior, using DSC, of physical mixtures of aspartame and caffeine in different molar ratios along with mixtures prepared by dissolving aspartame and caffeine, in the same molar ratios, in methanol followed by evaporation of the solvent.

EXPERIMENTAL

Materials

The following materials were used: Aspartame (G. D. Searle and Co.,), caffeine (Sandoz Pharmaceuticals) and methanol (Baker).

Preparation of Aspartame-Caffeine Mixtures:

Physical mixtures were prepared by mixing different molar ratios of aspartame and caffeine using motar and pestel (Set I). The molar ratios were: 1:0.17, 1:0.38, 1:0.65, 1:1.00, 1:1.50, 1:2.27, 1:3.53, 1:6.00 and 1:13.62.

Another set of aspartame-caffeine mixtures of the same molar ratios (Set II) was prepared by dissolving the respective molar ratios of aspartame and caffeine in a sufficient volume of methanol in a porcelain dish which was maintained for 24 hours at 25°C. The dish was then transferred to a vacuum desiccator until solvent

evaporation was complete. Separate samples of aspartame and caffeine were also prepared by the same method to be used as blank.

Differential Scanning Calorimetry

Samples (4 mg) were weighed after being finely powdered and encapsulated in volatile sample pans with tightly sealed lids. The samples were heated in an atmosphere of nitrogen and thermograms were obtained on a Perkin-Elmer DSC-1B Differential Scanning Calorimeter. Thermograms were obtained by heating at a constant heating rate of 10°C per minute, a constant range setting of 8 mcal per second, and recorded at a constant chart speed of one inch per minute. The individual substances and the two sets of aspartame-caffeine mixtures were heated over the temperature range, 30 to 300°C.

The area under the differential scanning calorimetric heating curve was measured using a K & E planimeter and the heat of transition was then calculated as described previously[14]. At least two replicates were made for each DSC thermogram.

RESULTS AND DISCUSSION

In a previous investigation[14], aspartame has been shown by differential scanning calorimetry to have two endothermic peaks. The first one, with a transition temperature range from 167-190°C and with a maximum peak of transition at 185°C, represents the loss of the methyl ester and conversion to the dipeptide, aspartyl phynylalanine. The second peak, with a transition temperature range from 234-254°C and with a maximum peak of transition at 240°C, represents the conversion to diketopiperazine (DKP).

DSC thermograms of caffeine showed a melting endothermic peak with a transition temperature range from 227-238°C and with a maximum peak of transition at 234°C.

Figure 1 illustrates the DSC thermograms of aspartame and caffeine, separately and in physical mixtures (Set I), while Table 1 and Figure 3 illustrate the enthalpy change of the physical mixtures as a function of composition. The DSC thermogram of a 1:0.17 molar ratio of aspartame-caffeine physical mixture showed three transitions. The first one (transition A) was a small endothermic peak with a transition temperature range from 116-140°C corresponding to the melting transition of an aspartame-caffeine complex. The second and third transitions (transitions B and D respectively) were two endothermic peaks corresponding to those of aspartame, with a shift to lower temperatures from that of pure aspartame. No exothermic peak due to the complex formation itself was observed upon examining at several heating speeds[12].

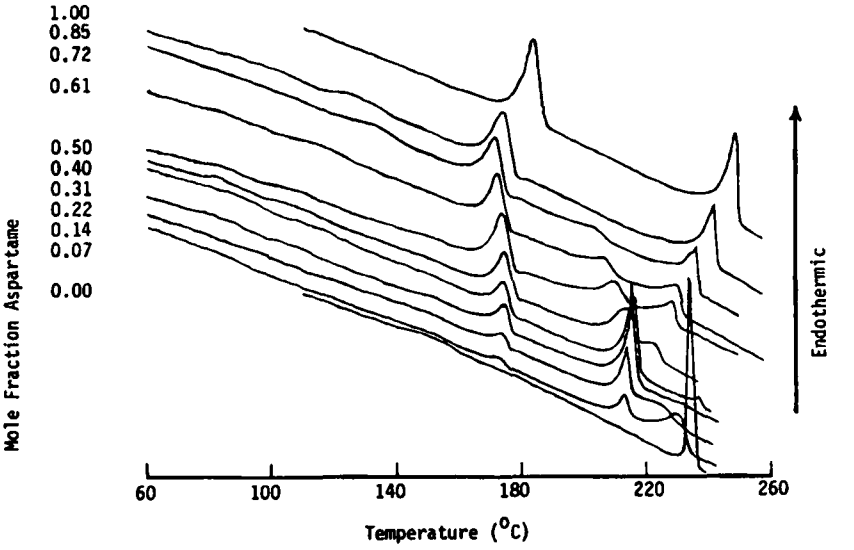

FIGURE 1
DSC thermograms of aspartame and caffeine separately and in mixtures (Set I).

TABLE 1

Enthalpy Change of Aspartame-Caffeine Mixtures (Set I) as a Function of Composition

Aspartame-Caffeine Molar Ratio (mole/mole)	Mole Fraction		Enthalpy Change, Cal/g			
	Aspartame	Caffeine	Transition A	Transition B	Transition C	Transition D
1:0.00	1.00	0.00	—	21.91	—	20.28
1:0.17	0.85	0.15	2.47	18.14	—	16.03
1:0.38	0.72	0.28	2.00	15.17	1.55	11.63
1:0.65	0.61	0.39	1.65	14.33	3.29	9.04
1:1.00	0.50	0.50	1.59	12.58	5.57	5.40
1:1.50	0.40	0.60	1.13	10.49	9.02	1.88
1:2.27	0.31	0.69	1.30	7.47	17.70	1.02
1:3.53	0.22	0.78	0.98	6.23	19.19	—
1:6.00	0.14	0.86	—	3.67	6.18	2.62
1:13.62	0.07	0.93	—	1.79	2.47	10.06
0:1.00	0.00	1.00	—	—	—	21.57

A 1:0.38 molar ratio of aspartame-caffeine physical mixture showed, in addition to the previously mentioned transitions, a new endothermic peak with a transition temperature range from 197-209°C (transition C) corresponding to the melting transition of an aspartylphenylalanine-caffeine complex.

As aspartame concentration in the mixture decreases, transitions A, B and D decrease while transition C increases until the molar ratio of aspartame-caffeine reaches 1:3.53 (2:7), after which transition A nearly disappears, transitions B and C decrease and transition D increases (Table 1 and Figure 3).

Transition A, which has a maximum enthalpy change of 2.47 cal/g at an aspartame-caffeine molar ratio of approximately 6:1, represents the melting endotherm of a complex very rich in aspartame; therefore, it is normal that transition A should decrease as the concentration of aspartame in the mixture decreases. Transition C which has a maximum enthalpy change of 19.19 cal/g at an aspartame-caffeine molar ratio of approximately 2:7 (Table 1 and Figure 3), represents the melting endotherm of a complex rich in caffeine and increases as the concentration of caffeine in the mixture increases.

At molar ratios 1:0, 1:0.17, 1:0.38, 1:0.65, 1:1, 1:1.5 and 1:2.27 of aspartame-caffeine physical mixtures, transition D represents the formation of DKP as there is free aspartylphenylalinine below the optimum complexation ratio of 1:3.53 (2:7). At aspartame-caffeine molar ratios of 1:6 and 1:13.62, however, there is no free aspartylphenylalanine; therefore, transition D represents the melting endotherm of uncomplexed caffeine and not of DKP.

Figure 2 illustrates the DSC thermograms of aspartame and caffeine, separately and in mixtures (Set II), while Table 2 and Figure 4 illustrate the enthalpy change of the same mixtures as a function

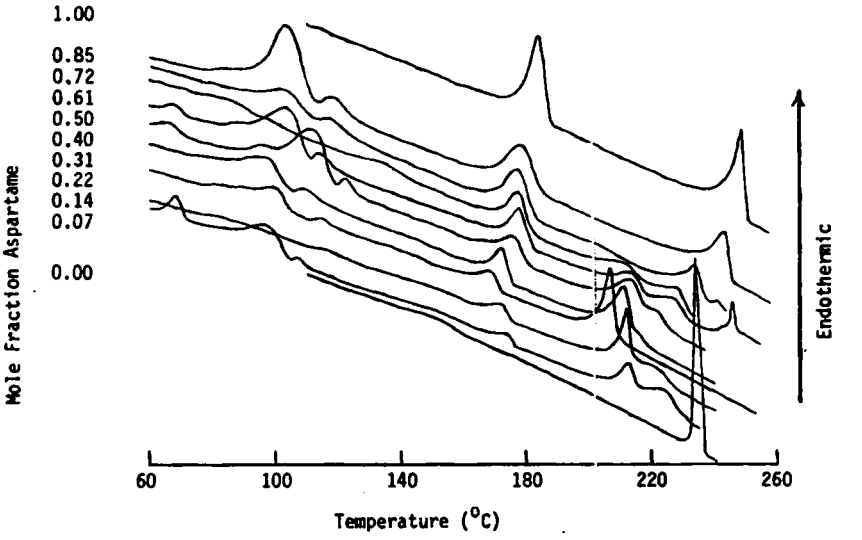

FIGURE 2

DSC thermograms of aspartame and caffeine separately and in mixtures (Set II)

of composition. It is apparent that transitions B, C and D are more or less the same as in the case of the physical mixtures. Transition A in the case of Set II mixtures is more distinct and complicated than in the case of physical mixtures as it represents the melting endotherms of several aspartame-caffeine complexes formed during co-precipitate preparation. One of the complexes, having a transition temperature range from 76-114°C, is very rich in aspartame as it has a maximum enthalpy change of 42.69 cal/g at an aspartame-caffeine molar ratio of approximately 6:1 (Table 2 and Figure 4).

Complexes also form at an aspartame-caffeine molar ratio of 2:3. There appears to be two molecular configuration of this complex, one having a temperature range of transition from 60-73°C and the other from 84-119°C. The latter complex appears to have the stronger

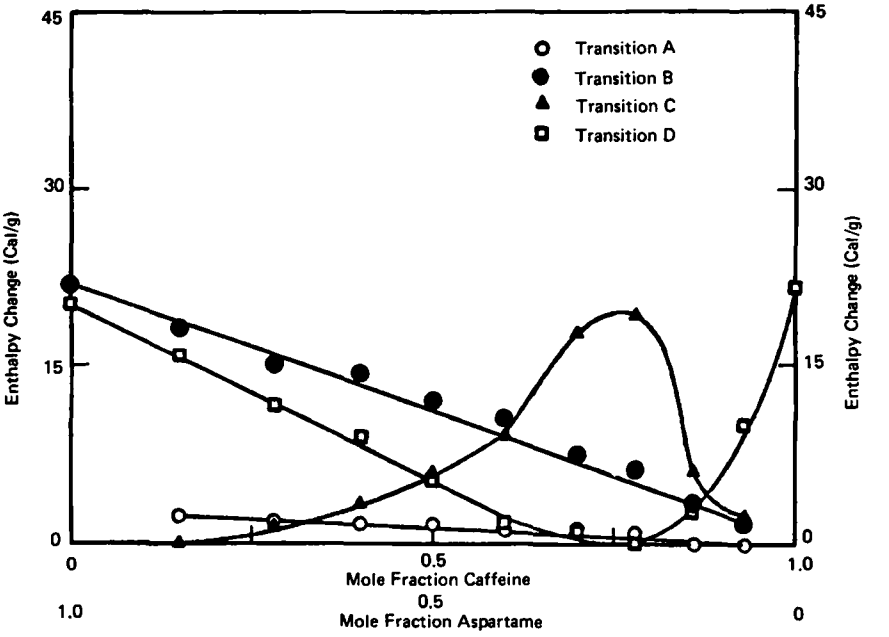

FIGURE 3

Enthalpy change of aspartame-caffeine mixtures (Set I) as a function of composition.

mutual binding with enthalpy change of 30.69 cal/g. Further, complexes rich in caffeine also appear to form with an aspartame-caffeine molar ratio of approximately 1:13 (Table 2 and Figure 4). Again two molecular configurations are apparent, one again having a transition temperature range from 60-73°C while the second, stronger complex has a transition temperature range from 87-105°C.

An interesting observation is that in addition to the previously mentioned complexes, a transition was observed immediately following the main complex transiton for all Set II mixtures and having a transition temperature ranging from 114-128°C to 105-111°C. The exact nature of this transition is not clear, but it may represent some form of molecular rearrangement of the melting complex.

TABLE 2
Enthalpy Change of Aspartame-Caffeine Mixtures (Set II) as a Function of Composition

Aspartame-Caffeine Molar Ratio (mole/mole)	Mole Fraction		Enthalpy Change, Cal/g			
	Aspartame	Caffeine	Transition A	Transition B	Transition C	Transition D
1:0.00	1.00	0.00	___	21.91	___	20.28
1:0.17	0.85	0.15	42.69	19.15	___	16.41
1:0.38	0.72	0.28	11.37	16.12	1.77	10.11
1:0.65	0.61	0.39	5.63	13.65	3.57	5.31
1:1.00	0.50	0.50	23.03	9.51	5.89	3.27
1:1.50	0.40	0.60	30.69	8.91	7.24	0.67
1:2.27	0.31	0.69	16.55	7.68	11.75	0.18
1:3.53	0.22	0.78	10.55	5.21	16.04	___
1:6.00	0.14	0.86	3.03	3.63	9.62	1.46
1:13.62	0.07	0.93	7.55	2.54	4.14	4.48
0:1.00	0.00	1.00	___	___	___	21.57

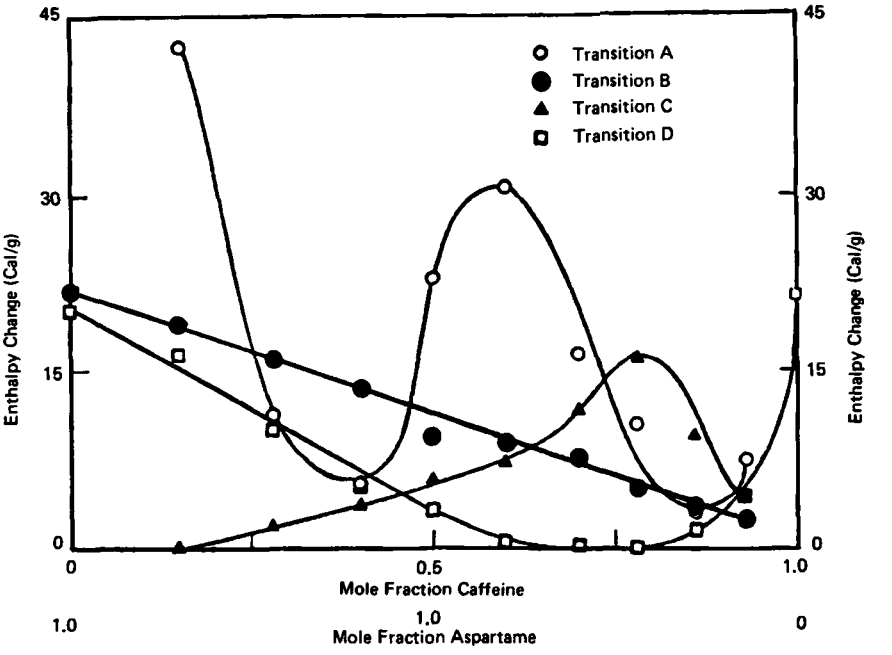

FIGURE 4

Enthalpy change of aspartame-caffeine mixtures (Set II) as a function of composition.

Chemically, aspartame is N-L-aspartyl-L-phenylalanine-1-methyl ester and, therefore, it has many polar centers which may serve as possible sites of complexation with caffeine. Caffeine in turn has been shown to have complexing tendencies with a number of organic acids, esters and aromatic and nonaromatic nitrogenous compounds[3-9]. Mazur et at. [15] reported that the presence of both the free, unsubstituted amino and one carboxyl group of aspartic acid, as well as the distance between them and the absolute configuration of the asymmetric carbon, are completely critical for sweetness. They reported also that sweetness fell off rapidly

with increasing size of the ester radical. The characterization of the aspartame-caffeine complexes and their effect, if any, on the sweetness of aspartame requires additional investigation.

CORRESPONDENCE

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REFERENCES

1. W.O. Emery and C.D. Wright, J. Am. Chem. Soc., 43, 2323 (1921).
2. M. Chambon, J. Bouvier and P. Duron, J. Pharm. Chim., 26, 216 (1937).
3. T. Higuchi and D.A. Zuck, J. Am. Pharm. Assoc., Sci. Ed., 41:1, 10 (1952).
4. T. Higuchi and D.A. Zuck, ibid, 42:3, 132 (1953).
5. T. Higuchi and D.A. Zuck, ibid, 42:3, 138 (1953).
6. T. Higuchi and J.L. Lach, ibid, 43:6, 349 (1954).
7. T. Higuchi and J.L. Lach, ibid, 43:9, 524 (1954).
8. T. Higuchi and J.L. Lach, ibid, 43:9, 527 (1954).
9. T. Higuchi and L. Lachman, ibid, 44:9, 521 (1955).
10. G. Levy and H. Reuning, J. Pharm. Sci., 53:12, 1471 (1964).
11. M.A. Zoglio, H.V. Maulding, Jr., and J.J. Windheuser, ibid, 58:2, 222 (1969).
12. K. Kono, Y. Takeda, H. Nogami and T. Nagai, Chem. Pharm. Bull., 22:1, 165 (1974).
13. Federal Register, 39:145, 27317 (1974).
14. H.H. El-Shattawy, G.E. Peck and D.O. Kildsig, Drug Dev. and Industrial Pharm., in press.
15. R.H. Mazur, A.H. Goldkamp, P.A. James and J.M. Schlatter, J. Med. Chem., 13:6, 1217 (1970).