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STUDIES OF ERGOTAMINE TARTRATE-CAFFEINE INTERACTIONS BY DIFFERENTIAL SCANNING CALORIMETRY

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ABSTRACT

Differential scanning calorimetry was used to evaluate the interactions between ergotamine tartrate and caffeine. Physical mixtures of ergotamine tartrate and caffeine, as well as mixtures formed by evaporation of ergotamine tartrate and caffeine from a methanol solution, were evaluated. The preparation and characterization of eleven different molar ratios of ergotamine tartrate-caffeine complexes is described. The drug was found to interact with caffeine in the solid state with the formation of complexes. The mixture obtained from the methanol solution showed complexes with ergotamine tartrate-caffeine molar ratios of 2:3 and 2:15, with possible complexes having 1:10, 1:15 and 1:20 molar

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ratios. A phase diagram was constructed. Physical mixtures of the same molar ratios showed possible complex formation at molar ratios of 1:1, 1:1 and 1:3.

INTRODUCTION

Ergotamine as the tartrate salt is widely used in the treatment of migraine headache[1]. When administered parenterally, it is effective in relieving migraine pain[2-4] but oral administration often affords weak and delayed relief[5,6]. The frequent failure of oral ergotamine therapy appears to be related to its relatively low water solubility (1:500) and the fact that its absorption from the G.I. tract into the systemic circulation often is slow or impaired during a migraine attack[4-7].

The use of caffeine and ergotamine tartrate in combination has long been known to be effective in the treatment of migraine headache[8,9]. The effectiveness of this combination may be due, at least in part, to complex formation leading to enhanced internal absorption of ergotamine[10]. The interaction of caffeine and ergotamine tartrate in aqueous solution was previously reported[10]. It has been postulated that caffeine forms one or more molecular complexes with ergotamine in aqueous solutions at pH values of 6.65 and 1, but the complex has not been isolated[10-11].

The present study was undertaken to evaluate the possible complex formation, if any, between ergotamine tartrate and caffeine in the solid state using differential scanning calorimetry.

EXPERIMENTAL

Materials

The ergotamine tartrate was obtained from Sigma Chemical Company. The caffeine was obtained from Mallinckrodt and the absolute methanol from J.T. Baker Chemical Company.

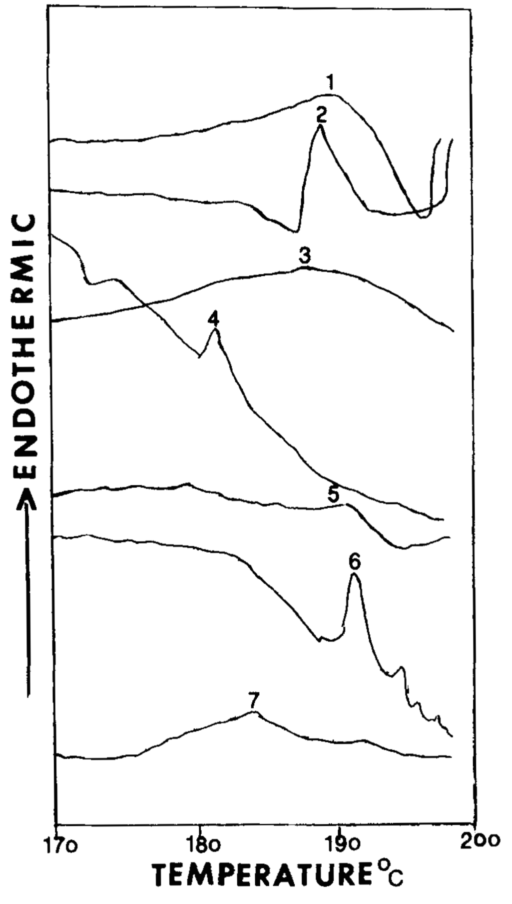

FIGURE 1

Thermograms of Ergotamine Tartrate-Caffeine Methanol Mixtures. Caffeine Mole Fractions Corresponding to the Thermograms are as Follows: 1-0.0, 2-0.200, 3-0.333, 4-0.500, 5-0.667, 6-0.750, 7-0.833. There was no Ergotamine Tartrate Peak Observed for Caffeine Mole Fractions of 0.600, 0.882, 0.909, 0.938 and 0.952.

TABLE 1

Thermodynamic Parameters for the Complex Formation Between Ergotamine Tartrate and Caffeine

Ergotamine Tartrate:Caffeine Molar Ratio (mole/mole)	Caffeine Mole Fraction	Ergot. Tart. Sample Transition ΔH		Peak Temp. °C	
		Cal g^{-1}	Kcal mol^{-1}	Ergot. Tart.	Caff.
1 : 0.000	0.000	6.26	8.22	191	N.P.*
1 : 0.250	0.200	4.27	5.60	189	N.P.
1 : 0.500	0.333	2.56	3.36	188	N.P.
1 : 1.000	0.500	1.34	1.76	180	N.P.

1 : 1.500	0.600	0.00	0.00	N.P.	N.P.
1 : 2.000	0.667	1.00	1.31	191.5	N.P.
1 : 3.000	0.750	0.77	1.01	190.5	N.P.
1 : 5.000	0.833	1.99	2.61	183.5	N.P.
1 : 7.500	0.882	0.00	0.00	N.P.	N.P.
1 : 10.000	0.909	0.00	0.00	N.P.	206.0
1 :15.000	0.938	0.00	0.00	N.P.	216.0
1 : 20.000	0.952	0.00	0.00	N.P.	227.0
1 : 1.000	1.000	0.00	0.00	N.P.	238.5

*N.P. = No endotherm obtained and therefore no peak temperature was observed.

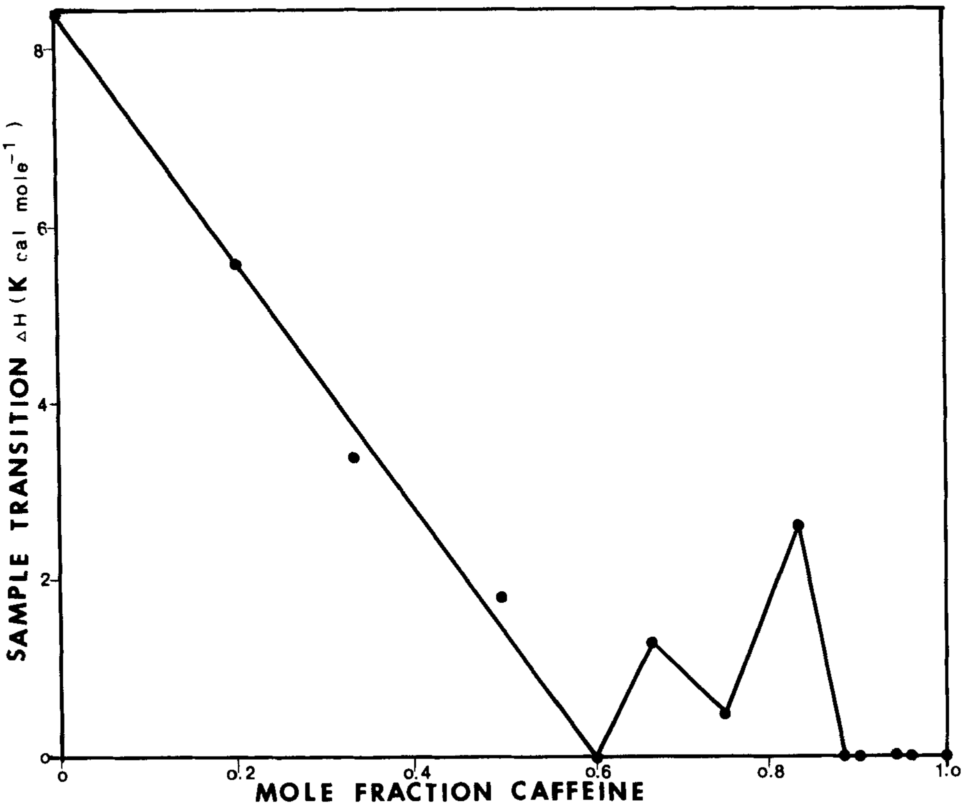

FIGURE 2

Phase Diagrams of Ergotamine Tartrate-Caffeine Methanol Mixtures

Differential Scanning Calorimetry

Samples containing an equivalent of 3 mg ergotamine tartrate were weighed and encapsulated in expandable aluminum pans with crimped-on lids especially designed for samples which exert significant vapor pressure in the range of interest. These samples were heated in an atmosphere of nitrogen and the thermograms were obtained on a Perkin Elmer DSC-1B Differential Scanning Calorimeter. The heating rate was $10^{o}C\ min^{-1}$ at a constant range setting of 8 mcal sec^{-1} and the thermograms were recorded at a constant chart speed of one inch per minute. The area under the curve, providing the basis for the calculation of the transition energy was measured with a mechanical planimeter (K & E).

Ergotamine tartrate-caffeine mixtures were prepared by dissolving different molar ratios of the drug and caffeine in a sufficient volume of absolute methanol in a porcelin dish. The dish was then transferred to a vacuum desiccator. After solvent evaporation under vacuum, the container was kept in the desiccator away from any source of heat and light until carrying out the DSC measurements. Physical mixtures of the same molar ratios were also evaluated by DSC. Duplicates of each DSC thermogram were made.

RESULTS AND DISCUSSION

Eleven different molar ratios of ergotamine tartrate to caffeine were evaluated in order to obtain the optimum ratio for complex formation. The molar ratios were 1:0.25, 1:0.50, 1:1.0, 1:1.5, 1:2.0, 1:3.0, 1:50, 1:7.5, 1:10.0, 1:15.0 and 1:20.0. Blank experiments for both ergotamine tartrate and caffeine, tested in the same manner as the mixtures, were also carried out.

Trace 1 of Figure 1 represents the endothermic peak of ergotamine tartrate, evaporated from methanol, with a maximum peak of transition at 191^{o}C immediately followed by a decomposition exotherm. The ergotamine tartrate sample transition energy was calculated to be 8.22 kcal mol^{-1}.

Traces 2-7 of Figure 1 are the thermograms of the six different molar ratios of ergotamine tartrate-caffeine mixtures, obtained from methanol solution, which exhibited significant values of heat of transition. All peaks differed considerably from those of plain ergotamine tartrate or caffeine. The results presented in Table 1 show that the transition energy values range from 5.60 kcal mol^{-1} for the 1:0.25 molar ratio to 1.02 kcal mol^{-1} for the 1:3.0 molar ratio of ergotamine tartrate to caffeine. The thermogram for the 1:1.5, 1:7.5, 1:10, and 1:20 molar ratios were not presented in Figure 1 as no ergotamine transition was observed for these mixtures.

The phase diagram in Figure 2 shows the heat of transition data for all molar ratios. The absence of an ergotamine tartrate endotherm at molar ratios of 1:1.5, 1:7.5, 1:10, 1:15 and 1:20 indicates the formation of complexes of ergotamine tartrate with caffeine. There appears to be a 2:3 complex corresponding to the 1:1.5 ratio and a 2:15 complex corresponding to the 1:7.5 molar ratio. Higher order complexes may also form when the caffeine mole fraction exceeds 0.882 (Table 1) as no endotherm was observed at molar ratios of 1:10, 1:15, and 1:20. There is an excess of caffeine in the system at this point as the caffeine peak appears at the 1:10 molar ratio. The 1:15, or 2:30, complex is indeed a multiple of the 2:3 and 2:15 complex. The existence of ergotamine tartrate complexes finding that these complexes containing more than one caffeine molecule was proposed by Anderson and Pitman[11] based on an analysis of their phase solubility diagrams.

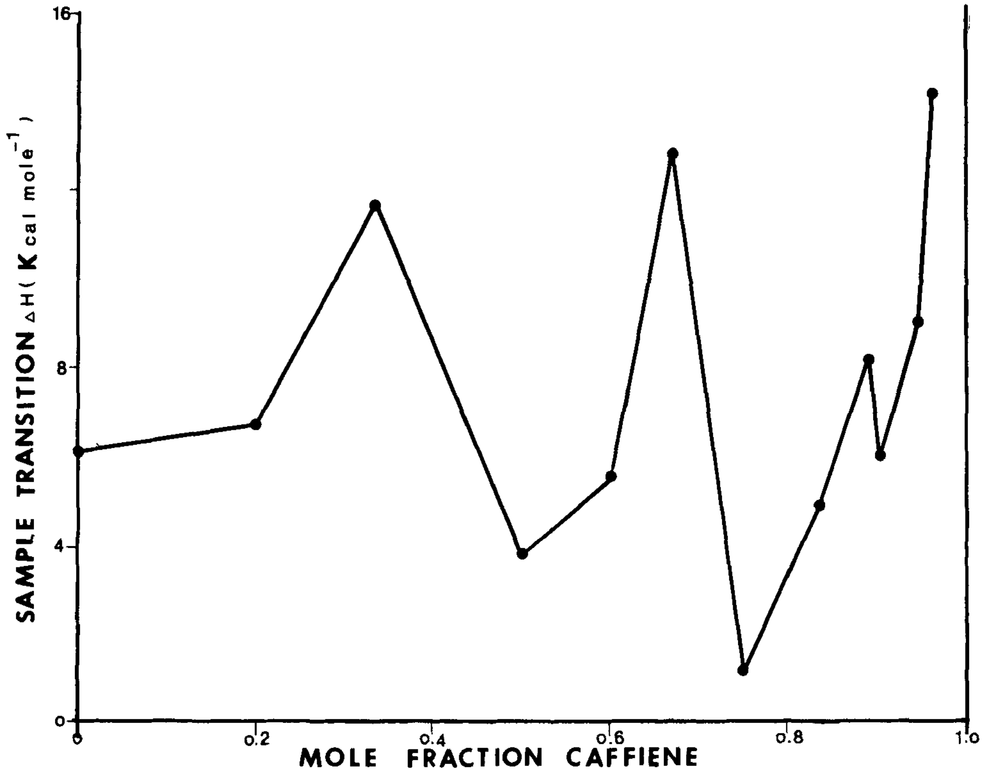

FIGURE 3

Phase Diagram of Ergotamine Tartrate-Caffeine Physical Mixtures

The phase diagram of the physical mixtures shown in Figure 3 also indicates the presence of ergotamine tartrate-caffeine interactions. These interactions differs from that of the mixtures obtained from methanol solution. Table 2 gives the values of the heat of transition of ergotamine tartrate-caffeine physical mixtures of the same molar ratios considered for the "methanol mixtures." A significant difference was observed between the heat of transition values for the "methanol mixtures" and those for the physical mixtures. There were no zero values

TABLE 2

Thermodynamic Parameters for the Complex Formation Between Ergotamine Tartrate and Caffeine Physical Mixtures

Ergotamine Tartrate:Caffeine Molar Ratio (mole/mole)	Caffeine Mole Fraction	Ergot. Tart. Sample Transition ΔH		Peak Temp. °C	
		$Cal\ g^{-1}$	$Kcal\ mol^{-1}$	Ergot. Tart.	Caff.
1 : 0.000	0.000	4.69	6.16	198.5	N.P.*
1 : 0.250	0.200	5.12	6.62	191	N.P.
1 : 0.500	0.333	8.96	11.76	191	N.P.
1 : 1.000	0.500	2.84	3.73	183.5	N.P.

1 : 1.500	0.600	4.12	5.41	189	N.P.
1 : 2.000	0.667	9.81	12.88	178.5	N.P.
1 : 3.000	0.750	0.85	1.12	190.5	N.P.
1 : 5.000	0.833	3.70	4.85	180.0	N.P.
1 : 7.500	0.882	6.26	8.22	186.5	N.P.
1 :10.000	0.909	4.55	5.98	182.1	207
1 : 15.000	0.938	6.82	8.96	187.0	214
1 : 20.000	0.952	10.81	14.19	179.0	221
1 : 1.00	1.000	00.00	00.00	N.P.	240.0

*N.P. = No endotherm was obtained and therefore no peak temperature was observed.

for the heat of transition of ergotamine tartrate-caffeine physical mixtures compared to five zero values for the different molar ratios obtained from methanol solution. In addition, all of the ergotamine tartrate sample transition values for the different molar ratios of the physical mixtures were higher than those of the corresponding ratios of the "methanol mixtures." There is an indication in this phase diagram that complexation may be occurring at molar ratios of 1:1 and 1:3. This data differs from that obtained for the "methanol mixtures." It should be noted that the endotherm of ergotamine tartrate following methanol evaporation differed from that of original material. A comparison of Tables 1 and 2 shows a decreased transition temperature (191^o vs 198.5^o) and an increased heat of transition (8.22 vs 6.16 Kcal/mole) for the ergotamine tartrate from methanol. It has been previously reported that ergotamine tartrate may contain 2 molecules of methanol of crystallization[14]. The inclusion of methanol in the structure may enhance the ability of ergotamine tratrate to complex with caffeine. It is apparent, however, that complexation is occurring between caffeine and both forms of ergotamine tartrate and that complexes containing more than one mole of caffeine are formed.

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