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Heat of Dissolution of Chloramphenicol Palmitate in Organic Solvents

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The higher fatty acid ester of chloramphenicol exhibits polymorphism. For medical purposes, α-form crystals are used. The heats of dissolution of chloramphenicol (CP) and chloramphenicol palmitate (CPP) in organic solvents (ethanol, dioxane, butanol and ethylacetate) were measured with a calorimeter. The heat in dissolution of CPP was endothermic larger than that of CP by about 10 kcal/mol. The heat of dissolution of α-form CPP was found to be less than that of β-form CPP, while the rate of dissolution of the former was slightly faster than the latter.

Keywords——heat of dissolution ; chloramphenicol ; chloramphenicol palmitate ; ethanol ; n-butanol ; ethylacetate ; 1,4-dioxane, conduction type micro calorimeter

Chloramphenicol (CP) and chloramphenicol palmitate (CPP) are both slightly soluble in water. The latter is polymorphic. The β-form crystals being stable at room temperature, α-form crystals are somewhat unstable. Amorphous CPP is also known. Tamura et al. [1,2,3] reported that all of the hydrocarbonchains of the β-form ester (mp 91℃) are in a trans configuration, while part of the chains of the α-form ester (mp 86—87℃) are in a cis configuration. Due to the partial cis configuration of the α-CPP, the interplanar spacing measured by an X-ray diffraction method is 36 Å, and only 28 Å for the β-CPP. This indicates that part of the chain is distorted in the α-form, hence the molecules are more loosely packed and resulting in the slightly lower specific gravity compared to the β-form.

In this report, the heats of dissolution of CP, α-CPP and β-CPP in the four organic solvents, ethanol, dioxane, n-butanol and ethylacetate, were measured with a twin type micro calorimeter. The measurements were made at 25℃ and 37℃.

Experimental

Materials and Methods——Chloramphenicol and β-chloramphenicol palmitate were obtained from Sankyo Ltd. For purification, 15 grams of β-CPP were dissolved in 25 ml of xylol while keeping the temperature under 70℃ in a water bath. Following this, the warm solution was filtered and recrystallized. A melting point 92℃ for β-CPP was measured. To prepare α-CPP, 50 grams of purified β-CPP were added to 100 ml of methanol and dissolved at a temperature of 50℃ or below in a water bath, then, after

filtering, the warm solution was recrystallized by cooling rapidly in 200 ml of cooling water at a temperature of 10°C or below followed by vacuum drying. The melting point of the purified α-CPP was 87°C. These experimental melting points including one of 151°C obtained for CP are in agreement with the literature values.[2)]

The solvents, dioxane, ethanol, n-butanol and ethylacetate, were of guranted reagent grade and were distilled before use.

The apparatus[4)] employed was a twin conduction calorimeter, Type CM-20, made by Oyodenki Kenkyusho. This apparatus has an aluminium block for the constant temperature body and, with a thermomodule, detects the heat of dissolution produced in the sample vessel when a sealed ampule containing the solid sample is broken in the solvent by a remote control device. The standard heat is obtained from the Joules heat generated by a constant electric current conducted to the heater in the apparatus.

About 0.5—2.5 m mol of the sample was weighed accurately and sealed in an ampule. The ampule was then set in the calorimeter together with 50 ml of the solvent. After a constant temperature was reached in the calorimeter, the ampule was broken by a remote control device and the heat generated by the dissolution of the sample into the solvent was measured.

Results and Discussion

The measured heats of dissolution are shown as curves in Figures 1 and 2. The vertical co-ordinate represents time and the horizontal co-ordinate represents the thermo-electromotive force detected by the thermomodule. The heat of dissolution can be obtained by comparing the area under the sample curve with the area of the standard heat curve. In the case of ethanol as shown in Fig. 1(a), CP has the fastest rate of dissolution followed by α-CPP with β-CPP being the slowest. With a twin conduction calorimeter, the amount of electric current passing through the thermomodule after the completion of dissolution is proportional to the temperature difference, hence the curve should be exponential when it returns to the base line. It is therefore understood that the dissolution of β-CPP continued slowly over an extended period of time. When dioxane was used as a solvent, there were almost no differences observed among the rates of dissolution as shown in Fig. 1(b). As Fig. 2(a) shows, the curves obtained with utilizing butanol as the solvent were similar to those obtained with ethanol. With ethylacetate, as shown in Fig. 2(b), the rates of dissolution were faster compared to the other three solvents and differences among CP, α-CPP and β-CPP were small. This is probably owing to the better solubility of CP and its esters in ethylacetate than in the other three solvents.

Comparing the four solvents, ethylacetate effected the greatest rate of dissolution followed by dioxane, ethanol and butanol in oder of decreasing dissolution power. This indicates that the rate of dissolution does not necessarily correlated with solvent polarity because the non-polar dioxane had a higher solvent power than the polar alcohols. It is

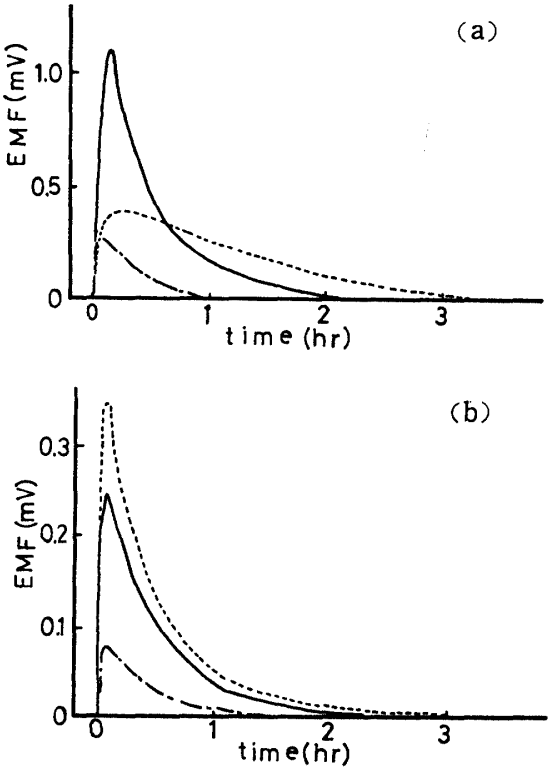

Fig. 1 Peak Area of Dissolution Enthalpy (Endothermic) CP and CPP in Ethanol (a) and 1,4-Dioxane (b) at 25°C
—·—·— : CP
——— : α-CPP
--------- : β-CPP

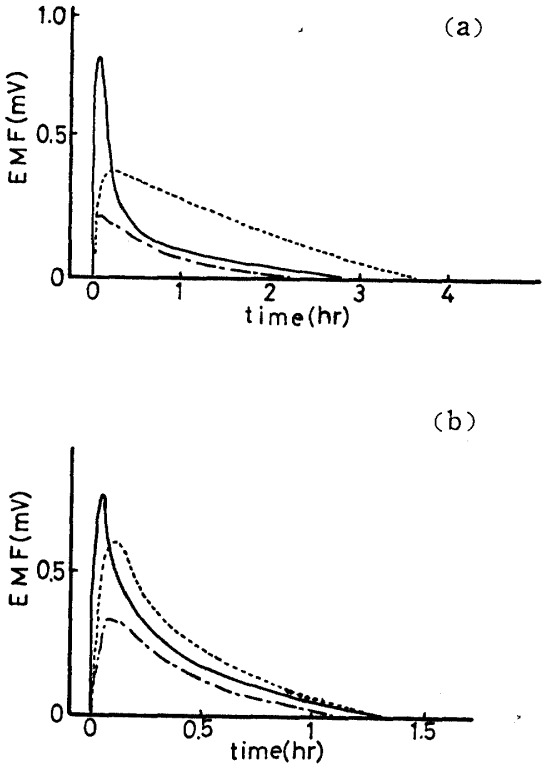

Fig. 2 Peak Area of Dissolution Enthalpy (Endothermic) CP and CPP in n-Butanol (a) and Ethylacetate (b) at 37°C
—·—·— : CP
——— : α-CPP
--------- : β-CPP

to be noted that β-CPP dissolved relatively slowly in alcohols.

The heats of dissolution at 25°C and 37°C are tabulated in Table I. All of the values in Table I are enthalpies of endotherm. The differences in the heat of dissolution among CP, α-CPP and β-CPP in various solvents are presented in Table II. Regardless of the solvent, CP was the smallest in the heat of dissolution followed by α-CPP and β-CPP with the largest. The differences in the heat of dissolution between CP and α-CPP were in the range of 9—10 kcal/mol except in ethylacetate. This difference is considered mainly attributable to the long chain alkyl group of CPP. Generally, dissolution of a molecular crystal is a process by which each molecule in the crystal separates and an energy equvalent to the van der Waals force is measured as the heat of dissolution. Therefore, if the molecular volume is large and the polarizability is also large, then the heat of dissolution should become large. Furthermore, the heat of dissolution is affected by the interaction between the solvent and the solute. In reflection on aforementioned experimental results, however, the slightly lower heat of dissolution of CPP in ethylacetate may be explained by the fact that both of them are esters and their

Table. I Heats of Dissolution (kcal/mol) of CP, α-CPP and β-CPP at 25° and 37°C

Solvate	CP		α-CPP		β-CPP	
Temp.	25°	37°	25°	37°	25°	37°
Solvent						
Ethanol	3. 75	3. 09	13. 62	12. 05	16. 65	16. 86
n-Butanol	2. 06	1. 79	12. 54	14. 52	17. 68	17. 02
Ethylacetate	5. 20	5. 00	11. 64	11. 39	16. 63	15. 70
1,4-Dioxane	3. 67	3. 60	12. 82	12. 80	17. 35	17. 27

Table. II Differences Heats of Dissolution between CP, α-CPP and β-CPP

Solvate	α-CPP−CP		β-CPP−CP		β-CPP−α-CPP	
Temp.	25°	37°	25°	37°	25°	37°
Solvent						
Ethanol	10. 05	8. 96	13. 08	13. 77	3. 03	4. 81
n-Butanol	10. 48	12. 73	15. 62	15. 27	5. 14	2. 50
Ethylacetate	6. 44	6. 39	11. 43	10. 7	4. 99	4. 31
1, 4-Dioxane	9. 15	9. 2	13. 68	13. 67	4. 53	4. 47

mutual affinity may be greater in the other solvent systems. The differences in the heat of dissolution between α-CPP and β-CPP were in the range of 4—5 kcal/nol, a fairly large increment. In the β-form, all of the hydrocarbon chains of the ester have a stable trans configuration, while in the α-form, part of them have a cis configuration. The specific gravity of the β-ester is 1. 31, which is 5 percent larger than specific gravity 1. 27 of the α-form due to the denser packing of molecules in the β-form. Hence, to summarize, the heat of dissolution of the α-form is less than that of the β-form and the melting point of the former is also lower by 4—5°C than the latter. The difference in the heat of dissolution between the two crystalline forms of this polymorphic compound is fairly considerable and is attributable to individually characteristic stability and packing rates.

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