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KINETIC STUDY OF THE SOLID-STATE THERMAL INTERCONVERSION OF THE POLYMORPHIC FORMS OF CHLORAMPHENICOL PALMITATE

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Abstract

Kinetic studies revealed that the solid-state thermal interconversion of polymorphic forms of chloramphenicol palmitate at different temperatures followed apparent zero-order kinetics. The transformation between the metastable forms C and B was faster than the subsequent transformation of form B to form A. However, starting with form B the transformation to form A was slower than the transformation of form B, formed by the transformation of form C, to form A. The rate constant (k_0) plotted versus temperature (K) according to the Arrhenius equation was linear. There were significant differences in the activation energy and other thermodynamic parameters.

Introduction

The solid-state transformation of the polymorphic forms of chloramphenicol palmitate have been studied[1,2,3]. These studies revealed that the stability of the metastable polymorphic forms, C and B, depended on physical stress induced on it from the environment, for instance prolonged grinding or increased temperatures.

Wadke and Reier[4] reported the use of intrinsic dissolution rates to determine thermodynamic parameters associated with the phase transitions of chloramphenicol palmitate. Otsuka and Kaneniwa[5] reported the use of x-ray powder diffraction analysis to follow quantitatively the interconversion of the polymorphic forms of chloramphenicol palmitate. They calculated rate constants according to the Avrami equation[6].

In this study the interconversion of the polymorphic forms of chloramphenicol palmitate were followed at various temperatures using x-ray powder diffraction analysis. From the results the thermodynamic values according to the transition state theory were calculated and compared to that found in the literature.

Experimental

Chloramphenicol palmitate (Batch no. CMM 23B) supplied by Fine Chemicals (Cape Town, RSA) was used. Polymorph A, B and C were prepared as described by Aguiar **et al.**[7]. X-ray powder diffraction profiles were used to identify the three forms. The x-ray diffraction profiles were measured at room temperature with a Phillips PM9901/00 diffractometer. The measurement conditions were as follows: target, CoKα; filter, Fe; voltage, 40 kV; current, 20 mA; slit, 0.2; counting range, 2×10^2 cpm; scanning speed, $1°min^{-1}$. About 100 mg of the sample was loaded into a aluminium sample holder without introducing a preferred orientation of the crystals. Samples, 15 g of polymorph C, were stored in desiccators containing silica at 45, 55, 75, 85 and 90 ±1 °C. About 100 mg samples was withdrawn at appropriate intervals and the x-ray powder diffraction profiles recorded. Samples of form B, 15 g, was also stored at 55, 75, 85 and 90 ±1°C. Figure 1 are examples of the x-ray diffraction profiles of the polymorphs and known mixtures of form C and B and B and A. In table 1 the main x-ray powder diffraction angles and peak intensity ratios are listed.

Kaneniwa and Otsuka[2] found a good linear calibration curve when they plotted the content of form B or A against the natural logarithm of the ratio in the intensity of the main diffraction peaks of the different forms. Figure 2 shows the relation between contents of polymorphs and the log values for x-ray diffraction intensity ratios at $2\theta° = 26.2$ and 23.0 for the relation between form C and B, at $2\theta° = 23.0$ and 11.6 for the relation between form B and A and at $2\theta° = 26.2$ and 11.6 for the relation between form C and A. The plots each gave a straight line with mean correlation coefficient of 0.996 and coefficient of variation of 0.98%.

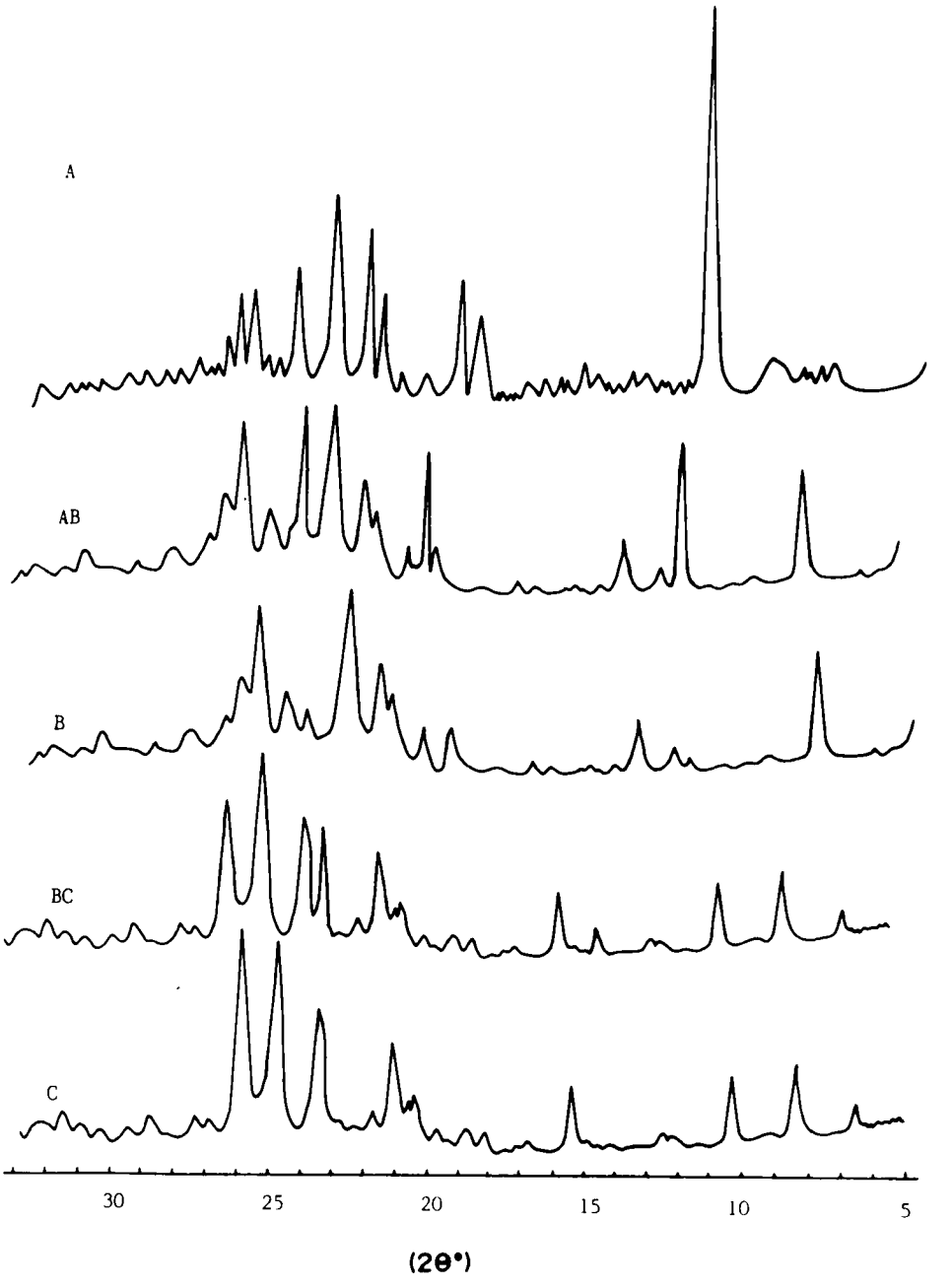

FIGURE 1

X-ray powder diffraction profiles of polymorphic forms of chloramphenicol palmitate (A) form A (AB) mixture form A and B (B) form B (BC) mixture form B and C and (C) form C.

TABLE 1

The main x-ray powder diffraction peak angles and peak intensity ratios for the polymorphic forms of chloramphenicol palmitate.

Form A		Form B		Form C	
2θ°	I/Io	2θ°	I/Io	2θ°	I/Io
11.6	1.00	23.0	1.00	26.2	1.00
23.6	0.57	25.8	0.92	25.0	0.94
22.5	0.48	8.3	0.72	23.7	0.65
24.8	0.40	21.9	0.64	21.3	0.49
19.5	0.34	25.0	0.50	8.7	0.39

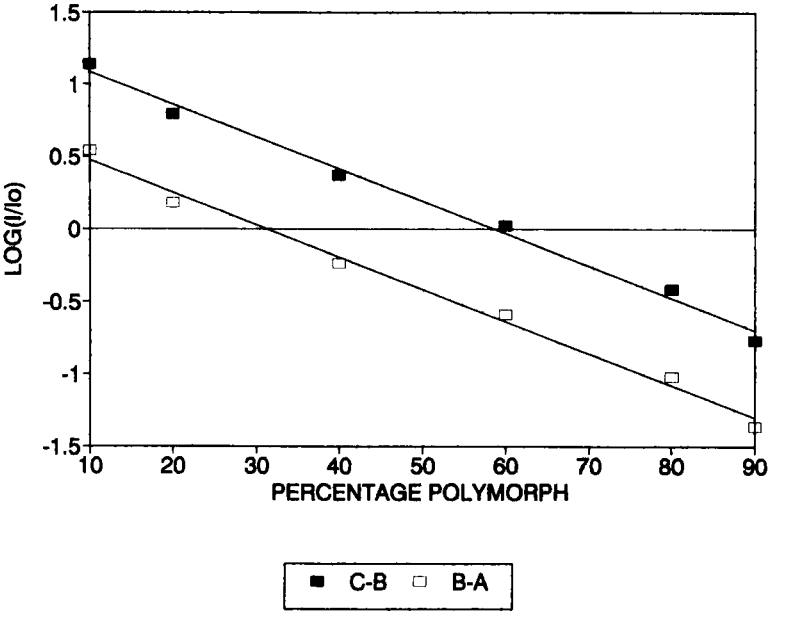

FIGURE 2

Relation between polymorph content and the log values for x-ray diffraction intensity ratios (I/Io). (C-B) relation between Form C and B at 2θ° = 26.2 and 23.0 and (B-A) relation between form B and A at 2θ° = 23.0 and 11.6. The markers represent measured values and the lines the best fit.

TABLE 2

The percentage of polymorph A and B present with time calculated from x-ray powder diffraction peak intensity ratios for form C kept at different temperatures.

Time	45°C		55°C		75°C		85°C		90°C	
(min)	B	A	B	A	B	A	B	A	B	A
0	0	0	0	0	0	0	0	0	0	0
30	0	0	6	0	10	0	23	0	29	7
60	0	0	19	0	15	0	48	0	80	12
90	0	0	31	0	37	0	74	0	81	19
120	0	0	45	0	58	0	100	0	77	23
240	0	0	93	0	98	2	89	11	43	57
480	3	0	100	0	96	4	65	35	0	100
600	8	0	100	0	87	13	32	68	0	100
800	16	0	99	1	65	35	8	92	0	100
1000	19	0	9	2	59	41	0	100	0	100
1600	34	0	95	5	51	49	0	100	0	100
3200	59	8	86	14	3	97	0	100	0	100
6400	87	13	75	25	0	100	0	100	0	100
7400	83	17	70	30	0	100	0	100	0	100

From the ratio in intensity of the main diffraction peaks with time and the data displayed in figure 2 the percentage of each polymorph present in the samples were calculated. The values for the percentage polymorph versus time were plotted and several kinetic equations used to analyse the plots[6]. The equation for zero-order kinetics best described the plots. A computer program was used to calculate the zero-order rate constants (k_0)[8]. The same program was used to calculate the Arrhenius relationships between the rate constants, at different temperatures.

Results and discussion

In table 2 and 3 the percentage of each polymorph present with time, for samples kept at different temperatures, are listed. This data showed that the transformation of

TABLE 3

The percentage of polymorph A and B present with time calculated from x-ray powder diffraction peak intensity ratios for form B kept at different temperatures.

Time	55°C		75°C		85°C		90°C	
(min)	B	A	B	A	B	A	B	A
0	100	0	100	0	100	0	100	0
30	100	0	100	0	100	0	100	0
60	100	0	100	0	100	0	100	0
90	100	0	100	0	100	0	100	0
120	100	0	100	0	100	0	98	2
240	100	0	100	0	100	0	94	6
480	100	0	100	0	94	6	86	14
600	100	0	96	5	85	15	70	30
800	100	0	91	9	73	27	29	71
1000	100	0	85	15	42	58	4	96
1600	99	1	79	21	12	88	0	100
3200	96	4	63	37	0	100	0	100
6400	90	10	24	76	0	100	0	100
7400	78	22	3	97	0	100	0	100

form C to form B reached a maximum after 7 hours at 55°C and after 1 hour 20 minutes at 90°C. The subsequent transformation of form B to form A reached a maximum after 53 hours at 75°C and 8 hours at 90°C. Starting with form B the transformation to form A reached a maximum after 132 hours at 75°C and 20 hours at 90°C.

The zero-order transformation values of chloramphenicol palmitate polymorphs at different temperatures are listed in table 4. The mean correlation coefficient was 0.981 with a coefficient of variation of 2.35%. The rate of transformation increased with an increase in the temperature at which the samples were kept. Overall the transformation of form C to form B was the quickest. There was a significant difference in the rate of transformation of form B, obtained from form C, to form A and form B to form A. The transformation of form B to form A was slower.

TABLE 4

The influence of increased temperature on the apparent zero-order transformation of metastable polymorphs of chloramphenicol palmitate, C and B, to the stable form A.

Transformation between Polymorphs	Zero-order Regression Values	45°C	55°C	75°C	85°C	90°C
C-B	slope	0.0164	0.2223	0.4358	0.8367	1.2100
	intercept	1.995	9.603	-2.558	-1.200	0.800
	correlation	0.982	0.922	0.989	1.000	0.964
C/B-A	slope	0.0024	0.0042	0.0317	0.1123	0.2123
	intercept	-1.220	-1.253	-1.213	-7.375	0.213
	correlation	0.974	0.996	0.975	0.975	0.997
B-A	slope		0.0026	0.0128	0.0349	0.0970
	intercept		-2.396	-1.822	3.613	-13.59
	correlation		0.913	0.996	0.905	0.940

Arrhenius type plots of the zero-order rate constants (slope values) against temperature are given in figure 3. The mean correlation coefficient was 0.968 with a coefficient of variation of 3.14%. The activation energy and other thermodynamic parameters, calculated according to the transition state theory[9], and obtained in the literature are listed in table 5. The activation energy necessary to induce the transformation of form C to B, 78 $kJmol^{-1}$, was significantly less than that required by form B for its transformation to form A, 96 $kJmol^{-1}$. The calculated $t_{1/2}$ values at 20°C showed that form C is less stable than form B and that the transformation of form B to form A was quicker when starting with form C as supposed to form B. The values for the thermodynamic parameters differs from that reported by Wadke and Reier[4] but were of the same order as that reported for other solid-state transformations[7]. The values for k_0 were of the same order as that reported by Otsuka and Kaneniwa[5].

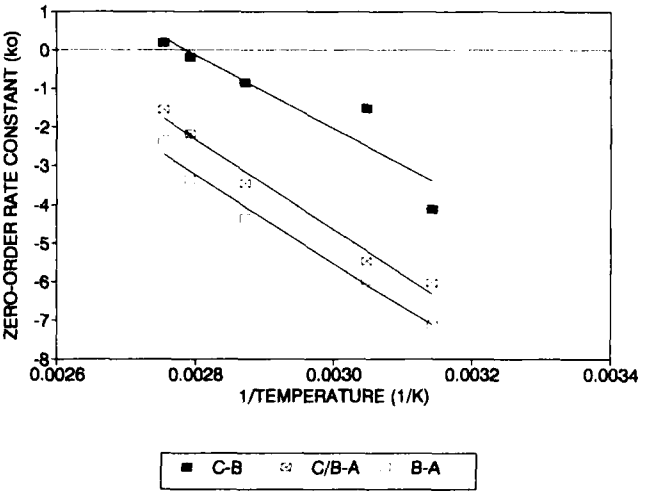

FIGURE 3

Arrhenius type plots showing temperature dependence of k_0, the apparent zero-order rate constant, for the interconversion of polymorphic form C and B to form A. (C-B) the conversion of form C to B (C/B-A) the conversion of form B formed from form C to form A and (B-A) the conversion of form B to A. The markers represent measured values and the lines the best fit.

TABLE 5

Thermodynamic parameters for the transformation of form C and B of chloramphenicol palmitate to form A at 20°C obtained from Arrhenius type plots and reports in the literature.

Polymorphic inter-conversion	Activation energy (kJmol^{-1})	Zero-order rate constant (min^{-1})	Pre-exponential factor (1/K)	Half life t½ (hours)	Gibbs free energy (kJmol^{-1})	Entropy ΔS	Enthalpy ΔH (kJmol^{-1})
C-B	78.98	2.64×10^{-2}	3.13×10^{11}	315	86.23	-24.7	78.98
C/B-A	96.91	7.92×10^{-5}	1.47×10^{13}	10524	94.77	7.279	96.91
B-A	95.97	3.41×10^{-5}	4.29×10^{12}	24415	96.65	-2.341	95.97
C-B[5]		4.52×10^{-2}					
B-A[5]		6.12×10^{-2}					
B-A[4]	33.08				33.08	115.00	22.22

Conclusion

The values for the activation energy and other thermodynamic values were of the same order as that reported for other solid state transformations[7] but differed from that reported by Wadke and Reier[4] calculated from intrinsic dissolution rate data for chloramphenicol palmitate. The activation energy for the interconversion of form C to B was significantly smaller than that of the interconversion of from B to A. However, the calculated Gibbs free energies were not significantly different. These values confirmed that form C is considerably less stable than form B, and that form C and B are less stable than form A when subjected to physical stresses, in this study increased temperature. X-ray powder diffraction analysis seems to be an ideal way to study quantitatively the stability of the polymorphic forms of chloramphenicol palmitate.

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