Journal of Thermal Analysis and Calorimetry, Vol. 56 (1999) 1329-1334

THERMOANALYTICAL STUDY OF THE DEHYDRATION OF CYCLODEXTRIN INCLUSION COMPLEXES OF CLOFIBRIC ACID

M. R. Caira, S. A. Bourne and E. Mvula*

Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa

Abstract

Hydrated inclusion complexes of the hosts β-CD (*CD*=cyclodextrin), γ-CD and permethylated β-CD with the guest clofibric acid were analysed by TG and DSC methods to characterise their dehydration behaviours. Activation energies for dehydration of the β- and γ-CD clofibric acid complexes, determined by isothermal thermogravimetry, are significantly lower (~20–25%) than those for the corresponding uncomplexed hydrated CDs. These data can be reconciled with X-ray structural data which show that H_2O molecules in the complexes occupy different crystal sites from those occupied in the parent CDs.

Keywords: cyclodextrin complexes, dehydration, kinetics, TG-DSC

Introduction

This study forms part of an on-going investigation of the structures, thermal stability and kinetics of decomposition of cyclodextrin (CD) inclusion complexes of poorly soluble drug substances. The CDs referred to in this study contain seven (β-CD) and eight (γ-CD) α-(1→4)-linked *D*-glucopyranose units respectively.

Water molecules play an essential role in stabilizing the crystalline structures of cyclodextrin inclusion complexes. Complex water content and the nature and rate of dehydration affect properties such as cohesive strength and stability under storage. Recent studies of the dehydration of CD complexes by thermal analysis include those of β-CD hydrate [1, 2], native and modified CDs as well as metal-β-CD complexes [3], and hydrated CD complexes of drug substances [4].

The dehydration of three CD complexes containing the guest clofibric acid, [2-(4-chlorophenoxy)-2-methylpropanoic acid, or CPIB], a cholesterol-lowering drug, was investigated here by TG, DSC and isothermal thermogravimetry. The drug CPIB is poorly soluble in water and we are investigating its CD-inclusion complexes for the purpose of improving its delivery properties. The complexes are **1** β-CD·CPIB·8.4H_2O, **2** γ-CD·CPIB·15.5H_2O and **3** TRIMEB·CPIB·1.4H_2O [TRIMEB=heptakis(2,3,6-tri-O-methyl)-β-CD]. These complexes were chosen for study since we had obtained

* Author to whom all correspondence should be addressed.

1418–2874/99/ $ 5.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

preliminary X-ray structural information which could complement the thermal and kinetic results. It was of particular interest to compare the activation energies of dehydration of the complexes with those for the uncomplexed hydrated parent cyclodextrins and to relate the results to possible dehydration pathways within the crystal structures.

Experimental

Full details of the preparations of **1–3** and their structural analyses by X-ray diffraction will be reported elsewhere [5]. All of the complexes were obtained as crystalline precipitates from aqueous solutions containing the host-CD and the drug in 1:1 molar proportions. The formulae quoted above were derived from UV spectrophotometry (host-guest ratios) and TG (H_2O content). TG and DSC traces were obtained on a Perkin Elmer PC7 series system at a heating rate of 10°C min^{-1} using sample masses in the range 1–4 mg. Samples were purged with N_2 flowing at 40 ml min^{-1}. Isothermal TG at 5° intervals in the range 35–70°C was performed using microcrystals (10–100 μm) obtained by complex crystallization from rapidly stirred aqueous solutions. Mass losses measured with time were used to obtain α(extent of reaction) *vs.* time curves which were analysed using various kinetic models [6] to seek the best linear fits over the α range 0.05–0.95.

Results and discussion

Figure 1 is the DSC trace for the guest compound CPIB, showing its characteristic melting endotherm at 120.2°C. The absence of this endotherm in any of the DSC traces which follow is evidence of inclusion of the drug in the CDs investigated. Complexes **1–3** are readily distinguished from their combined TG-DSC traces, shown in Fig. 2. Characteristic temperatures, estimated water contents and relevant X-ray crystal data are listed in Table 1. The first stage in the decomposition of the complexes is dehydration. For the β-CD complex **1**, dehydration occurs in two steps as indicated by an inflection point in the TG trace and as distinct endotherms (A, B) in the DSC trace. This is followed by gradual mass loss with major decompo-

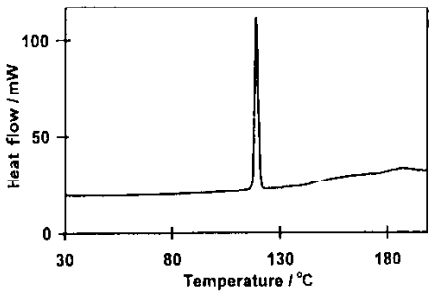

Fig. 1 DSC trace for the drug guest CPIB

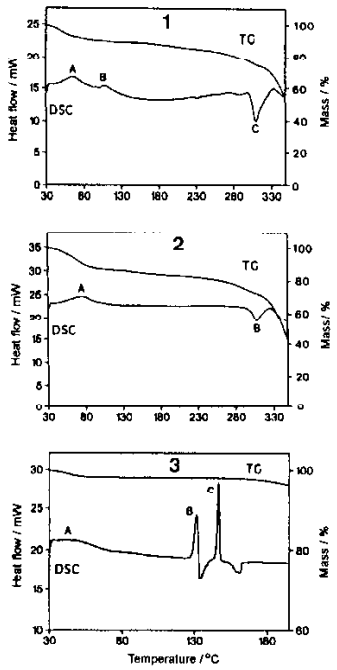

Fig. 2 Combined TG and DSC traces for complexes **1–3**

sition occurring exothermically (peak C). The γ-CD complex **2** behaves similarly, except that what appears as two-step dehydration in TG is reflected only as a single endotherm (A) in DSC. Dehydration of the TRIMEB complex **3** occurs in one step which appears as a broad endotherm (peak A) in the DSC trace. The anhydrous com-

Table 1 TG-DSC and crystal data for complexes **1–3**

Complex	Event/ DSC	Onset/ T_i/°C	Peak/	%H_2O/ TG	Space group	Z
1	A	48	66	10.1	C2	4
	B	104	110			
	C	302	309			
2	A	50	75	15.6	$P42_12$	6
	B	301	309			
3	A	30	45	1.5	$P2_12_12_1$	4
	B	129	132			
	C	145	147			

plex then undergoes an endothermic phase change (peak B), recrystallization, and finally melting (peak C). Similar sharp melting behaviour was found for anhydrous TRIMEB complexes with naproxen [7] and ibuprofen [8] as guests. The proposed phase transition is consistent with zero mass loss over the temperature interval which includes peaks B and C. To confirm the nature of this transition, X-ray powder diffractograms were also recorded for samples heated to approximately 100, 135 and 200°C, i.e. for the anhydrous complex, the presumed recrystallized species and the residue after melting. The first two samples yielded different X-ray powder patterns, thus confirming the existence of two distinct crystalline phases, while the last yielded a somewhat diffuse pattern only, indicating that the final residue was essentially amorphous.

Due to the small water content of complex **3** (only $1.4H_2O$ molecules per CD molecule), isothermal thermogravimetry experiments with this complex were unsuccessful. Table 2 lists the kinetic data obtained for the dehydration of complexes **1** and **2**, and for comparison, data for the dehydration of β-CD·$12.5H_2O$ and γ-CD·$16.8H_2O$. Kinetic data for dehydration of both **1** and **2** were best described by the D3 (three-dimensional diffusion-controlled) model, whereas F1 (first-order) and F2 (second-order) models were appropriate for the dehydration of the corresponding parent hydrated CDs. Furthermore, the activation energies (E_a) for dehydration derived from ln$k$ *vs.* $1/T$ plots were similar for the two complexes and significantly lower than those obtained for their corresponding parent hydrated CDs (Table 2). It should be noted that the E_a value obtained here for dehydration of β-CD·$12.5H_2O$, 64±2 kJ mol^{-1}, compares favourably with the value 65.7±3.1 kJ mol^{-1} obtained earlier [1], although the non-isothermal methods used there led to the conclusion that the dehydration is a zero-order process. On the other hand, first-order dehydration kinetics were reported for hydrated β-CD from an analysis of diffraction data measured from a single crystal exposed to a range of relative humidities [9]. In any event, the use of the value 64±2 kJ mol^{-1} for hydrated β-CD obtained in this study seems justified in view of the known insensitivity of the derived E_a value to reaction order and the fact that it is being compared with E_a values for the other compounds whose kinetics were studied and analysed under the same conditions.

Analysis of complexes **1** and **2** by X-ray diffraction revealed the following essential features: (a) severe disorder of the guest CPIB molecule in both the β-CD and γ-CD cavities which precluded their crystallographic modelling, (b) crystallo-

Table 2 Kinetic parameters for dehydration of complexes **1** and **2** and those for the corresponding uncomplexed parent CD hydrates

Species	Kinetic model for dehydration	Regression coeff. range	E_a/ kJ mol^{-1}	Regr. coeff. Arrhenius plot
1	D3	0.9947–0.9979	50±2	0.9911
2	D3	0.9903–0.9991	43±1	0.9973
β-CD·$12.5H_2O$	F1	0.9790–0.9988	64±2	0.9978
γ-CD·$16.8H_2O$	F2	0.9853–0.9982	58±4	0.9951

graphically well-behaved host molecules which pack in 'channel' mode in both crystals, (c) ordered and disordered water molecules located solely in the interstitial sites of complex **1** (i.e. outside the CD cavity), and almost exclusively in the interstitial sites of complex **2**. It should be noted that for **1**, structure refinement accounted for $7.0H_2O$ molecules per CD molecule out of the total of 8.4 estimated from TG analysis, while for **2** these figures were 6.3 and 15.5 respectively. In the latter case, location of water molecules was rendered more difficult due to their extensive disorder. The possibility that a considerable proportion of the water is also located in the γ-CD cavity cannot therefore be ruled out.

Figure 3 shows projections of the crystal structures of **1** and **2** parallel to both the host channels (containing disordered guest molecules) and the channels occupied by the H_2O molecules. The program MOLMAP [10] was used to examine the water-filled channel topologies. This revealed their continuity and unconstricted nature along the *z*-directions in the crystals. The channel cross-sectional areas vary from 34–57 $Å^2$ in **1** and from 44–97 $Å^2$ in **2**. Thus, migration of H_2O molecules along these channels should be unimpeded by the host CD molecules in both complexes. These structural results are consistent with the TG-DSC profiles for **1** and **2** which have similar overall features, including relatively low onset temperatures for dehydration. They are also consistent with the finding that dehydration of both **1** and **2** follow a diffusion-controlled kinetic model.

A detailed study of the packing in the β-CD hydrate structure [9] showed that there are no diffusion paths for H_2O molecules in the static crystal structure and that dehydration must involve conformational flexure of the host molecules to create

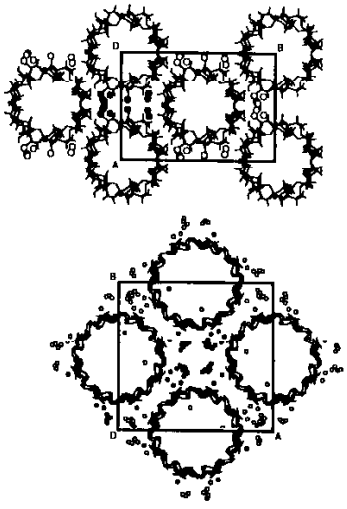

Fig. 3 [001] Projections of the crystal structures of **1** (upper) and **2** (lower), showing oxygen atoms (filled circles) of H_2O molecules occupying representative interstitial channels. The CD cavities contain severely disordered guest molecules (not shown)

such pathways. This crystal structure and that of the γ-CD hydrate are of the 'cage' or 'fishbone' type [11], with water molecules 'locked' in interstitial cavities and within the CD cavities. Similar E_a values obtained here for dehydration of these parent CD hydrates (64.58 kJ mol^{-1}) are thus in keeping with their known crystal structures which are devoid of channels. It is therefore reasonable to conclude that the significantly smaller values of E_a we obtained for dehydration of complexes **1** and **2** (50.43 kJ mol^{-1}) are consistent with the location of H_2O molecules in unobstructed channels which could facilitate water escape from the crystals. β-CD and γ-CD complexes frequently crystallize in the respective space groups C2 and $P42_12$ and we predict, on the basis of their isomorphism with **1** and **2**, that their dehydration will also be characterised by relatively low activation energies.

Further investigation of the dehydration of complex **3** is warranted since X-ray analysis revealed that, unlike the arrangement in complexes **1** and **2**, water molecules in this species are located inside the TRIMEB cavity where they mediate host-guest interaction through hydrogen bonding.

* * *

We thank the FRD (Pretoria) and the University of Cape Town for financial assistance.

References

1 A. Szafranek, J. Thermal Anal., 34 (1988) 917.
2 A. Szafranek and J. Szafranek, J. Incl. Phenom., 30 (1998) 163.
3 S. Kohata, K. Jyodoi and A. Ohyoshi, Thermochim. Acta, 217 (1993) 187.
4 M. R. Caira, V. J. Griffith and L. R. Nassimbeni, J. Therm. Anal. Cal., 51 (1998) 981.
5 M. R. Caira, S. A. Bourne and E. Mvula, In preparation (1998).
6 P. J. Haines, Thermal Methods of Analysis, Chapman and Hall, London 1995, p. 31.
7 M. R. Caira, V. J. Griffith, L. R. Nassimbeni and B. van Oudtshoorn, J. Incl. Phenom., 20 (1995) 277.
8 G. R. Brown, M. R. Caira, L. R. Nassimbeni and B. van Oudtshoorn, J. Incl. Phenom., 26 (1996) 281.
9 T. Steiner and G. Koellner, J. Am. Chem. Soc., 116 (1994) 5122.
10 L. J. Barbour, Clathration by Diol Hosts: Thermodynamics and Structure, Ph.D. Thesis, University of Cape Town 1994.
11 K. Harata, Bull. Chem. Soc. Jpn., 60 (1987) 2763.