Synthesis, structure and spectroscopic properties of bismuth citrate compounds
Part II. Comparison between crystal structures of solid bismuth citrates and commercial CBS, using thermal and spectroscopic methods

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Abstract

Spectroscopic and thermal properties of colloidal bismuth subcitrate (CBS) have been studied in the solid state, using thermal analysis (both under dinitrogen and under dioxygen), infrared spectroscopy and mass spectroscopy. The properties have been compared with previously studied (crystalline) potassium/ammonium bismuth citrate compounds, both in the solid and in aqueous solution. The thermal analysis study allows the assignments for the presence of K^+, NH_4^+ and citrate(3−) ions. The major conclusions of this investigation are: (i) the solid product CBS most likely contains units $[Bi(cit)]_2$, aggregated using bridging citrates into networks, separated by cations and water molecules, and similar to earlier reported crystalline Bi citrate compounds; (ii) the citrate(4−) anions universally form bridges towards two (or in same cases to even more) neighbouring Bi ions.

Introduction

A previous paper in the series [1a] described the synthesis, crystal structures and spectroscopic characterisation of five different K/NH_4 bismuth citrate complexes, as models for the complex bismuth citrates used in medicine [1b–d]. Papers from another research group [1e, f] very recently described the X-ray structures of related solid products, i.e. $KBi(cit)\cdot 3H_2O$ and $(NH_4)Bi(cit)\cdot 2H_2O$.

Colloidal bismuth subcitrate (CBS), a complex bismuth salt of citric acid (H_4cit), is amongst the most effective peptic ulcer healing agents, and has been thoroughly investigated from the viewpoint of pharmacology in the last two decades [2]. Also other Bi salts, such as the subcarbonate and the subsalicylate, have been used for medical applications [2j].

CBS is known to be an effective ulcer healer; various mechanisms of action have been proposed. CBS is highly soluble [3] in water, but bismuth citrate precipitates at pH value <5 [4]. The nature of the precipitates, however, is not well known. It has been proposed that bismuth is deposited in ulcer craters in preference to surrounding mucosa [5], and that Bi(III) forms a complex with proteins on the ulcer base, which may create a protective layer against digestion by gastric juice. There are some reports suggesting that effects of CBS partially include a prostaglandin mechanism [6a, b], since local prostaglandin E_2 production and secretion of alkali are stimulated in CBS-treated patients [2c–g]. CBS also possesses some antipepsin activity [7], but has little effect on gastric acid secretion. The relationship between *Helicobacter pylori* (formerly called *Campylobacter pylori*) and gastritis and peptic ulcers has recently been described convincingly [2e, 8] and, further, CBS has proved to be an effective inhibitory agent against this organism both *in vivo* and *in vitro* [9]. In the gastroduodenal mucus the glycoprotein–bismuth complex forms an H^+ diffusion barrier, which may counteract the ability of *H. pylori* to decrease mucus viscosity and increase H^+ back diffusion. A recent review describes the pharmacokinetics of bismuth compounds [10].

The chemical information on CBS is limited in spite of a great deal of pharmacological and clinical infor-

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mation. Although the most recent Merck index [2k] states that CBS consists of the empirical formula $K_3(NH_4)_2Bi_6O_3(OH)_5(Hcit)_4$, most likely with co-precipitated potassium or ammonium citrate, its chemical composition is not clear. Some authors use the formula $K_3Bi(Hcit)_2$ (Hcit being the triple dehydronated trianionic form of citric acid) for the solid, but water soluble, CBS. However, a physical mixture of potassium hydroxide, bismuth citrate and citric acid in the 3:1:1 ratio, corresponding to $3K^+$, Bi^{3+} and $2Hcit^{3-}$, is not soluble in water, suggesting that some kind of colloidal particles, or polynuclear metal complexes, has been formed during the production of commercial CBS.

This product is the active ingredient of De-Nol® and Telen® preparations available from Brocades Pharma, Netherlands (formerly from Gist-Brocades). It is a non-crystalline product, highly soluble in water and obtained by a careful spray-drying process [10].

In earlier work various crystalline species have been found on the ulcer craters of patients treated with CBS, depending upon the pH [11]; at pH 1.5 only amorphous, weakly refractile material is seen, while at pH 2 complex crystalline structures resembling wheat-sheaves, or mulberries are formed. At pH 3, distinct diamond shapes appear and at pH 4 and 5, rhomboids and needles develop. Bismuth oxychloride (BiOCl) and bismuth citrate (unspecified) have been reported to be constituents of the precipitates [5].

In theory one could predict certain species for the bismuth citrate complexes, by considering the ratio in bismuth, citric acid and, if any, potassium or ammonium as counter cations, using the fact that citric acid has at least four coordinating or chelating oxygen donors, i.e. three carboxylic groups and one hydroxy group.

As a result, our interest has been focussed on the composition and structure of the main species present in CBS as a solid and in solution. The first part of this investigation dealt with the crystallisation and solid state structures of a number of crystalline bismuth citrate complexes [1a]. In this first study five different bismuth citrate complexes were characterised unambiguously – in two cases even with 3D structures. A third and a fourth 3D structure were recently published by Herrmann *et al.* [1e, f]. Most recently a hexanuclear cluster, i.e. $[Bi_6O_4(OH)(cit)_3(H_2O)_3]^{3-}$, was found in the solid state [12] and also two different structures of $K_{0.5}(NH_4)_{0.5}[Bi(cit)](H_2O)_x$ ($x = 2,3$) were found by us [13]. The solution behaviour of these synthetic, crystalline compounds has been studied by ^1H and ^{13}C NMR spectroscopy [1a]. It appears that the dinuclear dimeric units [(cit)BiBi(cit)] are found not only in two previously reported compounds, but in at least three other crystalline compounds (see Fig. 1), and must have a high stability. They are likely to be also present in concentrated aqueous solution, possibly with the additional presence of a hexanuclear cluster, at least when starting in concentrated solutions in the presence of ammonia [12].

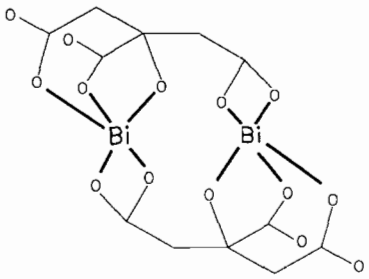

Fig. 1. Schematic representation of the dinuclear building block [(cit)BiBi(cit)], as first found in the crystal structures of compounds **1** and **5**

The present paper deals with a detailed spectroscopic and thermal analytical study of commercial CBS and its comparison with the presently known structures in the crystalline state.

Experimental

Materials

Citric acid monohydrate ($H_4cit \cdot H_2O$, Brocacef bv), bismuth citrate (BiHcit, ICN), potassium hydroxide (85%, Merck), ammonia solution (25%, Merck), deuterium oxide (99.8%, Aldrich), 10% NaOD in D_2O (Aldrich), and 10% DCl in D_2O (Aldrich) were commercially obtained and used without further purification. CBS was donated from Brocades Pharma, Netherlands. Reference compounds **1–5** (Table 1) were prepared as previously described [1a]. Some other newly prepared products are described below.

Preparation

All compounds were prepared as described previously [1a]. They are numbered as **1, 2a, 2b, 3a, 4a, 4b, 5**. In addition the following three new solid samples were prepared.

$K_{0.8}(NH_4)_{0.2}[Bi(cit)](H_2O)$ (2c)

5 g of CBS (batch no. 85BC82) were dissolved in 20 ml of water, and the solution was allowed to stand at room temperature. In a few hours, a very thin plate-like crystalline compound started to separate. After a week, the product was collected and washed with mixtures of water and methanol (3:1, 1:1, 1:3), methanol and diethyl ether, and dried in air. Yield 0.52 g. *Anal.* Calc. for $C_6H_{6.8}N_{0.2}O_8K_{0.8}Bi$: C, 16.02; H, 1.52; N, 0.62; K, 6.95; Bi, 46.44. Found: C, 15.80; H, 1.61; N, 0.62; K, 7.04; Bi, 45.9%.

TABLE 1. Experimentally observed solid complex Bi citrate salts with potassium and ammonium counterions

Type	Formula	K/NH_4	Crystal shape	Bi/Citrate
1	$K_{5-x}(NH_4)_x[Bi_2(cit^{4-})_2(Hcit^{3-})](H_2O)_{13}$ ($x = 0.25$–1.0)	19 > 4	needle-like	1 1.5
2	$K_{1-x}(NH_4)_x[Bi(cit^{4-})](H_2O)$ ($x = 0$–0.1)	> 9	thin plate-like	1 1
3	$K_{1-x}(NH_4)_x[Bi(cit^{4-})(H_2O](H_2O)$ ($x = 0.5$–1)	< 1.5	columnar	1 1
4	$K_{6-x}(HN_4)_x[Bi_6O_4(OH)(cit^{4-})_3(H_2O)_3](Hcit)$ ($x = 3$–6)	< 1	cubic	1.5:1
5	$(NH_4)_4[Bi(cit^{4-})(Hcit^{3-})(H_2O)_2](H_2O)$	0	needle-like	1·2
6	$K_{1-x}(NH_4)_x[Bi(cit^{4-})(H_2O)](H_2O)_2$ ($x = 0.5$–1)	< 1[a]	needle-like	1 1

[a]Probably the compound of Herrmann *et al.* [1e], i.e. $K[Bi(cit^{4-})(H_2O](H_2O)_2$ belongs to type **6**, the ratio should be 0–∞.

*$K_{0.6}(NH_4)_{0.4}[Bi(cit)](H_2O)_2$ (**3b**)*

The compound was obtained as microcrystals in the same way as that of **2b** except for using CBS (batch no. 87BC03, a batch somewhat richer in ammonia instead of 85BC82). *Anal.* Calc. for $C_6H_{9.6}N_{0.4}O_9K_{0.6}Bi$: C, 15.54; H, 2.09; N, 1.21; O, 31.05; K, 5.05; Bi, 45.06. Found: C, 15.56; H, 2.16; N, 1.37; O, 30.2; K, 4.98; Bi, 44.5%.

*$K_{0.5}(NH_4)_{0.5}[Bi(cit)](H_2O)_3$ (**6**)*

To 20 ml of a suspension containing bismuth citrate (10 g, 0.025 mol) an ammonia solution was added until the mixed solution became clear. After that 10 ml of an aqueous KOH solution (0.66 g, 0.01 mol) were added, and the resulting solution was boiled to remove the excess of ammonia, resulting in a solution with a pH of 7. Upon standing at room temperature for a few weeks, two types of crystals (needles and columnar crystals) started to grow slowly, and were collected after two months. The needle-like crystals (**6**) were separated, after washing with water, methanol and diethyl ether. *Anal.* Calc. for $C_6H_{12}N_{0.5}O_{10}K_{0.5}Bi$: C, 15.02; H, 2.52; N, 1.46; Bi, 43.56. Found: C, 15.01; H, 2.62; N, 1.78; Bi, 43.4. The columnar crystals were identified as type **3**, based on elemental analysis and IR spectra.

Instruments, analyses and measurements

Carbon, hydrogen, nitrogen, oxygen, potassium and bismuth analyses for compounds **2c** and **3b** were carried out at the Mikroanalytisches Labor Pascher, Germany. For compound **6**, C, H and N analyses were carried out at the Serves Centre of Elemental Analysis, Kyusyu University, Japan. The Bi content was determined by edta titration. IR spectra were recorded on a Perkin-Elmer model 580 spectrophotometer using KBr disks. X-ray powder diffraction patterns were registered with a Nonius Guinier-de Wolff camera, using Cu Kα radiation. All pH measurements were performed at 298 K. The pH meter was calibrated with Fisher certified solutions of pH 4.00 and 7.00.

DSC curves were recorded in the DCS30 of a Mettler TA 4000 system. The scanning range was 20–480 °C at a heating rate of 10 °C/min. The sample weight was 1–2 mg for the under dioxygen recorded curves and 6–7 mg for the recorded curves under a dinitrogen atmosphere. An open empty aluminum pan was used as a reference sample.

Results and discussion

General considerations

All compounds obtained by both synthetic methods and recrystallisation of CBS can be divided into at least six types of stoichiometry, as summarised in Table 1. Compounds belonging to a certain type give an identical IR and X-ray powder diffraction spectrum, and have the same crystal shape. However, according to the elemental analyses, the NH_4^+/K^+ ratio varies slightly within one type, e.g. in type **2** (**2a, 2b, 2c**) and type **3** (**3a** and **3b**). It is also likely that the compounds reported by Herrmann *et al.* [1e, f] fall in the same category of compounds as type **3** and **6**. The amount of water in the compound suggests a similarity between the only K-containing compound of Herrmann *et al.* [1e] and type **6**, and between the ammonium compound [1f] and type **3**. These observation would imply that potassium and ammonium ions as counter cations can exchange relatively easily in the crystal lattice; this is not unexpected because the two ions are very close in ionic size: 1.33 and 1.43 Å for potassium and ammonium, respectively [1a]. The solubility of the resulting products may differ, however.

All CBS samples are amorphous and give practically identical IR spectra; their analyses are close to compounds **1** and **2**. Purification of CBS was attempted by crystallisation from water with the aim of elucidating the structure of main species in the solid. When starting from CBS some batches indeed yield crystalline compounds (e.g. **2b** from 85BC82 and **3b** from 87BC03, see 'Experimental'), whose IR spectra and X-ray powder diffraction patterns are quite different from those of CBS. Many trials to separate pure crystalline compounds from CBS batches show the tendency that relatively aged material yields type **2** or type **3** compounds as a first precipitation while relatively fresh CBS does not.

Since commercial CBS has some smell of ammonia, the difference in the crystallised products has tentatively been attributed to the (varying) amounts of ammonia in the solids.

In order to confirm this assumption, all CBS samples were preheated at 50–60 °C for 3 days to remove any excess ammonia from the solids, and then recrystallised. As expected, all preheated samples now only yield type **2** compounds, immediately after dissolution. These results clearly indicate that an important role of the excess ammonia in solid CBS is to create a high solubility in water by controlling the pH of the solutions. Further, the fact that both type **2** and **3** have the same Bi/cit ratio (i.e. 1:1) may lead to the conclusion that the formation of type **2** and type **3** is determined either by the amount of ammonia (high pH), or by the ratio of NH_4^+/K^+ in the solutions. When a large excess of ammonia is present in solutions, type **4** compounds seem to be predominantly crystallised irrespective of the Bi/cit ratios. For example, although recrystallisation of **2a** from water yields a type **2**, compound **4b** is obtained from an ammonia solution. Preliminary recrystallisation of **3b** from an ammonia solution also yields a type **4** compound. In addition, compound **4a** can be obtained from the mixture of bismuth citrate and citric acid in a 2:3 ratio (corresponding to an overall Bi:cit ratio of 2:5) in an ammonia solution.

Comparison of solution behaviour between synthetic compounds and CBS: pharmacological relevance

In the first paper of this series [1a] the solution behaviour of synthetic bismuth citrate compounds was studied in detail by use of NMR spectroscopy. At citrate/Bi ratios <1.0, citrate are rigidly coordinated to Bi(III). If, on the other hand, under acidic conditions the citrate/Bi ratio becomes >1.0, all citrates were found to rapidly exchange at Bi(III) on the NMR time scale. Under alkaline conditions in dilute solutions (i.e. $[Bi]<20$ mM) the citrates are hardly, if at all, coordinated to bismuth.

Since all CBS samples have citrate/bismuth ratios >1.0, the solution chemistry may be interpreted on the basis of NMR results for the synthetic compounds, except for type **4**, which has a Cit:Bi ratio <1.0. In fact the solution NMR results for commercially available CBS are the same as those of the synthetic compounds with a citrate/Bi ratio >1.0 (i.e. with the rapid ligand atom exchange under acidic conditions, and non-coordination under basic conditions [1a, 13].

Bismuth–citrato compounds are thought to precipitate as a mixture of bismuth citrate and bismuth oxychloride [4], because of the acidic gastric juices. However, in view of NMR results on synthetic compounds at low concentration and low pH conditions, part of the bismuth is definitely dissolved in the stomach and may strongly interact with citrates even though the ligand-exchange process is fast. A typical dose of CBS for patients is 120 mg (calculated as Bi_2O_3) four times a day, corresponding to relatively low concentrations in the stomach. This would make the presence of compound **4** in the stomach unlikely.

Herrmann *et al.* [2e, f] have noticed a very strong interaction between the Bi ion and the hydroxy oxygen from the cit(4−) ion (Bi–O = 2.16 Å in their compound) and have attributed the apparent chemical stability in gastric juices to a 'remarkable covalent character'. In fact compounds **1** and **5** reported in our previous paper [1a], and compounds **3** and **6** in a recent study [13] have equally short Bi–O distances, but both of these compounds do have rapid citrate ligand exchange on Bi under acidic conditions. This would suggest that the resistance of CBS to hydrolysis in gastric juices is rather related to the rapid ligand exchange and not so much to the (kinetically non-labile) 'covalent' Bi–O bond.

Thermal analysis of the solid samples

Reference compounds

Thermal analysis has been used by several authors as a tool to characterise structural relationships in citric acid and citrates [14]. Recently this topic was mentioned by Briehl and Butenuth [15] in a review article about the application of thermal analysis for studying chemical reactions of organic compounds. Barbooti and Al-Sammerai [14a] showed that the decomposition of citric acid starts with a dehydration reaction to give aconitic acid in the region 150–200 °C, immediately followed by pyrolysis. These results were more or less confirmed by Heide *et al.* [14d] by means of thermomicroscopy. They demonstrated that the decomposition of citric acid can be explained in terms of superimposing reactions which have different reaction rates.

According to Maslowska *et al.* [14c] the decomposition of complex salts of the transition metals with citric acid in static air is also a rather complicated series of mainly endothermic reactions.

To interpret the differential scanning calorimetry (DSC) curves of the crystalline bismuth citrate compounds and of CBS we started with a series of measurements on the citrates of bismuth, ammonium and potassium (see Fig. 2(a) and (b)). The complex irregular decomposition pattern of K_3HCit under an O_2 atmosphere is in agreement with the results of Maslowska *et al.* [14c]. While the type of atmosphere does not influence the results for $(NH_4)_3HCit$, BiHCit reacts endothermically under dinitrogen but exothermically under dioxygen. In this respect it is interesting to note that the DSC curves of $Bi(NH_4)Cit$ appear to be composed from the independent curves of BiHCit and $(NH_4)_3HCit$; this indicates that decomposition reactions can take place independently of each other.

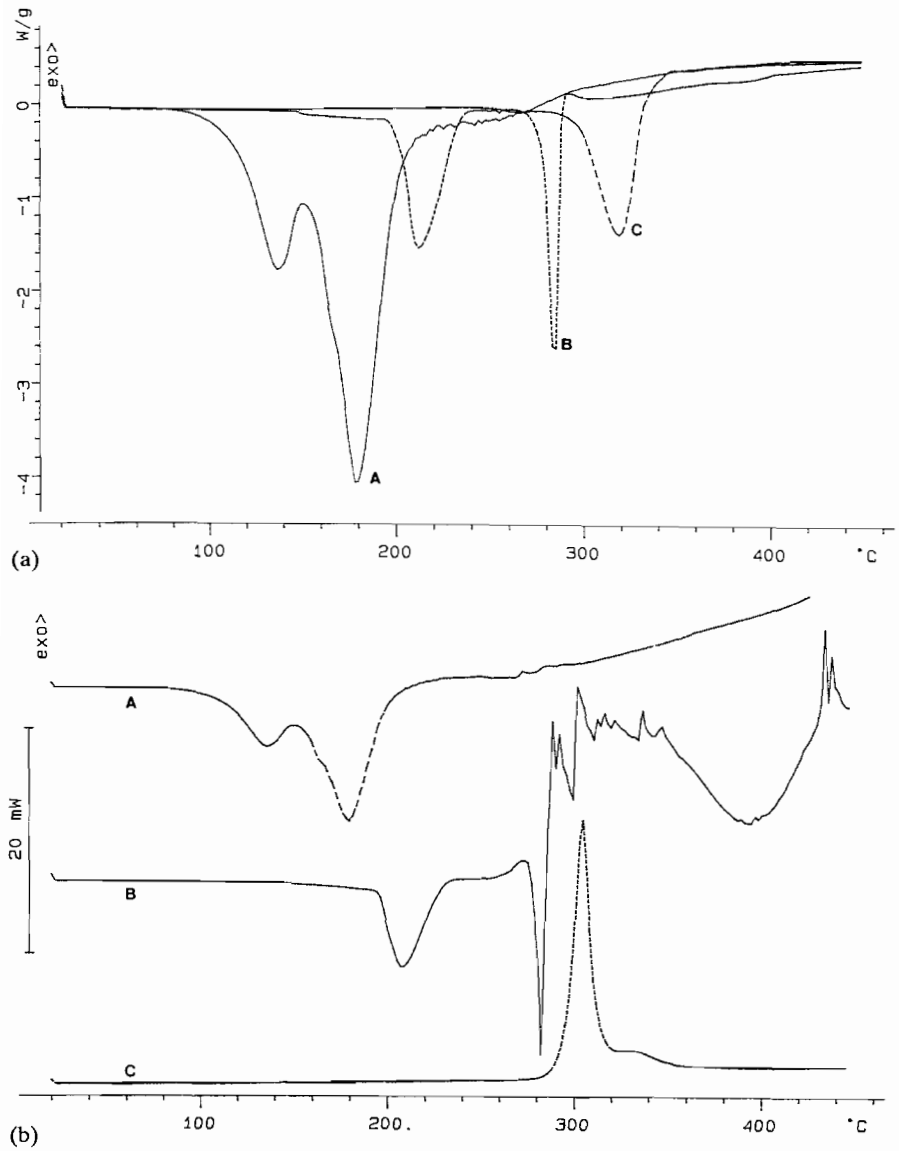

Fig. 2. Thermal analysis of ammonium citrate (A) potassium citrate (B) and bismuth citrate (C) under dinitrogen (a) and under dioxygen (b).

Crystalline Bi citrates

Compound 5. Results for **5** are given in Fig. 3. It was found that the position of the endotherm corresponding with the dehydration reaction of citrate is influenced by the presence of K or NH_4. Here, because K is absent, no major peaks are visible around 290 °C. However, the absence of a bismuth related citrate decomposition peak (compare with results for, for example, bismuth citrate) is more striking. This indicates that ammonium is the principal factor in determining the decomposition of this crystal.

Compounds 1, 2, 3 and 6. From Fig. 4(a) it appears that the absence of $Hcit^{3-}$ in **2** is reflected in a shift of 20 °C and an increase in size of the endotherm at 284 °C in the curve recorded under dinitrogen atmosphere. Also the differences in size and shape of the exothermic effects around 290 °C recorded DSC curves under dioxygen, are indicative of the absence of $HCit^{3-}$ in **2** (see Fig. 4(b)). It is assumed that the dehydration reaction to aconitate can hardly, if at all, take place for compounds with cit^{4-}.

The DSC curves of **3** were found to be in agreement with those of **2**, as far as the size and place of the above mentioned endotherm is concerned. However, the curves of these compounds also showed dissimilarities, as expected because of the different crystal structure. In addition to this – and especially for scans recorded under dinitrogen – crystals of compounds **3** and **6** (Fig. 4(c)) that were synthesised with different

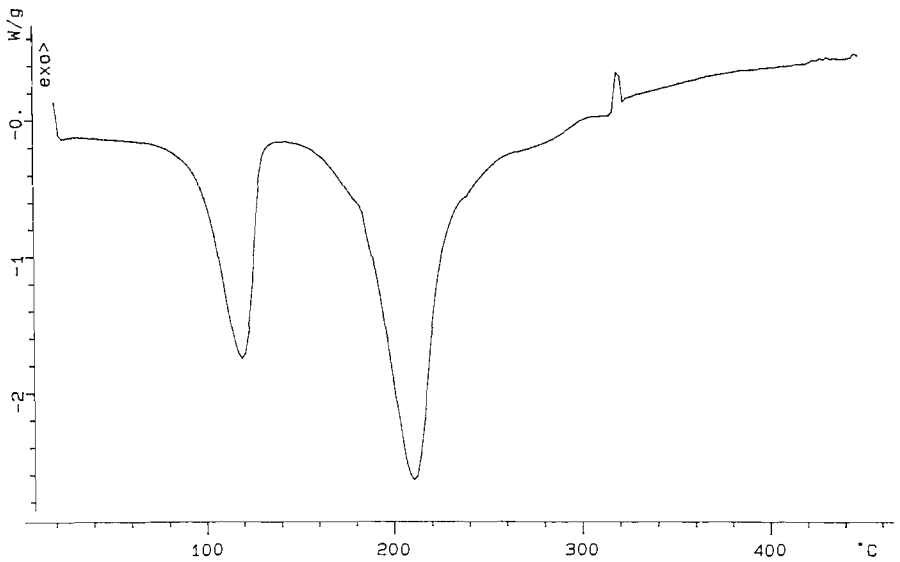

Fig. 3. Thermal analysis of ammonium bismuth citrate (5) under dinitrogen.

K/NH_4 ratios (varying between 2 and 0.5), clearly showed different peak ratios around 300 °C. This again indicates the suitability of DSC for studying the relative amount of K in a bismuth citrate sample.

Compound 4. The DSC curve of **4** under a dioxygen atmosphere shows a typical exotherm at 330 °C that was not detected in any of the other crystal curves. At this can have nothing to do with decomposition of citrate, it is likely that this large exotherm reflects the decomposition of the $Bi_6O_4(OH)$ units in the lattice. The second exotherm in Fig. 5. is probably caused by a rearrangement in the crystal structure of Bi_2O_3, just as found for Fe_2O_3 (data not shown).

Analysis of CBS

Based on the results for the several crystals it is suggested that the DSC curves of CBS, given in Fig. 6, can be interpreted as follows:

(i) the position of the endotherm around 300 °C under N_2 indicates the presence of K and of $Hcit^{3-}$;

(ii) the small endotherms between 200 and 240 °C (N_2 atmosphere) confirm the presence of NH_4^+;

(iii) it appears that compound **4**, if present at all, cannot be detected in CBS.

So, CBS in the solid state can best be described as a complex Bi citrate, consisting of dinuclear [(cit)BiBi(cit)] units connected by water molecules, potassium ions and ammonium ions.

Conclusions

In the present investigation different types of crystalline Bi citrate compounds have been compared with commercial samples of CBS. All the crystalline types, except type **5**, can be also obtained – depending upon the condition used – from commercial CBS by crystallisation. The thermal analyses of the several crystalline and CBS samples indicate a great similarity. At the present stage, it is tempting to conclude that CBS consists of a mixture of several, if not all of such types, except type **4**. However, as seen in the structural relation between compounds **1** and **5**, a dinuclear structure (cit)BiBi(cit), with bridging citrates (see Fig. 1), seems to be the most stable 'sub-unit' in bismuth–citrato compounds. It should be noted that such a dinuclear unit structure is also seen in the structure of the polymeric compound of Herrmann *et al.* [1e], even though these authors did not particularly speak of dinuclear units. Furthermore, our preliminary results on the structure of type **3** and **6** show that the same dinuclear units are building blocks in polymers. Detailed structural investigations on these compounds are in progress (to be published elsewhere). Such 'sub-units' could easily aggregate through citrate bridging and/or hydrogen bridging in solid CBS.

The solution behaviour [1a] of commercial CBS samples was interpreted based on both NMR spectral behaviour and the previously reported NMR results on synthetic bismuth–citrato complexes. When a sufficient amount of citrate is present in solution, i.e. cit/Bi > 1.0, the citrates take part in rapid ligand exchange processes with bismuth under acidic conditions. This behaviour seems to be the main reason for the high solubility in acidic media, unlike the other Bi-containing drugs, such as the subsalicylate and the subcarbonate. When CBS is dosed it will arrive in the stomach at a relatively high concentration, due to its very good

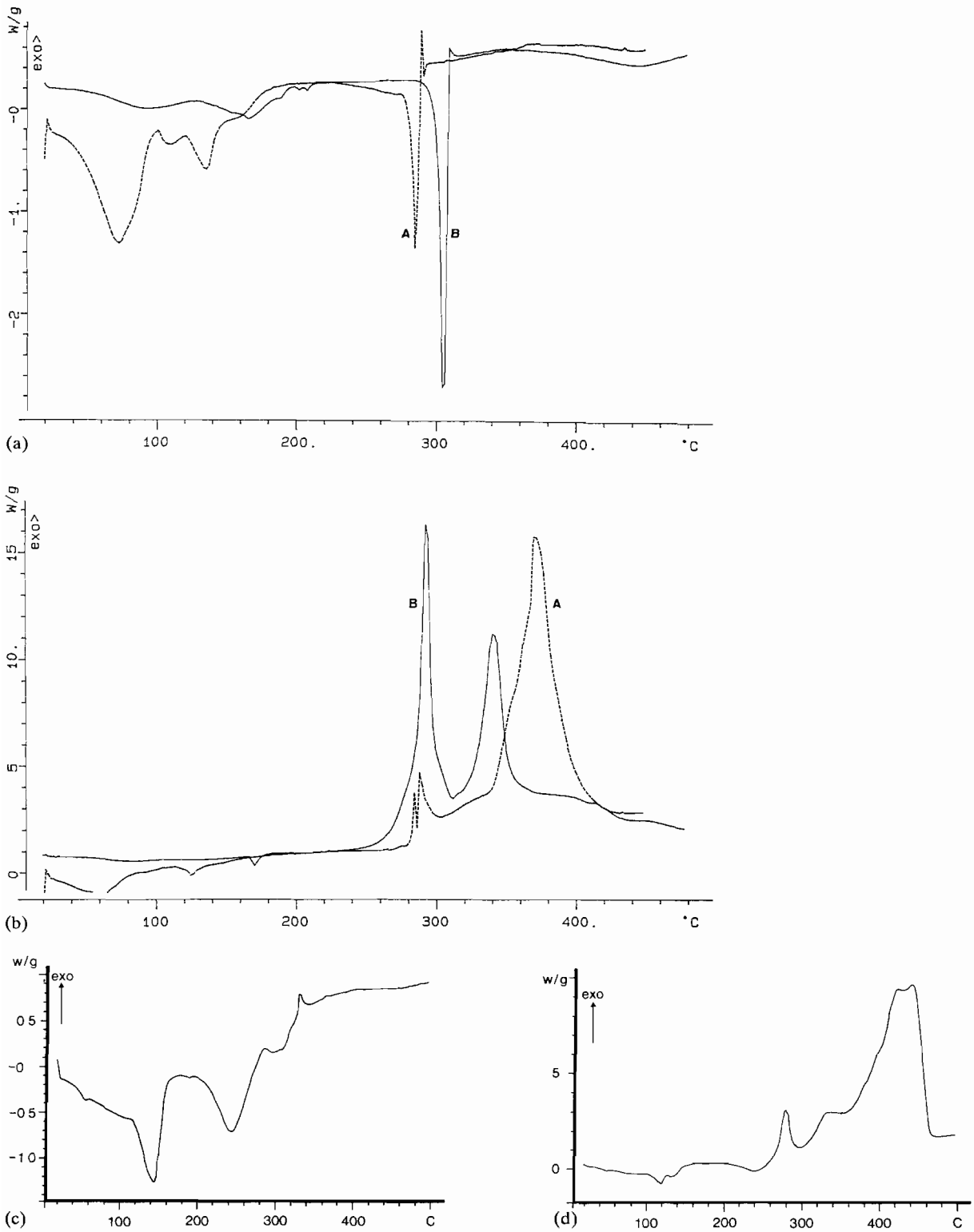

Fig. 4. Thermal analysis of compounds **1** (A) and **2** (B) under dinitrogen (a) and under dioxygen (b), compound **6** under dinitrogen (c) and dioxygen (d).

solubility, and still allow for rapid ligand exchange. In the stomach hydrolysis by the acidic HCl will become possible, which makes the Bi available for reactions with the ulcer surface, e.g. by binding to proteins. Since free citric acid is not known to exhibit ulcer-healing properties, it is most likely that the citrate in CBS

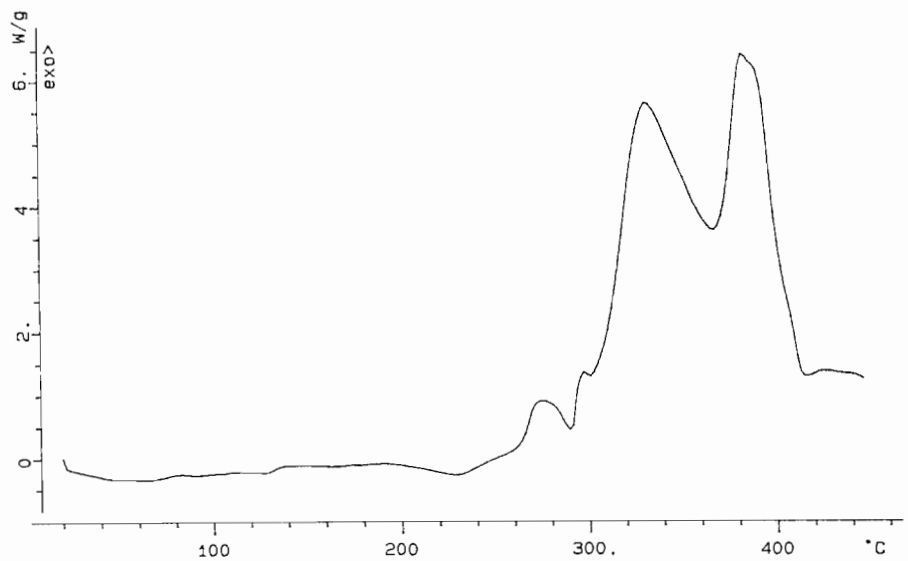

Fig. 5. Thermal analysis of cluster compound **4** under dioxygen.

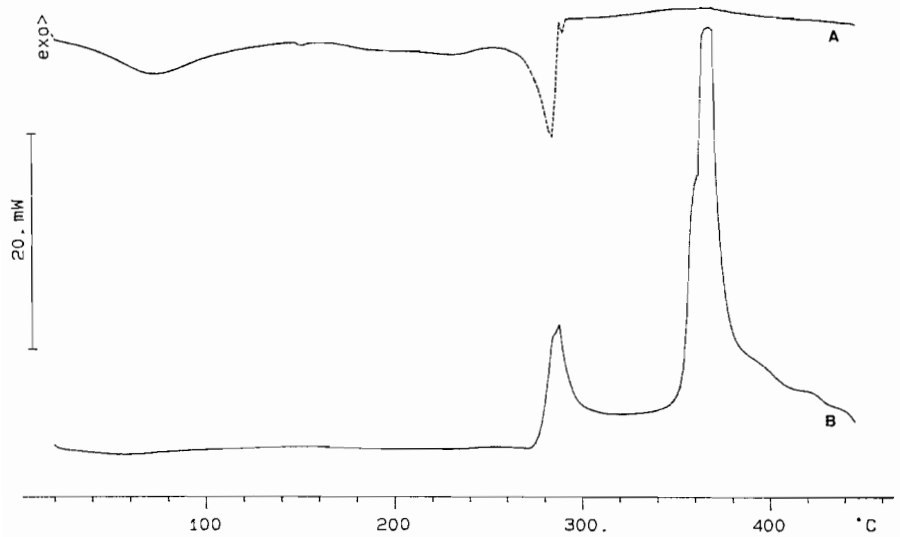

Fig 6 Thermal analysis of CBS under dinitrogen (A) and under dioxygen (B).

functions as a carrier for Bi(III) to the ulcer region. It is possible that, analogous to Al(III), an active membrane transport of Bi, which is connected to citrate transport, may take place [16, 17].

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