Synthesis, Structure, and Spectroscopic Characterization of Bismuth Citrate Compounds and Bismuth-Containing Ulcer Healing Agent Colloidal Bismuth Subcitrate (CBS). 3.[1] Crystal and Solution Structures of $K(NH_4)[Bi_2(cit)_2(H_2O)_2](H_2O)_x$ ($x = 2, 4$)

Eiji Asato,*[2a] **Kosho Katsura,**[2a] **Masahiro Mikuriya,**[2b] **Toshinori Fujii,**[2b] **and Jan Reedijk**[2c]

Departments of Chemistry, College of Science, University of the Ryukyus, Nishihara-cho,
Okinawa 903-01, Japan, School of Science, Kwansei Gakuin University, Uegahara,
Nishinomiya 662, Japan, and Gorlaeus Laboratories, Leiden University, P.O. Box 9502,
2300 RA Leiden, The Netherlands

Received February 17, 1993®

Four new stoichiometrically closely-related bismuth complexes with citrate (cit^{4-}) are synthesized by the reaction of bismuth citrate $Bi^{3+}(Hcit^{3-})$ and potassium hydroxide in the presence of ammonia, they have also been obtained by recrystallization of commercially available colloidal bismuth subcitrate (CBS; a well-known ulcer healing agent). Compounds $K(NH_4)[Bi_2(cit^{4-})_2(H_2O)_2](H_2O)_4$ (**3a**) and $K(NH_4)[Bi_2(cit^{4-})_2(H_2O)_2](H_2O)_4$ (**6**) isolated as a mixture from aqueous solution containing bismuth citrate, potassium, and ammonium have been fully characterized by using three-dimensional X-ray analysis. Two other compounds $K_{0.8}(NH_4)_{0.2}Bi(cit)(H_2O)$ (**2c**) and $K_{0.6}(NH_4)_{0.4}Bi(cit)(H_2O)_2$ (**3b**), which were isolated from CBS aqueous solutions, have been characterized on the basis of elemental analyses and spectroscopic data only. Compound **3a** crystallizes in the space group $C2/c$ with a = 16.860(4) Å, b = 12.395(2) Å, c = 10.328(3) Å, β = 91.79(2)°, V = 2157.2 Å^3, and Z=8. The asymmetric unit, which contains a $Bi(cit^{4-})(H_2O)$ unit, is linked to another by the symmetry operation $(1 - x, y, {}^1/_2 - z)$ to form a dinuclear subunit with a Bi–Bi distance of 6.11 Å. The dinuclear subunit is paired to itself by an inversion center to form a tetranuclear aggregate. The resultant units are further interlinked by citrate bridges and hydrogen bond bridges to result in a complicated polymeric network. Compound **6** crystallizes in the space group $P2_1/n$ with a = 10.923(2) Å, b = 15.424(2) Å, c = 15.037(2) Å, β = 105.67(1)°, V = 2439.3 Å^3, and Z = 4. In this compound the dinuclear unit $[Bi_2(cit^{4-})_2(H_2O)_2]^{2-}$ from the asymmetric unit functions as the building block for the polymeric architecture. Although the mode of citrato bridging to yield the tetranuclear unit is the same as that of **3a**, the different asymmetric unit structure compared to that of **3a** is eventually reflected in the slight difference in the two polymeric network structures. The solution behavior of CBS samples has been investigated by using ^{1}H and ^{13}C NMR spectroscopy. At low pH (<7), rapid ligand exchange is observed and all citrates are averaged on the NMR time scale. At high pH the citrate are hardly coordinated to Bi(III) anymore. The behavior is the same as that of the previously reported "$[(cit^{4-})BiBi(cit^{4-})]^{2-}$ aggregated polymer", but different from that of the "$[Bi_6O_4(OH)(cit)_3(H_2O)_3]^{3-}$ aggregated polymer". On the basis of a comparison of the CBS solution behavior with that of CBS model complexes, it was concluded that solid samples of CBS which are amorphous could be formed by aggregation of the dinuclear building block $[(cit^{4-})BiBi(cit^{4-})]^{2-}$ through citrato bridges and hydrogen bonding.

Introduction

Bismuth compounds have been used in medicine for 200 years in a variety of gastrointestinal disorders, because of their demulcent properties.[3] Among the modern bismuth-based pharmaceuticals, colloidal bismuth subcitrate (CBS) is the most widely used in many countries to treat peptic ulcers. This compound, which is a complex bismuth salt of citric acid (H_4cit), has been thoroughly investigated from the viewpoint of pharmacology in the last 2 decades.[4] In spite of much pharmacological and clinical information on CBS, little chemistry has been investigated on this important compound. According to the most recent Merck index,[5] CBS consists of the empirical formula $K_3(NH_4)_2Bi_6O_3(OH)_5(Hcit)_4$ (Hcit being the triply dehydronated trianionic form of citric acid), most likely with coprecipitated potassium or ammonium citrate. However, because of its amorphous property, no structural information has been obtained as yet.

In 1991 we reported the first example of a detailed chemical investigation[1a] on model compounds for the complex bismuth citrate CBS. In that first study five types of different bismuth citrate complex were characterized on the basis of composition (countercations K and/or NH_4/Bi/cit/H_2O ratios), the crystal shape, the X-ray diffraction pattern, and IR and NMR spectroscopy (see Table I). Additionally, in two cases 3D structural characterization was carried out.

As for Bi–citrate interaction in solution, we found a boundary ratio for citrate/bismuth which determines the citrate coordination behavior, *i.e.* when the ratio of citrate/Bi ≥ 1.0, the ligand rapidly exchanges on the metal to be averaged on the NMR time scale under acidic conditions, but hardly coordinates on the metal in alkaline solutions. On the other hand, when the amount of ligand is less than the metal in aqueous solutions, most of the citrate rigidly coordinate to Bi(III) even in low concentrations.

The most interesting finding from the solid-structural investigation was that a common subunit (cit)BiBi(cit)—see Figure

---

® Abstract published in *Advance ACS Abstracts,* October 1, 1993.

(1) (a) Part 1: Asato, E.; Driessen, W. L.; De Graaff, R. A. G.; Hulsbergen, F. B.; Reedijk, J. *Inorg. Chem.* **1991**, *30*, 4210. (b) Part 2 treating thermal properties of CBS and CBS model compounds: Asato, E.; Hol, C. M.; Hulsbergen, F. B.; Klooster, N. T. M.; Reedijk, J. *Inorg. Chim. Acta*, in press.

(2) (a) University of the Ryukyus. (b) Kwansei Gakuin University. (c) Leiden University.

(3) (a) Reynolds, J. E. F., Ed. *Martindale, The Extra Pharmacopoeia*, 20th ed.; The Pharmaceutical Press: London, 1982. (b) Manhart, M. D. *Rev. Infect. Dis.* **1990**, *12*, S11-S15.

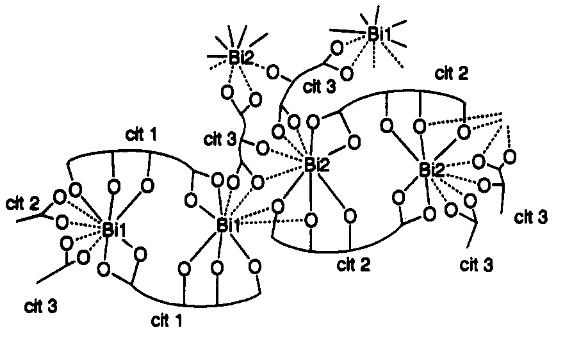
(4) For examples: (a) Wagstaff, A. J.; Benfield, P.; Monk, J. P. *Drugs* **1988**, *36*, 132–157. (b) Tytget, G. N. J. *Digestion* **1987**, *suppl 2*, 31–41. (c) Miller, J. P.; Faragher, E. B. *Br. Med. J.* **1986**, *293*, 1117. (d) Axon, A. T. R. *Br. Med. J.* **1986**, *293*, 772. (e) Goodwin, C. S.; Armstrong, J. A.; Marshall, B. J. *J. Clin. Pathol.* **1986**, *39*, 353. (f) Tytget, G. N. J. *Afr. Med. J.* **1986**, *70*, 31. (g) Marshall, B. J. *J. Infect. Dis.* **1986**, *53*, 650. (h) Pickard, R. *Proc. Cairo.* **1985**, 55. (i) Vogt, K.; Warrelmann, M.; Hahn, H. *Zbl. Bakt.* **1990**, *273*, 33–35.

(5) *Merck Index* **1989**, *11*, 197.

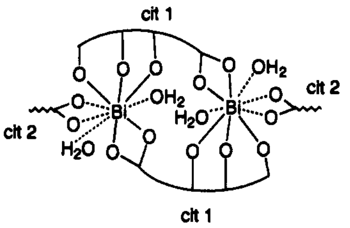
0020-1669/93/1332-5322$04.00/0

Table I. Experimentally Observed Solid Complex Bi Salts with Potassium and Ammonium Counterions

type	formula	Bi/citrate	K^+/NH^{4+}	cryst shape
1	$K_{5-x}(NH_4)_x[Bi_2(cit^{4-})_2(Hcit)](H_2O)_{13}$ ($x = 0.25–1.0$)	2:3	19>4	needlelike
2	$K_{1-x}(NH_4)_x[Bi(cit^{4-})](H_2O)$ ($x = 0–0.1$)	1:1	>9	thin platelike
3	$K_{1-x}(NH_4)_x[Bi(cit^{4-})](H_2O)_2$ ($x = 0.5–1$)	1:1	<1.5	columnar
4	$K_{6-x}(NH_4)_x[Bi_6O_4OH(cit^{4-})_3(H_2O)_3](Hcit^{3-})(H_2O)_2$ ($x = 3–6$)	3:2	<1	cubic
5	$(NH_4)_4[Bi(cit^{4-})(Hcit^{3-})(H_2O)_2](H_2O)$	1:2	0	needlelike
6	$K_{1-x}(NH_4)_x[Bi(cit^{4-})](H_2O)_3$ ($x = 0.5–1$)	1:1	0–∞	needlelike



Comp.1 (dimer → chain → sheet)



Comp.5 (dimer)

Figure 1. Common dinuclear subunit ($(cit^{4-})BiBi(cit^{4-})$) found in compounds **1** and **5**.[1a]

1—was found in the two compounds $K_{4.75}(NH_4)_{0.25}[Bi_2(cit)_2(Hcit)](H_2O)_{13}$ (compound **1**: two-dimensional sheet polymer) and $(NH_4)_8[Bi_2(cit)_2(Hcit)_2(H_2O)_4](H_2O)_2$ (compound **5**: discrete dimer).

In the same year, a third 3D structure[6a] was independently reported by Herrmann *et al.* Interestingly, the related solid product $KBi(cit)\cdot 3H_2O$, a sixth type according to our classification, also contains the similar "subunits", which are aggregated by citrato bridges to form a polymeric architecture, though they did not mention this subunit as such. This characteristic dinuclear subunit was further found in $(NH_4)Bi(cit)\cdot 2H_2O$ (**3h**), a fourth 3D structure reported by Herrmann et al. in 1992,[6b] as the building blocks of the polymer. These findings led us to the hypothesis that such a dinuclear subunit could be the most stable in all bismuth citrate complexes and also in solid CBS samples, which are noncrystalline amorphous products and could be formed from these units by aggregation through hydrogen bonding and citrate bridging. Consequently, our interest has been directed to see if the dinuclear unit is prevalently contained in bismuth citrate complexes, with the aim to give support for the theory. Thus, we undertook the structure determination of the newly isolated complexes $K(NH_4)Bi_2(cit)_2(H_2O)_4$ (**3a**) and $K(NH_4)Bi_2(cit)_2(H_2O)_6$ (**6**), the former briefly reported in the previous paper[1a] and the latter closely related to one compound reported by Herrmann,[6a] although he did not mention whether the compound is a pure K salt or mixed cationic species containing NH_4^+ as is present in CBS. In the present paper, the two structures, in particular, the recognized dinuclear "subunits" are described and compared with the previously reported two structures.[1a] Further, the solution behavior of CBS samples[7] is studied by using NMR spectroscopy and compared with those of previously reported[1a] crystalline bismuth citrate compounds. To avoid the confusion in the naming of compounds from a series of earlier bismuth citrato compounds, the newly reported compounds in this article are named according to the previously used classification given in Table I.

Experimental Section

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. Three commercial samples of CBS (batch no. 85BC82, 87BC03, and 89A31)[7] were made available from Gist Brocades, Delft, The Netherlands. Some newly synthesized products and those obtained from CBS samples by recrystallization are described below.

Preparation. $K_{0.8}(NH_4)_{0.2}Bi(cit)(H_2O)$ (2c). A 5-g amount of CBS (batch no. 85BC82) was dissolved in 20 mL of water, and the solution was allowed to stand at room temperature. In a few hours, very thin platelike crystals started to separate. After 1 week, the product was collected, 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. Calcd 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.

$K_{0.5}(NH_4)_{0.5}Bi(cit)(H_2O)_2$ (3a) and $K_{0.5}(NH_4)_{0.5}Bi(cit)(H_2O)_3$ (6). To 20 mL of a suspended solution containing bismuth citrate (10 g, 0.025 mol) was added an ammonia solution till the mixture became clear, and then 10 mL of an aqueous KOH solution (0.66 g, 0.01 mol) was added. The resultant solution was boiled to remove the excess ammonia, resulting in a solution with pH of 7. Upon standing at room temperature for a few weeks, two types of colorless crystals (needles and diamond-like columnar crystals) started to grow slowly, which were collected after 2 months. The mixture was washed with water, methanol, and diethyl ether and dried in air. According to the difference in the shape of two types of crystals, each compound was separated by manually with tweezers, and the separated samples were used for analyses. Columnar crystals: **3a**. Anal. Calcd for $C_6H_{10}N_{0.5}O_9K_{0.5}Bi$: C, 15.61; H, 2.18; N, 1.52; Bi, 45.27; Found: C, 15.65; H, 2.28; N, 1.83; Bi, 45.0. Needlelike crystals: **6**. Anal. Calcd for $C_6H_{12}N_{0.5}O_{10}K_{0.5}Bi$: C, 15.02; H, 2.52; N, 1.46; K, 4.08; Bi, 43.56. Found: C, 15.01; H, 2.62; N, 1.78, K, 4.00; Bi, 43.4. Suitable crystals of **3a** and **6** of diffraction quality were used for X-ray crystallography.

$K_{0.6}(NH_4)_{0.4}Bi(cit)(H_2O)_2$ (3b). The compound was obtained as microcrystals in the same way as that of **2c** except for using CBS (batch no. 87BC03, a batch somewhat richer in ammonia) instead of 85BC82. Yield: 0.48 g from 5.0 g of the CBS sample. Anal. Calcd 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. Some trials to obtain the single crystals with the same procedure often gave mixtures of **3b** and needles. The latter was assigned to be compound **6** (or a type **6** compound) on the basis of the infrared spectrum.

Further Attempt To Purify CBS Samples. The foregoing procedure that gave **2c** and **3b** with CBS samples was also applied to the CBS sample of batch no. 89A31, which is a relatively fresh sample compared to 85BC82 and 87BC03. Although four solution samples (5.0 g in 10 mL of H_2O (two samples) and 5.0 g in 20 mL of H_2O (two samples))

---

(6) (a) Herrmann, W. A.; Herdtweck, E.; Pajdla, L. *Inorg. Chem.* **1991**, *30*, 2579. (b) Herrmann, W. A.; Herdtweck, E.; Pajdla, L. *Z. Kristallogr.* **1992**, *198*, 257.

(7) Analytical data of commercially available CBS solid samples (averages of 90 batches): Bi, 35.3(4)%; K, 11.7(3)%; citrate/Bi ratio, 1.25–1.30; K/NH_4 ratio, 1.5–1.7. Analysis of CBS samples does not agree with the ratio 2:3 for citrate:Bi, according to *Merck Index* ref 5. Klooster, N. T. M. Private communication, 1992. Present address: Brocades-Pharma R&D, P.O. Box 5009, 2600 GA Delft, The Netherlands.

Table II. Crystallographic Data for $K(NH_4)[Bi_2(cit)_2(H_2O)_2](H_2O)_2$ (**3a**) and $K(NH_4)[Bi_2(cit)_2(H_2O)_2](H_2O)_4$ (**6**)

	3a	**6**
formula	$Bi_2O_{18}NKC_{12}H_{20}$	$Bi_2O_{20}NKC_{12}H_{24}$
fw	923.35	959.38
space group	*C*2/*c*	$P2_1/n$
a, Å	16.860(4)	10.923(2)
b, Å	12.395(2)	15.424(2)
c, Å	10.328(3)	15.037(2)
β, deg	91.79(2)	105.67(1)
V, Å^3	2157.2	2439.3
Z	8	4
D_{calcd}, g/cm^3	2.83	2.61
D_{measd}, g/cm^3	2.81	2.63
T, °C	25 ± 1	25 ± 1
μ, cm^{-1}	164.8	146.1
radiation (λ, Å)	Mo Kα (0.710 73) from graphite monochromater	
transm factor	1.00–0.61	
final residuals, %: *R*;[a] R_w[b]	4.0; 4.7	7.2; 8.5

[a] $R = \sum||F_o| - |F_c|| / \sum|F_o|$. [b] $R_w = [\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2]^{1/2}$.

Table III. Fractional Positional Parameters and Thermal Parameters of Non-Hydrogen Atoms of **3a** with Their Estimated Standard Deviations in Parentheses[a]

atom	*x*	*y*	*z*	B_{eq}, Å^2
Bi	0.39851(3)	0.63050(4)	0.48965(5)	1.092(8)
K	0.500	0.8425(5)	0.750	4.8(1)[b]
O1	0.2527(6)	0.6365(8)	0.4553(9)	1.8(2)
O2	0.1385(5)	0.7069(8)	0.3879(9)	1.5(2)
O3	0.4663(5)	0.5904(8)	0.080(1)	1.7(2)
O4	0.4821(6)	0.7578(8)	0.016(1)	1.7(2)
O5	0.3734(6)	0.5064(7)	0.3327(9)	1.6(2)
O6	0.2994(6)	0.4920(9)	0.153(1)	2.3(2)
O7	0.3823(6)	0.7212(8)	0.3158(9)	1.6(2)
Ow1	0.500	0.623(1)	0.750	2.5(3)[b]
Ow2	0.4361(8)	0.971(1)	0.110(1)	3.6(3)
NO	0.3670(8)	0.945(1)	0.359(1)	3.5(3)[c]
C1	0.2107(7)	0.680(1)	0.374(1)	1.0(2)*
C2	0.2440(8)	0.707(1)	0.241(1)	1.5(2)*
C3	0.3308(8)	0.672(1)	0.225(1)	1.2(2)*
C4	0.3538(9)	0.706(1)	0.089(1)	1.7(2)*
C5	0.4394(8)	0.683(1)	0.061(1)	1.5(2)*
C6	0.3344(8)	0.547(1)	0.236(1)	1.3(2)*

[a] Starred *B* values are for atoms that were refined isotropically. Anisotropically refined atoms are given in the form of the isotropically equivalent displacement parameter defined as $^4/_3[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)]$. [b] Atom refined with occupancy factor of 0.5. [c] This site is occupied by the disordered ammonium ion and water molecule. The ratio of the occupancies for the N and O atoms was set to 50/50.

were prepared and kept at 4 °C, the solutions did not give any solid product even after several weeks. The same samples were further allowed to stand at ambient temperature under reduced pressure. The solutions gradually became very sticky and finally gave a white sticky powder but no crystalline product. The powder could not be further characterized because of the difficulty in the isolation.

Isolation of Type 2[1a] Compounds (General Formula $K_{1-x}(NH_4)_xBi(cit)(H_2O)$) from CBS Samples. A bunch of CBS solid (batch no. 89A31) was kept at 50–60 °C in an oven for 3 days. When the preheated sample (2.0 g) was dissolved in water (5 mL), a white powder was immediately precipitated. After several hours, the product was collected, washed with mixtures of water and methanol (3:1, 1:1, 1:3), methanol, and diethyl ether, and dried in air. Yield: 1.3 g. Two other products which were obtained by applying the same procedure to 85BC82 and 87BC03 showed practically the same infrared spectrum and the same X-ray diffraction pattern as those of the compound from 89A31. By comparison of the spectroscopic features with those of previously obtained authentic samples,[1a] the white precipitates were assigned to type **2** compound shown in Table I.

Instruments, Analyses, and Measurements. Carbon, hydrogen, nitrogen, oxygen, potassium and bismuth analyses for compounds **2c** and **3b** were carried out at Mikroanalytisches Labor Pascher, Germany. For the compounds **3a** and **6**, carbon, hydrogen, and nitrogen analyses were carried out at the Serves Centre of Elemental Analysis, Kyusyu University, Japan. The Bi content was determined by edta titration. The potassium analysis was made with a Shimadzu AA-680 atomic absorption flame spectrophotometer. Water and ammonia contents were analyzed at the Analytical Laboratories of Gist Brocades, Delft, The Netherlands. Infrared 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. ^{1}H NMR spectra were recorded with a Bruker WM 300 spectrometer. D_2O was used as a solvent. Chemical shifts (*δ*) are reported in ppm relative to DSS (sodium 4,4-dimethyl-4-silapentansulfonate). The pH dependence of the chemical shifts of methylene protons of citrate was monitored by adding trace amount of DCl and NaOD in D_2O (0.1 and 1 M). The pH values reported as pH* have not been corrected for deuterium isotope effects. ^{13}C NMR spectra were measured with a Bruker MSL-400 spectrometer and with a 10-mm tunable probe. Millipore water was used as a solvent. Chemical shifts are reported in ppm relative to DSS, which was dissolved in a 10% D_2O/H_2O mixture as a external standard. HCl and ammonia solutions were used to adjust the pH for monitoring the pH dependence of the spectra.

X-ray Method and Structure Determination. Single crystals of **3a** and **6** were mounted in glass capillaries and subjected to graphite-monochromatized Mo Kα radiation on an Enraf-Nonius CAD 4 diffractometer at 25 ± 1 °C. A summary of the crystallographic data and refinement results is given in Table II. Complete crystal data and experimental details are deposited as supplementary material (Table S1). Lattice constants were determined by least-squares refinement based on 25 reflections with $20 \leq 2\theta \leq 30°$. The crystal stability was checked every 7200 s of radiation time by measuring three standard reflections. The intensity data were corrected for Lorentz–polarization effects. Both complexes crystallize in the monoclinic crystal system. For **3a** the systematic absences showed two possible space groups *Cc* and *C*2/*c*, the latter of which was confirmed during the refinement. The space group $P2_1/n$ was chosen for **6** on the basis of the systematic absences observed during the data collection. For **3a** no decay of the standards was observed and absorption corrections were applied by an empirical Φ scan method. The structure was solved by direct methods. Refinements were carried out by full-matrix least-squares methods. Since some of the carbon atoms gave negative temperature factors when refined anisotropically, all the carbon atoms were treated isotropically in the final stage of refinement. The chemical composition and the crystallographic symmetries suggested that one ammonium ion and one water molecule occupy the same position because of disordering. Therefore, the position was labeled as NO and treated with the same occupancy factor 0.50 for both the N and O atoms. For **6** the three standard reflections displayed a decay of 26.0% throughout the data collection and a decay correction was made but no absorption correction was applied. The structure was solved by direct methods. Refinements were carried out by full-matrix least-squares methods. Anisotropic refinement of the carbon, oxygen, and nitrogen atoms gave negative values for some of the temperature factor coefficients. Therefore, these atoms were treated isotropically at the final stage of the refinement. Thus, the Bi, K, O, and N atoms of **3a** and the Bi and K atoms of **6** were refined with anisotropic thermal parameters. All the H atoms of both compounds were not included in the calculations. All the calculations were carried out on a Micro-VAXII computer, using the Enraf-Nonius SDP program package.[8] Analytical scattering factors for neutral atoms were corrected for both Δ*f*′ and Δ*f*″ components of anomalous dispersion.[9]

Results

Crystal structure of Compound 3a. Compound **3a** was characterized by X-ray crystallography as a polymeric aggregation consisting of the $[Bi_2(cit)_2(H_2O)_2]^{2-}$ dinuclear unit through citrate and hydrogen bonding bridges. The asymmetric unit contains one Bi^{3+} ion, one tetraionized citrate (cit^{4-}), one coordinated and one lattice water molecule, and as countercations one potassium and one disordering ammonium ion, the latter of which is disordering (vide infra). The atomic coordinates and the thermal parameters for the non-hydrogen atoms are given in Table III.

---

(8) Frenz, B. A. *The SDP User's Guide*; Enraf-Nonius: Delft, The Netherlands, 1985.

(9) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV.

Table IV. Important Interatomic Distances and Angles of Non-Hydrogen Atoms of **3a**[a]

	Distances (Å)		
Bi–Bif	4.7123(7)	Bi–O3a	2.461(9)
Bi–Bid	5.8301(7)	Bi–O3b	3.104(9)
Bi–Bia	6.1090(7)	Bi–O4a	2.56(1)
Bi–Bij	6.2940(7)	Bi–O5	2.269(9)
Bi–Bik	6.1024(7)	Bi–O6b	2.85(1)
Bi–Bib	6.1024(7)	Bi–O7	2.132(9)
Bi–O1	2.474(9)	Bi–Ow1	3.1486(7)
Bi–O2d	2.47(1)		
	Angles (deg)		
O1–Bi–O2d	77.5(3)	O3a–Bi–O6b	129.1(3)
O1–Bi–O3a	152.7(3)	O3a–Bi–O7	87.5(4)
O1–Bi–O3b	115.2(3)	O3a–Bi–Ow1	76.1(2)
O1–Bi–O4a	139.2(3)	O3b–Bi–O4a	105.6(3)
O1–Bi–O5	75.8(3)	O3b–Bi–O5	71.0(3)
O1–Bi–O6b	60.2(3)	O3b–Bi–O6b	64.4(3)
O1–Bi–O7	76.2(3)	O3b–Bi–O7	139.2(3)
O1–Bi–Ow1	129.5(2)	O3b–Bi–Ow1	61.9(3)
O2d–Bi–O3a	124.4(3)	O4a–Bi–O5	122.3(3)
O2d–Bi–O3b	131.5(3)	O4a–Bi–O6b	144.8(3)
O2d–Bi–O4a	73.6(3)	O4a–Bi–O7	74.8(3)
O2d–Bi–O5	151.2(3)	O4a–Bi–Ow1	68.3(3)
O2d–Bi–O6b	88.3(3)	O5–Bi–O6b	87.8(3)
O2d–Bi–O7	88.5(3)	O5–Bi–O7	74.8(3)
O2d–Bi–Ow1	74.1(3)	O5–Bi–Ow1	132.5(3)
O3a–Bi–O3b	64.8(3)	O6b–Bi–O7	135.9(3)
O3a–Bi–O4a	51.9(3)	O6b–Bi–Ow1	77.9(3)
O3a–Bi–O5	78.9(3)	O7–Bi–Ow1	142.2(3)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits. Atomic equivalent positions are as follows: (a) $1 - x, y, {}^1/_2 - z$; (b) $x, 1 - y, {}^1/_2 + z$; (c) $1 - x, 1 - y, -z$; (d) ${}^1/_2 - x, {}^3/_2 - y, 1 - z$; (e) ${}^1/_2 + x, {}^3/_2 - y, z - {}^1/_2$; (f) $1 - x, 1 - y, 1 - z$; (g) ${}^1/_2 + x, y - {}^1/_2, z$; (h) ${}^1/_2 - x, y - {}^1/_2, {}^3/_2 - z$; (i) $x, y, z + 1$; (j) $1 - x, y, {}^3/_2 - z$; (k) $x, 1 - y, {}^1/_2 + z$; (l) ${}^1/_2 - x, {}^1/_2 + y, {}^1/_2 - z$; (m) $1 - x, 2 - y, -z$; (n) $x, 2 - y, z - {}^1/_2$; (o) ${}^1/_2 + x, {}^3/_2 - y, z + {}^1/_2$; (p) $1 - x, 2 - y, 1 - z$; (q) $x, 2 - y, {}^1/_2 + z$.

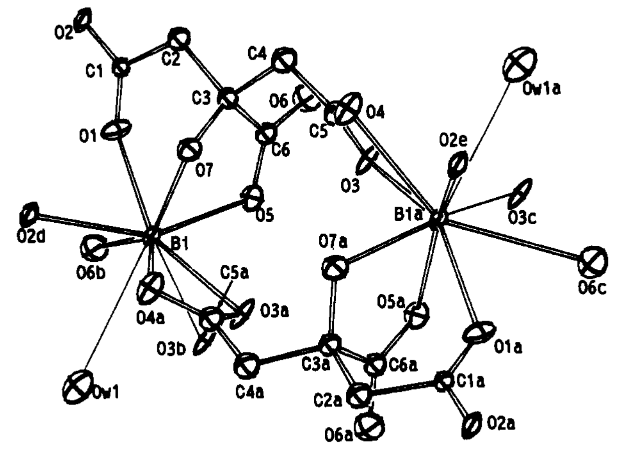


Figure 2. Perspective view and atom-labeling scheme of a dinuclear subunit in compound **3a**.

In Table IV the relevant bond distances and angles are listed. The $[Bi(cit)(H_2O)]^-$ unit from the asymmetric part is paired to itself by the symmetry operation $(1 - x, y, {}^1/_2 - z)$, to give the dinuclear unit $[Bi_2(cit)_2(H_2O)_2]^{2-}$ with a Bi–Bi distance of 6.1090(7) Å (see Figure 2). In the unit, three oxygen atoms from a citrate, a terminal carboxylate (O1), the central carboxylate (O5), and the hydroxo (O7), tridentately chelate to Bi^{3+} (Bi–O1 = 2.474(9) Å, Bi–O5 = 2.269(9) Å, Bi–O7 = 2.132(9) Å); further, the two oxygen atoms (O3 and O4) of the other terminal carboxylate group coordinate to the neighboring bismuth (Bia) in four-membered bidentate chelation (Bia–O3 = 2.461(9) Å, Bia–O4 = 2.56(1) Å). This dinuclear unit is further paired to itself by an inversion center to form a tetranuclear subunit as shown in Figure 3. The central and terminal carboxylate oxygen atoms (*i.e.* O6b and O3b in Figure 3), which do not participate in the tridentate chelation, are used to connect the two dimeric $[(cit)BiBi(cit)]^{2-}$ units (Bi–O6b = 2.85(1) Å, Bi–O3b = 3.104(9) Å). Furthermore, the tetranuclear subunits are linked to neighboring subunits by using citrato bridging; *e.g.*, the terminal carboxylate oxygen (O2) is located in a distance of 2.47 (1) Å from a bismuth (Bid) in a neighboring tetranuclear subunit, to yield a complicated three-dimensional polymer. The potassium and the ammonium ions can clearly be distinguished and are in contact with both citrate and water oxygens, with distances larger than 2.70 Å. Short distances (<3.40 Å) for both K-O and N-O contacts are listed in Table S2. From these data it is clear that the tetranuclear units are interlinked also by hydrogen bonds. The structure appears to be isostructural with $(NH_4)Bi(cit)\cdot 2H_2O$ reported recently by Herrmann *et al.*,[6b] except for the locations of K, OW1, and OW2. In their compound two water molecules are located at special positions with a site occupation factor of ${}^1/_2$, and one ammonium ion and one water molecule are located in a general position. In our compound, one potassium ion and one water molecule occupy special positions, and one water is found at a general position and another water is found at a general position as disordered with the occupation factor of ${}^1/_2$. The position for the last water molecule is further occupied by an ammonium ion, which is disordered with the same occupancy. Irrespective of the differences, however, both complexes should be regarded as isostructural. In fact, Bi-Bi and Bi-O distances in **3a** are very close to the corresponding distances of the ammonium salt, varying less than 0.04 Å.

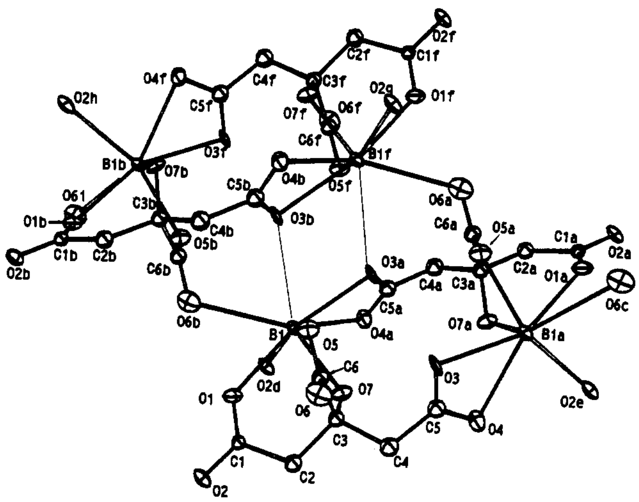


Figure 3. Perspective view of a tetranuclear subunit in compound **3a**, showing two dinuclear subunits pairing.

Crystal Structure of Compound 6. The dinuclear and tetranuclear units of this compound are almost identical to **3a**. Furthermore, this compound is organized in a complicated polymeric structure formed by tetranuclear subunit aggregation as is the case for **3a**. The tetranuclear subunit is shown in Figure 4. Contrary to **3a** in which all Bi atoms and citrate ligands are crystallographically equivalent, the asymmetric unit of **6** contains two bismuth atoms, two citrates, one potassium, and one ammonium ions as countercations, and two coordinated (Ow6 loosely to Bi1 which is not shown in Figure 4 because of the long distance, and Ow2 tightly to Bi2) and four lattice water molecules. An observed Bi-Bi distance (6.121(1) Å) from the asymmetric unit is very close to that of the dinuclear subunit in **3a**. In the unit of **6**, three oxygen atoms from a citrate (citrate 1), a terminal carboxylate (O3), the central carboxylate (O5), and the hydroxo (O7), tridentately chelate to Bi1 (Bi1–O3 = 2.45(2) Å, Bi1–O5 = 2.33(2) Å, Bi1–O7 = 2.11(1) Å); further, the two oxygen atoms (O1 and O2) of the other terminal carboxylate group coordinate to Bi2 as a four-membered bidentate chelate (Bi2–O1 = 2.47(2) Å, Bi2–O2 = 2.50(2) Å). Another citrate group (citrate 2) similarly coordinates to the two bismuth atoms with the same

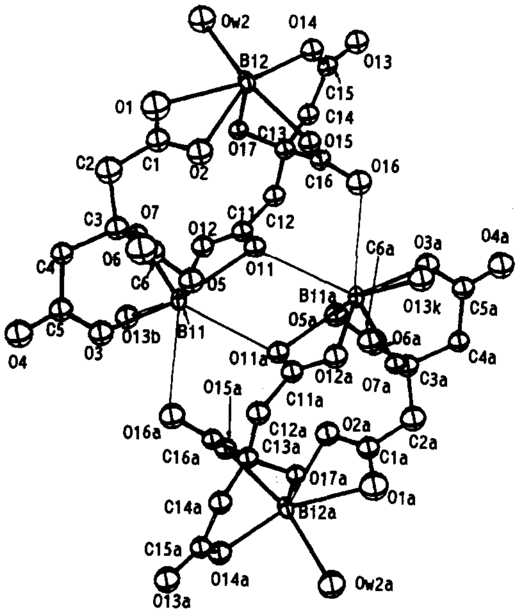


Figure 4. Perspective view of a tetranuclear subunit in compound **6**, showing two dinuclear subunits pairing.

donor set as that from citrate 1, *i.e.* tridentate chelation to Bi2 (Bi2–O14 = 2.44(2) Å, Bi2–O15 = 2.28(1) Å, Bi2–O17 = 2.12(2) Å) and four-membered bidentate chelation to Bi1 (Bi1–O11 = 2.51(2) Å, Bi1–O12 = 2.42(2) Å). Bi1 is further coordinated by the water oxygen atom OW6 (Bi1–OW6 = 3.32(2) Å), and Bi2 by the water oxygen atom OW2 (Bi2–OW2 = 2.53(2) Å). The atomic coordinates and the thermal parameters for the non-hydrogen atoms are given in Table V. In Table VI the relevant bond distances and angles are listed. For the citrate binding, the ligand behaves quite similarly to that in **3a**. Furthermore, the same oxygen set as that from citrate in **3a** is used to connect the two dinuclear units, yielding a tetranuclear subunit with an inversion center, *i.e.* O16 from a central carboxylate (Bi1a–O16 = 3.16(2) Å) and O11 from a terminal carboxylate (Bi1a–O11 = 3.08(1) Å). Again as is the case for **3a**, the tetranuclear subunits are linked to neighboring subunits by using citrato bridging; *e.g.* the terminal carboxylate oxygen (O13) is located in a distance of 2.45(2) Å from a bismuth (Bi1b) in a neighboring tetranuclear subunit, to yield a complicated three-dimensional polymer. A notable difference in the structures **3a** and **6** is that in **6** Bi1 and Bi2 are loosely and tightly coordinated by a water molecule, respectively (Bi1–Ow6 = 3.32(2) Å and Bi2–Ow2 = 2.53(2) Å; vide supra), whereas in **3a** only one water molecule is weakly coordinated to Bi (at 3.1486(7) Å). These differences in Bi–Ow distances are likely to be related to the differences in crystal packing.

As in the relation of **3a** and $(NH_4)Bi(cit)\cdot 2H_2O$ reported by Herrmann *et al.*,[6b] **6** is indeed isostructural with $KBi(cit)\cdot 3H_2O$ reported by the same group.[6a] However, the difference to be noted is that **6** contains an ammonium cation as evident from the elemental analysis and the IR feature (a broad and very strong band centered at 3150 cm^{-1}), whereas the other is a pure potassium salt irrespective of the use of ammonia to control pH conditions of the solution.

Solution Behavior of CBS. In the first paper of this series[1a] the solution behavior of synthetic bismuth citrate compounds was described in detail by use of NMR spectroscopy. The behavior strongly depends on the citrate/Bi ratio. When the ratio is ≥ 1.0 (type 1, 2, 3, and 5 compounds in Table I) and under acidic conditions, all citrates rapidly exchange at bismuth on the NMR time scale. Under alkaline conditions in diluted solutions (*i.e.* [Bi] < 20mM) the citrates are hardly, if at all, coordinated to bismuth. On the other hand, at citrate/Bi ratios < 1.0 (type 4 compound in Table I), the citrates rigidly coordinate to bismuth.

Table V. Fractional Positional Parameters and Thermal Parameters of Non-Hydrogen Atoms of **6** with Their Estimated Standard Deviations in Parentheses[a]

atom	x	y	z	B_{eq}, Å^2
Bi1	0.52917(7)	0.34960(5)	0.03254(5)	1.79(1)
Bi2	1.04259(7)	0.53525(5)	0.15542(5)	1.92(1)
K	0.781(1)	0.1907(8)	–0.2746(8)	11.1(3)
Ow1	0.353(2)	0.166(1)	–0.226(1)	3.5(3)*
Ow2	1.197(2)	0.481(1)	0.302(1)	4.0(4)*
Ow3	0.685(4)	0.301(3)	0.512(3)	11(1)*
Ow4	0.623(5)	0.388(4)	0.661(3)	15(2)*
Ow5	0.530(6)	0.387(4)	0.362(4)	20(2)*
Ow6	0.288(2)	0.440(1)	0.093(1)	3.7(4)*
O1	1.026(2)	0.376(1)	0.159(1)	4.6(4)*
O2	0.921(2)	0.438(1)	0.029(1)	3.3(3)*
O3	0.520(2)	0.213(1)	–0.053(1)	3.2(3)*
O4	0.573(2)	0.080(1)	–0.079(1)	3.9(4)*
O5	0.627(2)	0.384(1)	–0.083(1)	3.1(3)*
O6	0.764(2)	0.321(1)	–0.148(1)	4.7(4)*
O7	0.718(1)	0.303(1)	0.079(1)	2.1(3)*
O11	0.618(1)	0.498(1)	0.079(1)	2.4(3)*
O12	0.604(1)	0.407(1)	0.188(1)	2.8(3)*
O13	1.036(2)	0.746(1)	0.366(1)	3.3(3)*
O14	1.067(1)	0.658(1)	0.261(1)	2.8(3)*
O15	0.873(1)	0.620(1)	0.084(1)	2.5(3)*
O16	0.722(2)	0.695(1)	0.123(1)	3.5(3)*
O17	0.900(1)	0.5073(9)	0.2224(9)	1.9(2)*
N	0.321(3)	0.062(2)	–0.037(2)	6.6(8)*
C1	0.958(2)	0.372(2)	0.080(2)	2.8(4)*
C2	0.916(3)	0.282(2)	0.042(2)	3.7(5)*
C3	0.771(2)	0.276(2)	0.008(2)	2.8(4)*
C4	0.741(2)	0.178(2)	–0.015(2)	2.4(4)*
C5	0.604(2)	0.156(2)	–0.050(2)	2.8(4)*
C6	0.722(2)	0.330(2)	–0.077(2)	3.4(5)*
C11	0.636(2)	0.481(2)	0.162(2)	2.4(4)*
C12	0.693(2)	0.549(2)	0.235(2)	2.6(4)*
C13	0.822(2)	0.581(1)	0.227(1)	2.2(4)*
C14	0.879(2)	0.636(2)	0.312(2)	2.5(4)*
C15	1.000(2)	0.684(1)	0.312(1)	2.2(4)*
C16	0.803(2)	0.636(1)	0.138(1)	2.2(4)*

[a] Starred *B* values are for atoms that were refined isotropically. Anisotropically refined atoms are given in the form of the isotropically equivalent displacement parameter defined as $^4/_3[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)]$.

CBS solid samples are quite unique in their extremely high solubility in water unlike any other Bi-containing drugs, such as basic bismuth subsalicylate (BSS).[5] However, the samples hydrolyze in acidic solutions (pH < 4) to yield a white finely divided precipitate, which was reported to be a mixture of bismuth citrate and bismuth oxychloride.[10] This property allowed a solution study by using NMR spectroscopy to compare the behavior of synthetic bismuth citrate compounds. A typical dose of CBS for a patient is 120 mg (calculated as Bi_2O_3) four times a day, corresponding to relatively low concentration in a body. Therefore, ^{1}H-NMR spectra of CBS at low concentrations were measured first. Figure 5 shows the spectra (batch no. 87BC03) in D_2O measured at different pH* values. The spectra show an AB pattern assignable to CH_2 groups of citrates included in CBS with no other peaks. The chemical shifts and the peak widths are pH dependent. However, above pH* 7 the peaks become very sharp and the chemical shifts are invariably constant. In addition, the chemical shifts (2.64 and 2.53 ppm from DSS) are practically the same as that of free citrate measured at the same pH. Finally, CBS solutions to which free citrate was added did not give any other peaks besides an AB pattern, whose chemical shifts depend on the pH used. These results clearly indicate that all citrates in CBS rapidly exchange on Bi(III), to become averaged on the NMR time scale at pH* < 7, even though a part of citrate precipitates as insoluble Bi salt below pH* 4, and are hardly coordinated at pH* > 7. The solution behavior of concentrated CBS solutions slightly differs from that of diluted

---

(10) Williams, R. D. *J. Inorg. Nucl. Chem.* **1977**, *39*, 711.

Table VI. Important Interatomic Distances and Angles of Non-Hydrogen Atoms of **6**[a]

	Distances (Å)		
Bi1–Bi1a	4.750(1)	Bi1–O13b	2.45(2)
Bi1–Bi2	6.121(1)	Bi1–O16a	3.16(2)
Bi1–Bi2a	6.372(1)	Bi2–Ow2	2.53(2)
Bi1–Bi2d	6.342(1)	Bi2–Ow6c	3.41(2)
Bi2–Bi2d	4.644(1)	Bi2–O1	2.47(2)
Bi1–Ow6	3.32(2)	Bi2–O2	2.50(2)
Bi1–O3	2.45(2)	Bi2–O2d	2.94(2)
Bi1–O5	2.33(2)	Bi2–O6d	3.09(2)
Bi1–O7	2.11(1)	Bi2–O14	2.44(2)
Bi1–O11	2.51(2)	Bi2–O15	2.28(1)
Bi1–O11a	3.08(1)	Bi2–O17	2.12(2)
Bi1–O12	2.42(2)		
	Angles (deg)		
Ow6–Bi1–O3	125.4(5)	Ow2–Bi2–Ow6c	73.1(6)
Ow6–Bi1–O5	132.0(5)	Ow2–Bi2–O1	71.8(6)
Ow6–Bi1–O7	145.9(5)	Ow2–Bi2–O2	123.6(6)
Ow6–Bi1–O11	79.6(5)	Ow2–Bi2–O2d	130.0(6)
Ow6–Bi1–O11a	59.4(5)	Ow2–Bi2–O6d	88.3(6)
Ow6–Bi1–O12	70.6(5)	Ow2–Bi2–O14	76.2(6)
Ow6–Bi1–O13b	73.4(5)	Ow2–Bi2–O15	149.9(6)
Ow6–Bi1–O16a	72.5(5)	Ow2–Bi2–O17	85.4(6)
O3–Bi1–O5	76.4(6)	Ow6c–Bi2–O1	68.9(6)
O3–Bi1–O7	77.2(5)	Ow6c–Bi2–O2	80.0(5)
O3–Bi1–O11	152.1(6)	Ow6c–Bi2–O2d	58.9(5)
O3–Bi1–O11a	115.4(5)	Ow6c–Bi2–O6d	72.8(5)
O3–Bi1–O12	140.6(5)	Ow6c–Bi2–O14	124.1(5)
O3–Bi1–O13b	77.9(6)	Ow6c–Bi2–O15	135.6(5)
O3–Bi1–O16a	61.3(5)	Ow6c–Bi2–O17	141.1(5)
O5–Bi1–O7	73.7(6)	O1–Bi2–O2	52.3(6)
O5–Bi1–O11	77.2(6)	O1–Bi2–O2d	100.8(6)
O5–Bi1–O11a	72.7(5)	O1–Bi2–O6d	140.6(7)
O5–Bi1–O12	122.3(6)	O1–Bi2–O14	139.3(6)
O5–Bi1–O13b	151.9(6)	O1–Bi2–O15	121.8(6)
O5–Bi1–O16a	88.9(5)	O1–Bi2–O17	73.8(7)
O7–Bi1–O11	87.1(5)	O2–Bi2–O2d	63.1(6)
O7–Bi1–O11a	139.5(5)	O2–Bi2–O6d	129.2(6)
O7–Bi1–O12	76.4(6)	O2–Bi2–O14	154.4(5)
O7–Bi1–O13b	89.7(6)	O2–Bi2–O15	77.9(5)
O7–Bi1–O16a	137.8(5)	O2–Bi2–O17	86.0(6)
O11–Bi1–O11a	63.9(4)	O2d–Bi2–O6d	66.1(5)
O11–Bi1–O12	53.1(5)	O2d–Bi2–O14	119.1(5)
O11–Bi1–O13b	125.5(5)	O2d–Bi2–O15	76.8(5)
O11–Bi1–O16a	126.7(5)	O2d–Bi2–O17	141.6(5)
O11a–Bi1–O12	103.6(5)	O6d–Bi2–O14	60.7(6)
O11a–Bi1–O13b	129.8(5)	O6d–Bi2–O15	92.4(6)
O11a–Bi1–O16a	62.9(4)	O6d–Bi2–O17	139.7(6)
O12–Bi1–O13b	73.4(6)	O14–Bi2–O15	78.0(5)
O12–Bi1–O16a	142.2(5)	O14–Bi2–O17	79.2(6)
O13b–Bi1–O16a	88.6(5)	O15–Bi2–O17	74.8(6)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits. Atomic equivalent positions are as follows: (a) $1 - x, 1 - y, -z$; (b) $^3/_2 - x, y - ^1/_2, ^1/_2 - z$; (c) $x + 1, y, z$; (d) $2 - x, 1 - y, -z$; (e) $x - ^1/_2, ^1/_2 - y, z - ^1/_2$; (f) $x + ^1/_2, ^1/_2 - y, z - ^1/_2$; (g) $2 - x, 1 - y, 1 - z$; (h) $x + ^1/_2, ^1/_2 - y, ^1/_2 + z$; (i) $x, y, z + 1$; (j) $x - 1, y, z$; (k) $x - ^1/_2, ^3/_2 - y, z - ^1/_2$; (l) $1 - x, -y, -z$; (m) $^3/_2 - x, ^1/_2 + y, ^1/_2 - z$.

solutions. As shown in Figure 6a, when the sample is dissolved in water (220 mg/ml) without adding any pH buffer, the solution (pH 6.2) behaves quite similarly to that of the diluted solution, *i.e.* rapid ligand exchange occurs, which results in averaging on the NMR time scale. As shown in Figure 6b, however, under basic conditions new peaks with small intensity come up near the main peaks whose chemical shifts are practically the same as those of free citrate measured at the same pH. The extra peaks are undoubtedly due to coordinated citrate, and their intensities increase with increasing concentration. So, under high-concentration conditions, part of the bismuth is likely to form a polymeric aggregation, such as the solid products **3a** and **6**.

Discussion

Solid-State Structures. Most bismuth salts are usually insoluble in organic solvents and will undergo hydrolysis in water to form insoluble bismuth–oxy salts. This chemical property is responsible for the difficulty in preparing the complexes and has retarded the development of the structural chemistry, compared to other metal complexes. Recently, a renewed interest has risen in the Bi alkoxides[11] as potential precursors for new superconductor with high T_c. Through structural investigations, data on Bi–O interaction in solids are now increasing. Very recently, Rogers *et al.* reported 3D structure of many bismuth(III) complexes[12]

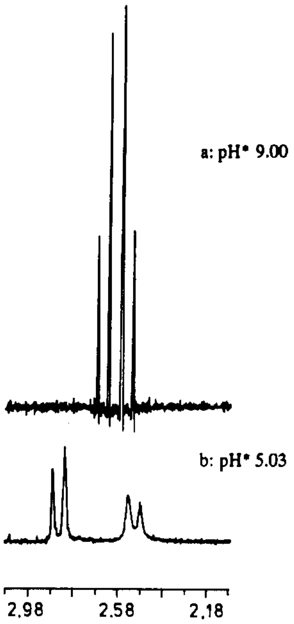


Figure 5. ^{1}H NMR spectra of a CBS sample (batch no. 87BC03) in D_2O at different pH* values.

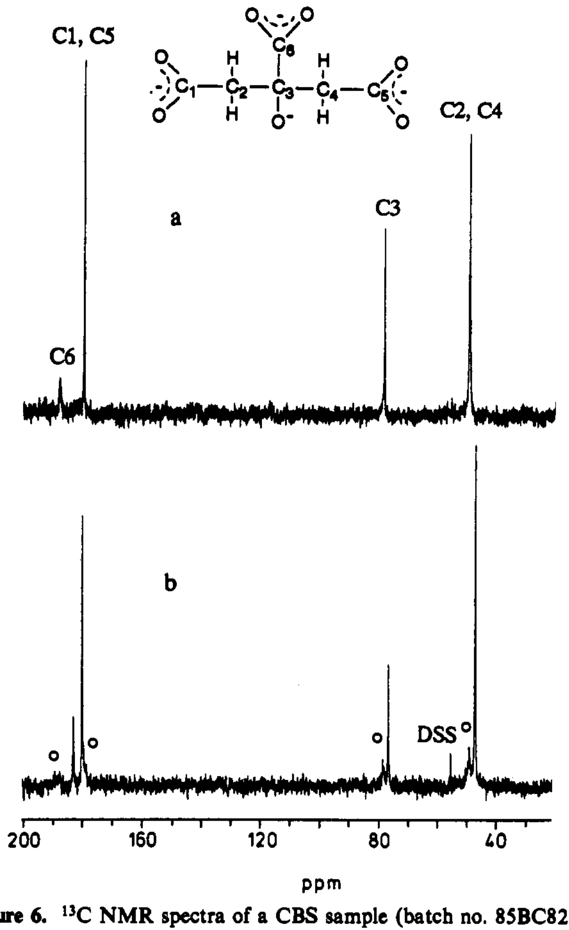
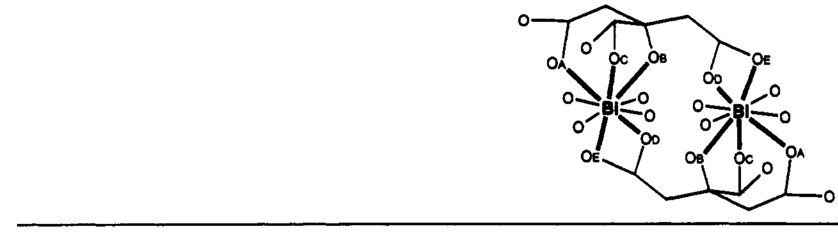


Figure 6. ^{13}C NMR spectra of a CBS sample (batch no. 85BC82) in H_2O: (a) 220 mg/mL at pH 6.20; (b) 302 mg/mL at pH 8.99. O : coordinated citrate.

Table VII. Interatomic Distances (Å) for the Dinuclear Subunit $Bi_2(cit^{4-})_2$ in the Bi–Citrate Aggregations[a]



	3a (Bi:cit = 1:1)	**3h**[b] (Bi:cit = 1:1)	6 (Bi:cit = 1:1)		**6h**[c] (Bi:cit = 1:1)		**1**[d] (Bi:cit = 2:3)		**5**[d] (Bi:cit = 1:2)
Bi–Bi	6.109	6.089	6.121		6.089		5.849	5.819	5.972
Bi–OA	2.474	2.452	2.455	2.440	2.414	2.423	2.552	2.559	2.526
Bi–OB	2.132	2.122	2.114	2.116	2.126	2.132	2.125	2.120	2.136
Bi–OC	2.269	2.265	2.333	2.285	2.297	2.275	2.339	2.336	2.348
Bi–OD	2.462	2.454	2.423	2.467	2.402	2.451	2.363	2.313	2.362
Bi–OE	2.562	2.526	2.507	2.500	2.493	2.459	2.772	2.943	2.868
Bi–O	2.473	2.476	2.447	2.528[e]	2.442	2.531[e]	2.474	2.368	2.448
Bi–O	2.851	2.860	3.078	2.944	3.055	2.983	2.802	2.811	2.746
Bi–O	3.104	3.083	3.158	3.091	3.232	3.116	2.988	2.817	2.790[e]
Bi–O	3.149[e]	3.172[e]	3.316[e]	3.408[e]	3.324[e]	3.392[e]	3.042	2.954	2.925[e]

[a] For the compound 6 and **6h** two citrate bridging modes for each bismuth are essentially the same but are crystallographically unequivalent. For the compound **1** two crystallographically independent dimeric units are interlinked by citrate (triply ionized $Hcit^{3-}$) bridges (see text). [b] Reference 6b. [c] Reference 6a. [d] Reference 1a. [e] Bi–water oxygen (coordinated).

with a variety of polyethylene glycols. It has been emphasized that lone-pair density of Bi^{3+} is stereochemically activated by the formation of Bi–O covalent bonds, and further that the activated lone pair at the trans position to the covalent bond results in long Bi–O secondary interactions near the pair.[12]

In our compound **3a** the shortest Bi-O interaction (2.132(9) Å) comes from the alkoxo (O7) atom of the central carbon in the citrate. Accordingly, the activated lone-pair density is located in its trans position. As expected, the longest interaction (Bi–Owl = 3.1486(7) Å) is found near this position (O7–Bi–Owl = 142.2(3)°). Furthermore, the second longest interaction is also found near the trans position (Bi–O3b = 3.104(9) Å, O7–Bi–O3b = 139.2(3)°). In this compound, Bi–O distances vary widely, *i.e.* from 2.13 to 3.15 Å, but even the long bonds are significantly shorter than the sum of the van der Waals radii (3.67 Å).[13] The wide range of Bi–O distances and the 9-coordination are consistent with those of previously reported compounds **1** and **5**.[1a] When Bi-O distances are <3.5 Å, they are regarded as coordinating; also the two crystallographically independent Bi atoms of compound **6** have CN (coordination number) 9, although some distances are quite long, *i.e.* Bil–Ow6 = 3.32(2) Å and Bi2–Ow6c = 3.41(2) Å. By introduction of the concept of the activated lone-pair effect, these interactions are also considered as coordination, since these oxygen atoms are located in the space nearly trans to each Bi–O covalent bond (Bil–O7 = 2.11(1) Å, O7–Bil–Ow6 = 145.9(5)°, O7–Bil–O16a = 137.8(5)°, Bi2–O17 = 2.12(2) Å, O17–Bi2–Ow6c = 141.1(5)°). If it is taken into account the fact that the stronger covalent character results in the weaker Bi–O interaction to the trans position, it could be regarded that compound **6** more strongly reflects the effect than **3a**, in fact even more than all the compounds reported by Rogers *et al.*[12] As a consequence, the two Bi atoms of **6** attained CN 9 as was the case for all Bi atoms in the compounds **1**, **5**, and **3a** (the dinuclear subunit with the geometry of CN 9 is given in Figure S1 as supplementary material).

In view of the biological interest in citric acid, many metal complexes of citrate have been investigated in the solid state[14] and in solution[15] in the past. Since citric acid has at least four coordinating and chelating donors, *i.e.* three carboxylate groups and one hydroxy group, these metal complexes show a strong tendency to form oligomeric or polymeric aggregation in the solid state[14] just as seen in the compounds **3a** and **6**. However, the most common coordination mode of citrate seems to be the tridentate chelation formed by two carboxylate groups (one central, one terminal) and one hydroxyl group. This chelation mode has been reported for both the triionized and tetraionized form, *e.g.* $Hcit^{3-}$ for Fe(II),[14a] Mg(II),[14b] Mn(II),[14C] $Mo^{VI}O_2$,[14e] Ca(II),[14f] and Zn(II)[14g] and cit^{4-} for Ni(II),[14a] and Al(III),[14d] respectively, indicating that the binding mode does not depend on the actual charge of the ligand.

In the present cases, the other terminal carboxylate group that does not participate in the tridentate chelation further bridges to the adjacent Bi but in a bidentate form, resulting in the dinuclear units $[(cit)BiBi(cit)]^{2-}$. It is to be noted that such dinuclear units function as a building block in the polymeric compounds **3a** and **6** and also in previously reported structures **1** and **5**.[1a] The unit structure is very similar in all bismuth complexes reported thus far and is also present in the two compounds reported by Herrmann *et al.*[6a,b] For better understanding the similarity in the units from all known Bi citrate complexes, all Bi–O and Bi–Bi distances in these units are listed in Table VII. In compounds **3a** and **6**, corresponding Bi–Bi and Bi–O (from the typical tridentate chelation) distances are nearly the same. However, when compared with those in compounds **1** and **5**, these distances differ

---

(11) (a) Hubert-Pfalzgraf, L. G. *New J. Chem.* **1987**, *11*, 663. (b) Katayama, S.; Sekine, M. *J. Mater. Res.* **1991**, *6*, 36. (c) Purdy, A. P.; George, C. F. *Inorg. Chem.* **1991**, *30*, 1969. (d) Vaarstra, B. A.; Huffman, J. C.; Streib, W. E.; Caulton, K. G. *Inorg. Chem.* **1991**, *30*, 3068.

(12) (a) Rogers, R. D.; Bond, A. H.; Aguinaga, S. *J. Am. Chem. Soc.* **1992**, *114*, 2960. (b) Rogers, R. D.; Bond, A. H.; Aguinaga, S.; Reyes, A. *J. Am. Chem. Soc.* **1992**, *114*, 2967.

(13) Alcock, N. W. In *Advances in Inorganic Chemistry and Radiochemistry*; Emeleus, H. J.; Sharpe, A. G., Eds.; Academic Press: New York, 1972; pp 1–58.

(14) (a) Strouse, J.; Layten, S. W.; Strouse, C. E. *J. Am. Chem. Soc.* **1977**, *99*, 562. (b) Johnson, C. K. *Acta Crystallogr.* **1965**, *18*, 1004. (c) Carrell, H. L.; Glusker, J. P. *Acta Crystallogr., Sect. B* **1973**, *29*, 638. (d) Feng, T. L.; Gurian, p.L.; Healy, M. D.; Barron, A.R. *Inorg. Chem.* **1990**, *29*, 408. (e) Alcock, N. W.; Dudek, M.; Grybos, R.; Hodorowick, E.; Kanas, A.; Samotus, A. *J. Chem. Soc., Dalton Trans.* **1990**, 707. (f) Sheldrick, B. *Acta Crystallogr., Sect. B* **1974**, *30*, 2056. (g) Swanson, R.; Ilsley, W. H.; Stanislowski, A. G. *J. Inorg. Biochem.* **1983**, *18*, 187–194.

(15) For example: (a) Glickson, J. D.; Pinter, T. P.; Webb, J.; Gams, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 1679. (b) Chang, C. H. F.; Pinter, T. P.; Lenkinsky, R. E.; Glickson, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 5858. (c) Vijverberg, C. A. M.; Peters, J. A.; Kieboom, A.P.G.; van Bekkum, H. *Trav. Chim. Pays-Bas* **1980**, *99*, 403. (d) Peters, J. A.; Kieboom, A. P. G. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 381. (e) Gregor, J. E.; Powell, H. K. J. *Aust. J. Chem.* **1986**, *39*, 1851. (f) Greenaway, F. T. *Inorg. Chim. Acta* **1986**, *116*, L21. (g) Cervilla, A.; Ramirez, J. A.; Llopis, E. *Transition Met. Chem.* **1986**, *11*, 186. (h) Vijverberg, C. A. M.; Peters, J. A.; Kieboom, A. P. G.; van Bekkum, H. *Tetrahedron* **1986**, *42*, 167. (i) Kakihana, M.; Nagumo, T.; Okamoto, M.; Kakihana, H. *J. Phys. Chem.* **1987**, *91*, 6128. (j) Nunes, M. T.; Gil, S. M. V. *Inorg. Chim. Acta* **1987**, *129*, 283. (k) Caldeira, M. M.; Ramos, M. L.; Caveleiro, A. M. A.; Gil, S. M. V. *J. Mol. Struct.* **1988**, *174*, 461.

slightly, *i.e.* Bi–Bi is ca. 6.1 Å for **3a** and **6** and ca. 5.9 Å for **1** and **5**, respectively.

As has already reported in the previous papers,[1a,16] citrate coordination behavior in solution strongly depends on the citrate/bismuth ratio. It should be worthy to note the fact that the different dependencies on the ratio are also reflected in the structural character in the solid state. Thus, for the compounds having the ratio of citrate:Bi = 2:3 the anionic hexanuclear Bi cluster $[Bi_6O_4(OH)(cit)_3(H_2O)_3]^{3-}$ functions as a building block of the polymer,[16] while the dinuclear unit $[(cit)BiBi(cit)]^{2-}$ is found to be the building block for the all compounds having the ratio ≥1.0. Commercially available CBS solid samples are categorized in the latter group on the basis of the chemical composition, *e.g.* the typical analysis for cit/Bi ratio is 1.25–1.30, *i.e.* cit/Bi ≥ 1.0.[7] Furthermore, as expected from the composition, the solution NMR results for commercially available CBS are indeed those of the synthetic compounds with the citrate/Bi ratio ≥ 1.0, *i.e.* with the rapid ligand exchange under acidic conditions and noncoordination under basic conditions. In view of the resemblance in chemical composition and NMR behavior between CBS samples and synthetic compounds with the citrate/Bi ratio ≥ 1.0, it may be concluded that solid CBS can be regarded as an aggregated form of the dinuclear $[(cit)BiBi(cit)]^{2-}$ building blocks. As discussed in the previous section, the Bi–O complexation yields long distances (*e.g.* Bi2–Ow6c = 3.41(2) Å in **6**) in the presence of the ligand which can covalently bind to the metal. In addition, Bi(III) favors a high coordination number. Therefore, the aggregation of $[(cit)BiBi(cit)]^{2-}$ building blocks becomes very easy by use of potential bridging mediators such as H_2O, NH_4, and K, in addition to citrate. Since the time taken for the spray dry process is too short to result in crystalline products, solid CBS, which is an amorphous powder, might be formed as a metastable product.

Relation between Synthetic Compounds and CBS: Pharmacological Relevance. All commercial CBS-like products, such as DeNol, are amorphous and give practically identical infrared spectra. Several CBS batches were recrystallized from water with the aim to be purified. When starting from CBS, one finds some batches indeed yield crystalline compounds (*e.g.* thin platelike crystals (**2c**) from batch no. 85BC82 and further columnar and needlelike crystals from batch no. 87BC03), whose infrared spectra and X-ray powder diffraction patterns are quite different from those of the original samples. Furthermore, the latter two crystals give practically the same infrared spectra as those of compounds **3a** and **6**, respectively. Many trials to separate pure crystalline compounds from CBS batches show a tendency that relatively aged material yields type **2**, **3**, or **6** compounds as a first precipitation, while relatively fresh CBS (89A31) does not. Since commercial CBS has some smell of ammonia, the difference in the crystallized products has tentatively been attributed to the (varying) amounts of ammonia in the solids.

In order to confirm this assumption, several CBS samples were preheated at 50–60 °C for three days to remove any excess ammonia from the solids, and then recrystallized. As expected, all preheated samples now only yield type **2** compounds, immediately after dissolution. These results clearly indicate that an important role of the ammonia in the solid CBS is to create a high solubility in water by controlling the pH of the solutions. Further, the fact that all the type **2**, **3**, and **6** have the same Bi/cit ratio (=1:1) may lead to the conclusion that type **2** compounds predominantly crystallize in the solution poor in ammonia.

Amorphous CBS samples rearrange in water to yield thermodynamically stable crystalline products such as type **2**, **3**, and **6** compounds. Such rearrangement could also be possible under circumstances in the stomach. In fact, various crystalline species have been found on the ulcer craters of patients treated with CBS, depending upon the pH;[17] at pH 1.5 only amorphous, weakly refractive 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. In earlier work, bismuth oxychloride (BiOCl) and bismuth citrate (unspecified) have been reported to be constituents of the precipitates.[10] Since the compounds **3a** and **6** have relatively high resistance to acid hydrolysis by HCl, these compounds could be regarded as the candidates for the crystalline species found on the ulcer craters.

The most remarkable difference of CBS compared with other bismuth-containing drugs is in its significantly high solubility in water. When bismuth is dosed as CBS, it will arrive in the ulcer regions at a relatively high concentration, because of the solubility. In the stomach hydrolysis by the acidic HCl will become possible, making the Bi available for reactions with the ulcer surface, *e.g.* by binding to proteins. Even if the Bi precipitates as BiOCl, or as a citrate such as in compounds **3a** and **6**, the precipitates will be useful to heal the ulcer, since many insoluble bismuth salts such as the subcarbonate, the subnitrate, and the subsalicylate exhibit more or less ulcer-healing properties.[5]

Concluding Remarks

In the present investigation, several new bismuth citrate complexes were obtained by chemical synthesis and recrystallization of commercially available CBS samples. In the case of two compounds, *i.e.* **3a** and **6**, a 3D structure could be determined by using X-ray diffraction on the single crystals. As seen in the previously reported two compounds **1** (citrate:Bi = 3:2) and **5** (citrate:Bi = 2:1), these two 1:1 polymeric compounds are also the aggregated form of the stable dinuclear subunit $[(cit)BiBi(cit)]^{2-}$ through citrato bridges and hydrogen bonding bridges. It should be noted that such a dinuclear subunit is also seen in the structure of the polymeric K and NH_4 compounds[6a,b] reported by Herrmann *et al.*, even though these authors did not particularly speak of dinuclear units. These findings strongly support the theory that, in the case of solid CBS, such subunits function as a building block to form polymeric amorphous material.

The solution behavior of commercial CBS samples was interpreted on the basis of both the NMR behavior and the previously reported NMR results[1a] on synthetic bismuth-citrato complexes. When sufficient amount of citrate is present in solution, *i.e.* cit/Bi ≥ 1.0, the citrates take part in rapid ligand-exchange processes on bismuth under acidic conditions. This behavior seems to be the main origin of the very high solubility of CBS in water, unlike the other bismuth-containing drugs, such as the subsalicylate and the subcarbonate. Because of the very high solubility, the rapid ligand exchange, and the noncrystalline (amorphous-like) property, the dinuclear subunits as the building block in solid CBS are likely to be easily separated from each other in solution. Then rearrangement could occur because of a thermodynamical reason, finally yielding crystalline products such as **3a** and **6**.

Acknowledgment. Financial support of Gist-Brocades (Delft, The Netherlands) is gratefully acknowledged. E.A. gratefully acknowledges the financial support from the Saneyosi Scholarship Foundation and a Grant-in-Aid for Scientific Research (No. 03854071) from the Ministry of Education, Science, and Culture, of Japan.

Supplementary Material Available: A figure (Figure S1) showing a dinuclear unit of compound **6** and tables of crystallographic data for **3a** and **6** (Table S1), complete bond lengths and bond angles (Table S2 for **3a**, Table S4 for **6**), and anisotropic thermal parameters (Table S3 for **3a**, Table S5 for **6**) (8 pages). Ordering information is given on any current masthead page.

---

[16] Asato, E.; Katsura, K.; Mikuriya, M.; Fujii, T.; Reedijk, J. *Chem. Lett.* **1992**, 1967.

[17] Coghill, S. B. In *Pathogenesis and the treatment of peptic ulcer diseas. Proceedings of an International Symposium*; Axon, A. T. R., Ed.; February, 1985, Cairo, Egypt. *Excerpta Med.* **1985**, 7–12.