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Synthesis, Structure, and Spectroscopic Properties of Bismuth Citrate Compounds and the Bismuth-Containing Ulcer-Healing Agent Colloidal Bismuth Subcitrate (CBS). 4.[1] Crystal Structure and Solution Behavior of a Unique Dodecanuclear Cluster $(NH_4)_{12}[Bi_{12}O_8(cit)_8](H_2O)_{10}$

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This paper describes the synthesis, crystal structure, and aqueous solution behavior of a polymeric bismuth citrate compound $(NH_4)_{12}[Bi_{12}O_8(cit^{4-})_8](H_2O)_{10}$ (**1**). Compound **1** was obtained from an aqueous solution containing commercially available bismuth citrate ($BiC_6H_5O_7$) in the presence of ammonia, which crystallizes in the rhombohedral space group $R\bar{3}$ with $a = b = 17.807(3)$ Å, $c = 31.596(6)$ Å, $V = 8684(4)$ Å^3, and $Z = 3$. The structure solution and refinement based on 1203 reflections with $I = 3\sigma(I)$ converged at $R = 0.055$ and $R_w = 0.062$. The polymeric structure of compound **1** is attained by carboxylate bridges from citrates in an anionic dodecanuclear bismuth–oxo citrate cluster unit $[Bi_{12}O_8(cit^{4-})_8]^{12-}$. The dodecanuclear unit with a symmetry of inversion can be composed of two hexanuclear $[Bi_6O_4(cit^{4-})_4]^{6-}$ cluster units, each of which uses three carboxylate bridges from three crystallographically equivalent citrate ions to connect the units. A fourth citrate in the smaller cluster unit does not obey the 3 symmetry within one unit but does obey the symmetry in the crystal lattice by orientational disorder. The solution behavior of compound **1** has been investigated by using ^1H and ^{13}C NMR spectroscopy. In highly concentrated solutions, the Bi_{12} clusters are still aggregated to some extent. However, the order of aggregation decreases with a decrease in the concentration, resulting in mixtures of Bi_{12}, Bi_{24}, and $(Bi_{12})_n$ species. In diluted solutions, even the Bi_{12} unit (or the smaller unit Bi_6) undergoes hydrolytic decomposition to release free citrates. Furthermore, when an excess of free citrate is added to the diluted solution, the cluster species completely decomposes, resulting in the ligand exchange process, and all citrates become averaged on the NMR time scale. The solution behavior of compound **1** was compared with that of earlier reported bismuth citrate compounds, including commercially available colloidal bismuth subcitrate (CBS; a well-known ulcer-healing agent), leading to the conclusion 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

Many of the main-group 15 (As, Sb, Bi) compounds have pronounced antimicrobial activity and were once widely used in the treatment of syphilis and yaw before the era of antibiotics.[3] Some bismuth compounds, *e.g.* the carbonate, the nitrate, and the subsalicylate, are still used against a variety of gastrointestinal disorders because of their demulcent properties and low toxicity.[4] Among the modern bismuth-based registered pharmaceuticals, colloidal bismuth subcitrate (CBS), which is the active ingredient of De-Nol and Telen preparations available from Brocades Pharma (formerly from Gist-Brocades), is the most widely used in many countries to treat peptic ulcers. This compound, which is a complex bismuth salt of citric acid (H_4-cit), has been thoroughly investigated from the viewpoint of pharmacology in the last two decades.[5] In spite of significant amounts of pharmacological and clinical information on CBS, little chemistry of this important compound has been investigated.

Very recently, our group[1] and Herrmann *et al.*[6] independently reported some 3D structures of bismuth citrate complexes as the CBS model. The results of the solid structural chemistry and comparison of solution behavior of CBS samples and that of the model compounds has led us to the conclusion that CBS

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(3) For example: (a) Ehrlich, P. *Berl. Klin. Wochenschr.* **1910**, *47*, 1996. (b) Doak, G. O.; Freedman, C. D. In *Medical Chemistry*, 3rd ed.; Burger, A., Ed.; Wiley-Interscience: New York, 1970; Part I, Chapter 25. (c) Harvey, S. C. In *The Pharmaceutical Basis of Therapeutics*, 5th ed.; Goodman, L. S., Gilman, A., Eds.; Macmillan Publishing Co. Inc.: New York, 1975; Chapter 46. (d) Alonzo, G.; Bertazzi, N.; Consiglio, M. *Inorg. Chim. Acta*, **1984**, *85*, L35–L37.

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(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.

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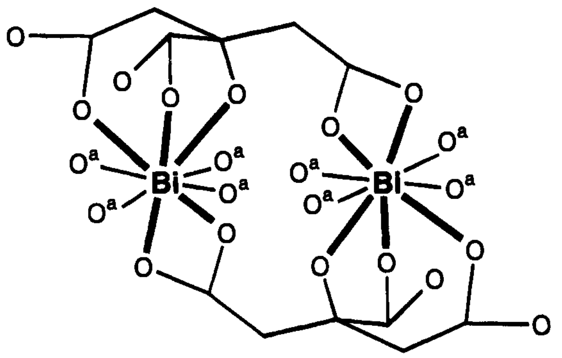

Figure 1. Common dinuclear subunit (cit^{4-})BiBi(cit^{4-}) found in six bismuth citrate compounds.[1c] O^a: oxygen atom from citrate or water molecule.

solid samples are metastable amorphous-like polymers aggregated by very stable dimeric subunits Bi(cit)(cit)Bi (see Figure 1).[1c]

According to the most recent *Merck Index*,[7] however, CBS is represented by the empirical formula $K_3(NH_4)_2[Bi_6O_3(OH)_5(Hcit)_4]$ (Hcit being the triply dehydrogenated trianionic form of citric acid). Since the predominance of several hexanuclear species, such as $[Bi_6O_4(OH)_4]^{6+}$, in acidic solutions is well established,[8] CBS was once thought to be a hexanuclear bismuth−oxo−hydroxo−citrato cluster.[9] Accordingly, our interest in Bi−citrate chemistry caused us to try isolating the compound which has a composition very close to that cited in the *Merck Index*, with the final aim of determining the crystal structure and comparing its solution behavior with that of CBS samples.

We have already succeeded in isolating such a species $(NH_4)_6Bi_6O_4(cit)_4(H_2O)_5$ (compound **1**). A preliminary structure determination of this compound[10] demonstrated that it indeed consists of unique hexanuclear bismuth−oxo−hydroxo−citrato clusters $[Bi_6O_4OH(cit)_3(H_2O)_3]^{3-}$, which are further connected by citrate bridges to form a polymeric aggregate. Although the compound should include four citrates per hexanuclear unit on the basis of the elemental analyses, the fourth citrate and some noncoordinating water molecules could not be detected by X-ray analysis, as a result of the poor quality of the crystal and disordering of the missing citrate. In the present paper, we report the crystal structure of **1** as more accurately redetermined from crystallization of a potassium-free batch and fully describe the disordering citrate which could not be detected in the preliminary work.[10] Furthermore, the solution behavior of **1** is investigated by using NMR spectroscopy and compared with that of commercially available CBS samples,[11] in order to investigate whether **1** is similar to the CBS that is listed in the *Merck Index*.[7]

Experimental Section

Materials. Citric acid hydrate ($H_4cit{\cdot}H_2O$, Kanto), bismuth citrate (BiHcit, Nakalai Tesque), ammonia solution (29%, Kanto), 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 nos. 85BC82, 87BC03, and 89A31)[11] were made available from Gist Brocades, Delft, The Netherlands.

Table 1. Crystallographic Data for $(NH_4)_{12}[Bi_{12}O_8(cit)_{12}](H_2O)_{10}$ (**1**)

formula	$C_{48}H_{100}N_{12}O_{74}Bi_{12}$
fw	4537.1
space group	$R\bar{3}$
$a = b$, Å	17.807(3)
c, Å	31.596(6)
V, Å^3	8684(4)
Z	3
D_{calcd}, g/cm^3	2.605
T, °C	25 ± 1
μ, cm^{-1}	18.29
radiation λ, Å[a]	0.710 69
transm factor	1.000−0.585
final residuals, %: R;[b] R_w[c]	5.5; 6.2

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

Preparation of $(NH_4)_6Bi_6O_4(cit)_4(H_2O)_5$ (1). To 20 mL of a suspended aqueous solution containing bismuth citrate BiHcit (10 g, 0.025 mol) was added a 29% ammonia solution (10 mL). The solution was filtered to remove minute amounts of insoluble material. The filtrate was placed in a desiccator with P_2O_5 to be slowly concentrated. After several days, colorless cubic crystals started to separate from the resultant viscous solution. The crystals were collected, washed with mixtures of water and methanol (3:1, 1:1, 1:3), methanol, and diethyl ether, and dried in air. Yield: 4.0 g. Anal. Calcd for $C_{24}H_{52}N_6O_{38}Bi_6$: C, 12.60; H, 2.31; N, 3.60; Bi, 54.0. Found: C, 12.61; H, 2.29; N, 3.68; Bi, 54.84.

As the crystallization proceeds, the citrate:Bi ratio in the solution increases, finally yielding needlelike crystals which have been fully characterized by X-ray analysis as a dimeric compound $(NH_4)_8[Bi_2(cit)_2(Hcit)_2(H_2O)_4](H_2O)_2$ (**2**), which has been previously described.[1a]

Instruments, Analyses, and Measurements. Carbon, hydrogen, and nitrogen analyses for compound **1** were carried out at the Service Center of Elemental Analysis, Kyusyu University, Kyusyu, Japan. The Bi content was determined by EDTA titration. Water and ammonia contents were analyzed at the Analytical Laboratories of Gist Brocades, Delft, The Netherlands. Infrared spectra were recorded on a JASCO FT/IR-300 spectrophotometer using KBr disks. All pH measurements were performed at 298 K with a Horiba F-12 pH meter, which was calibrated with Horiba pH standard solutions of pH 4.01 and 6.86. ^1H NMR spectra were recorded using a JEOL JNM-A400 spectrometer. D_2O was used as a solvent. Chemical shifts (δ) are reported in ppm relative to TMA (tetramethylammonium chloride). The pH dependence of the chemical shifts of the methylene protons of citrate was monitored by adding a trace amount of DCl and NaOD in D_2O (0.1 and 1M). The pH values reported as pH* have not been corrected for deuterium isotope effects. ^{13}C NMR spectra were measured using a JEOL GX-400 spectrometer and with a 10 mm tunable probe. Distilled water was used as a solvent. Chemical shifts are reported in ppm relative to DSS (sodium 4,4-dimethyl-4-silapentanesulfonate) which was dissolved in a 10% D_2O/H_2O mixture as an external standard.

X-ray Method and Structure Determination. The present crystalline compound **1** very easily loses lattice water in air to become a powder. Therefore, a single crystal suitable for X-ray crystallography was picked directly from the mother liquor, coated with hydrocarbon grease, and then sealed with the mother liquor in a capillary tube. Intensity data were collected at room temperature on a Nicolet P3 diffractometer using graphite-monochromatized Mo Kα radiation (λ = 0.710 69 Å) in the ω-scan mode. The crystal turned black during data collection while the three test reflections collected at an interval of 50 reflections lost 9.0% of their intensity towards the end of the data collection. The data were corrected for the crystal decomposition, Lorentz and polarization effects, and absorption from the empirical ϕ-scan data. Accurate unit cell parameters were obtained by a least-squares fit of 25 reflections with $15° \le 2\theta \le 20°$. A summary of the crystallographic data and refinement results is given in Table 1. Complete crystal data and experimental details are deposited as

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(9) Gist Brocades Internal Report, Delft, The Netherlands, 1984.

(10) Asato, E.; Katsura, K.; Mikuriya, M.; Fujii, T.; Reedijk, J. *Chem. Lett.* **1992**, 1967.

(11) 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 0.67 for citrate:Bi reported in the *Merck Index*.[7] Klooster, N. T. M., Private communication, 1992. Present address: Brocades-Pharma R&D, P.O. Box 5009, 2600 GA Delft, The Netherlands.

Table 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($Å^2 \times 10^3$) for Non-Hydrogen Atoms of **1**[a]

atom	*x*	*y*	*z*	U_{eq}
Bi1	3848(1)	8045(1)	2342(1)	35(1)
Bi2	4704(1)	7509(1)	3312(1)	42(1)
O1	4994(18)	9538(17)	2551(9)	52(7)
O2	6120(30)	10464(30)	2949(14)	124(15)
O3	5958(19)	7418(19)	3065(10)	64(9)
O4	7253(27)	7780(25)	2773(13)	113(14)
O5	4836(14)	8344(14)	1793(7)	27(5)
O6	6264(20)	9165(19)	1711(10)	70(9)
O7	4942(13)	7880(13)	2572(7)	22(5)
O8	3333	6667	3706(12)	41(11)
O9	4743(44)	5997(38)	4457(16)	136(26)
O10	4919(26)	6580(27)	3812(11)	55(12)
O11	3333	6667	2218(13)	30(9)
O12	3695(14)	7787(14)	3022(8)	34(6)
O13	4781(29)	7011(48)	4041(18)	41(19)
O14	4336(60)	6946(128)	4705(14)	234(92)
C1	5739(27)	9819(27)	2719(15)	54(12)
C2	6285(28)	9385(26)	2637(14)	54(12)
C3	5763(24)	8461(23)	2376(12)	40(9)
C4	6339(18)	8092(18)	2363(9)	14(6)
C5	6463(29)	7689(27)	2775(14)	57(13)
C6	5594(24)	8701(23)	1940(12)	36(9)
C7	3333	6667	4151(13)	50(19)
C8	4241(20)	6980(29)	4316(13)	83(16)
C9	4727(50)	6513(45)	4194(14)	83(24)
N1	9004(29)	2382(27)	23(15)	92(14)
N2	7661(48)	9209(50)	1290(25)	69(22)
N3	8766(41)	6605(41)	670(21)	77(20)
Ow1	6823(57)	1020(55)	1520(30)	237(38)
Ow2	8653(62)	9224(63)	533(30)	235(47)
Ow3	0	0	1157(63)	181(81)

[a] Equivalent isotropic *U* defined as one-third of the trace of the orthogonalized $\mathbf{U}_{ij}$ tensor.

supplementary material (Table S1). The structure was solved by Patterson and Fourier methods using the SHELXTL-Plus program[12] and refined using full-matrix least-squares procedures. Due to the limited number of reflections, only Bi atoms were anisotropically refined. The other atoms were isotropically refined. Hydrogen atoms were not determined. An occupancy factor of 0.667 was assigned to the C9, O9, and O10 atoms and 0.333 to the O13 and O14 atoms of the disordered citrate group. The ammonium nitrogen atoms N1, N2, and N3 and the water oxygen atoms Ow2 and Ow3 were also found to be disordered. Occupancy factors of 0.667 for N1, N2, and N3 and 0.5 for Ow2 and Ow3 were used. Maximum and minimum heights in the final difference Fourier synthesis were 1.67 and −1.42 e $Å^{-3}$ near the Bi atoms and with the largest Δ/σ of 0.070. Final coordinates and U_{eq} values are listed in Table 2.

Results and Discussion

Structure of $(NH_4)_{12}[Bi_{12}O_8(cit)_8](H_2O)_{10}$ (1). Slow evaporation of an aqueous solution containing bismuth citrate (BiHcit) and ammonia yields colorless cubic crystals of **1** as a first crystalline product. Further evaporation of the mother liquor gives colorless needles, already structurally characterized to be the discrete bismuth citrate dimer $(NH_4)_8[Bi_2(cit)_2(Hcit)_2(H_2O)_4](H_2O)_2$ (**2**).[1a]

According to the most recent *Merck Index*,[7] CBS is represented as the empirical formula $K_3(NH_4)_2[Bi_6O_3(OH)_5(Hcit)_4]$. The analytical results (C, H, N, Bi contents) for compound **1** showed that its composition is in fact very close to CBS, as its hexaammonium salt, *i.e.* with a slight charge difference ($[Bi_6O_4(OH)_4(Hcit)_4]^{6-}$ for **1** against $[Bi_6O_3(OH)_5(Hcit)_4]^{5-}$ for CBS), which tempted us to conclude that **1** is in fact a hexanuclear oxo−hydroxo−citrato ($Hcit^{3-}$) bismuth cluster $(NH_4)_6[Bi_6O_4(OH)_4(Hcit)_4](H_2O)_2$. However, the X-ray 3D structure analysis of **1** shows that it is rather a polymeric compound aggregated by dodecanuclear oxo−citrato (cit^{4-}) bismuth cluster units $[Bi_{12}O_8(cit)_8]^{12-}$. The anionic cluster unit with the atom-numbering scheme and the Bi_{12}-cluster core are shown in Figures 2 and 3, respectively. Selected bond distances and angles are given in Table 3.

Two crystallographically inequivalent bismuth atoms (Bi1 and Bi2), a citrate (citrate 1), and a μ_3-oxo (O12) from the asymmetric unit are located around a crystallographic 3-fold

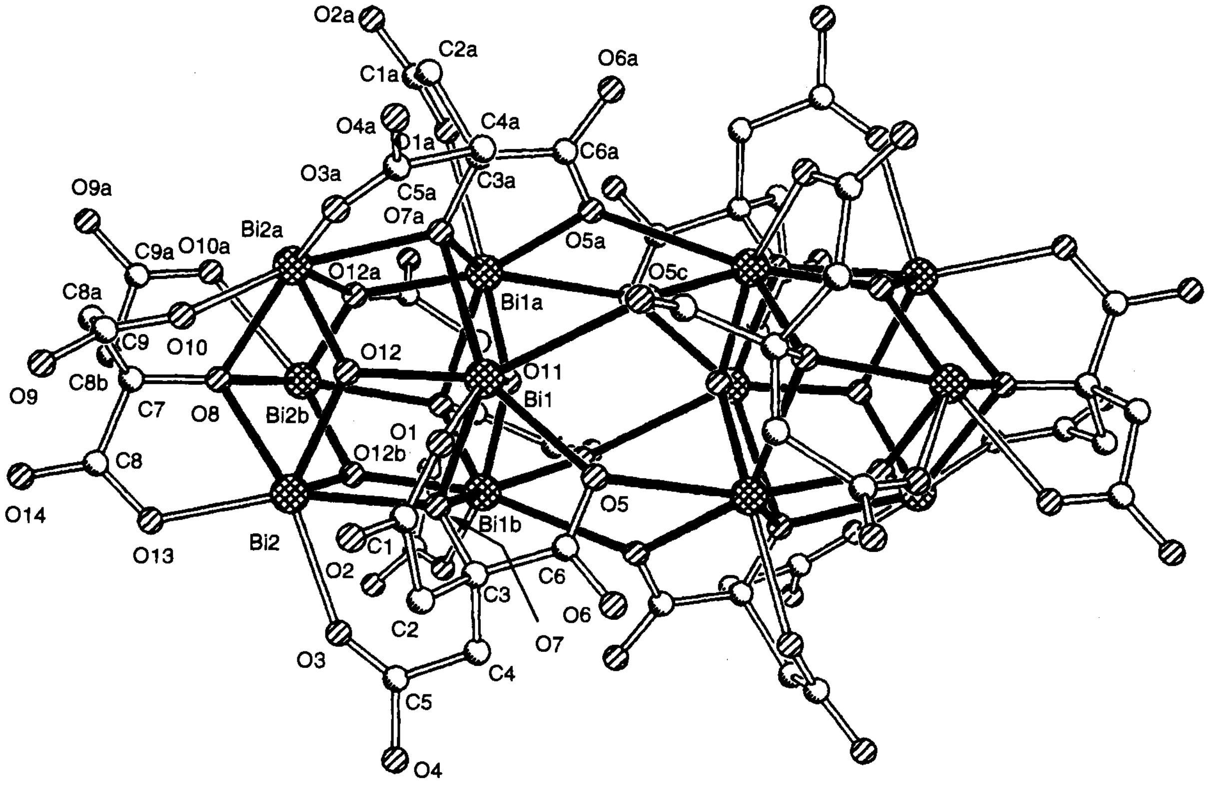

Figure 2. Perspective view and atom-labeling scheme of the dodecanuclear oxo−citrato−bismuth cluster unit $[Bi_{12}O_8(cit)_8]^{12-}$ in compound **1**.

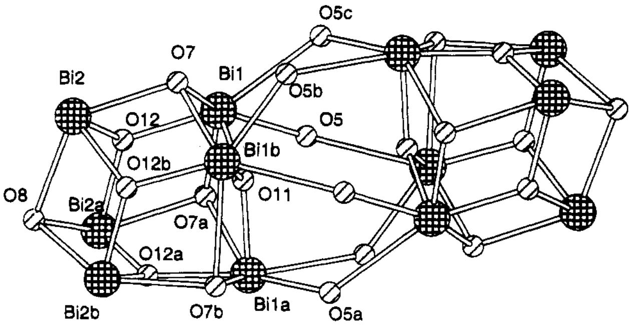

Figure 3. Structure of the $Bi_{12}O_{22}$ cluster core in compound **1**.

Table 3. Important Interatomic Distances and Angles for Non-Hydrogen Atoms of **1**[a]

	Distances (Å)		
Bi1−Bi2	3.755(3)	Bi2−O3	2.45(4)
Bi1−O1	2.50(2)	Bi2−O7	2.41(2)
Bi1−O5	2.33(2)	Bi2−O8	2.47(2)
Bi1−O7	2.23(3)	Bi2−O10	2.45(5)
Bi1−O11	2.183(8)	Bi2−O12	2.28(3)
Bi1−O12	2.19(2)	Bi2−O13	2.50(6)
Bi1−Bi1a	3.721(2)	Bi2−Bi1b	3.725(2)
Bi1−Bi1b	3.721(2)	Bi2−Bi2a	3.693(3)
Bi1−Bi2a	3.725(2)	Bi2−Bi2b	3.693(3)
Bi1−O5c	2.87(2)	Bi2−O12b	2.07(2)
Bi1−O7a	2.77(2)		
	Angles (deg)		
O1−Bi1−O5	80.3(8)	O3−Bi2−O10	72.9(13)
O1−Bi1−O7	75.6(10)	O7−Bi2−O10	138.2(13)
O5−Bi1−O7	70.4(8)	O8−Bi2−O10	72.9(11)
O5−Bi1−O11	88.2(10)	O3−Bi2−O12	136.8(10)
O7−Bi1−O11	79.3(6)	O7−Bi2−O12	66.4(9)
O1−Bi1−O12	85.0(8)	O8−Bi2−O12	71.8(7)
O7−Bi1−O12	71.1(9)	O10−Bi2−O12	144.2(11)
O11−Bi1−O12	90.0(12)	O3−Bi2−O13	93.3(18)
O1−Bi1−O5c	107.7(8)	O7−Bi2−O13	163.7(19)
O5−Bi1−O5c	68.3(3)	O8−Bi2−O13	62.2(13)
O7−Bi1−O5c	137.1(6)	O12−Bi2−O13	129.6(16)
O11−Bi1−O5c	88.5(10)	O3−Bi2−O12b	79.4(8)
O11−Bi1−O7a	68.1(7)	O7−Bi2−O12b	77.5(8)
O12−Bi1−O7a	68.1(7)	O8−Bi2−O12b	75.3(8)
O5c−Bi1−O7a	84.2(6)	O10−Bi2−O12b	76.5(10)
O3−Bi2−O7	70.5(10)	O12−Bi2−O12b	89.0(8)
O3−Bi2−O8	141.2(7)	O13−Bi2−O12b	97.8(18)
O7−Bi2−O8	129.8(9)		

[a] Numbers in parentheses are estimated standard deviations in the least significant digits. Atomic equivalent positions are as follows: (a) $-y + 1, x - y + 1, z$; (b) $y - {}^1/_3, -x + y + {}^1/_3, -z + {}^1/_3$; (c) $-x + y, -x + 1, z$.

axis on an imaginary line made by another apical μ_3-oxo (O11) and the μ_3-hydroxo atcm (O8) from another citrate (citrate 2) to form a hexanuclear Bi_6-cluster unit. For a better understanding of the structure, a schematic comparison of the hexanuclear Bi unit and that of an earlier reported hexanuclear cationic bismuth complex $[Bi_6O_4(OH)_4](ClO_4)_6{\cdot}7H_2O$[13] is shown in Figure 4. In compound **1**, each of the three equivalent bismuth atoms (Bi1, Bi1a, Bi1b) close to the apical μ_3-oxo O11 (Bi1−O11 = 2.183(8) Å) is coordinated by the other μ_3-oxo O12 (Bi1−O12 = 2.19(2) Å), the central carboxylate oxygen O5 from citrate 1 (Bi1−O5 = 2.33(2) Å), the terminal carboxylate oxygen O1 from citrate 1 (Bi1−O1 = 2.50(2) Å), and the two crystallographically equivalent alcoholic oxygen atoms μ_3-O7 and μ_3-O7a from citrate 1 and citrate 1a, respectively (Bi1−O7 = 2.23(3) Å, Bi1−O7a = 2.77(2) Å). Each of the other three equivalent bismuth atoms (Bi2, Bi2a, Bi2b) is apically coordinated by the other alcoholic oxygen atom μ_3-O8 from citrate 2 (Bi2−O8 = 2.47(2) Å), the μ_3-O7 from citrate 1 (Bi2−O7 = 2.41(2) Å), the two equivalent μ_3-oxo O12 and O12b (Bi2−O12 = 2.28(3) Å, Bi2−O12b = 2.07(2) Å), and the terminal carboxylate oxygen O3 from citrate 1 (Bi2−O3 = 2.45(4) Å). Citrate 2 resides on the 3-fold axis, coordinates to the three equivalent Bi atoms (Bi2, Bi2a, Bi2b), and is orientationally disordered; *i.e.* it does not obey the $\bar{3}$ symmetry in the cluster unit but obeys it in the crystal lattice (Bi2−O13 = 2.50(6) Å, Bi2−O10 = 2.45(5) Å). In comparison with the structure of $[Bi_6O_4(OH)_4]^{6+}$,[13] four hydroxides in the cationic cluster are substituted by the alcoholic oxygen of each citrate in $[Bi_6O_4(cit)_4]^{6-}$. However, the two cluster units have essentially the same Bi_6O_8 core. The $[Bi_6O_4(cit)_4]^{6-}$ unit is further paired to itself by an inversion center using carboxylate bridges (O5c from the neighboring unit; Bi1−O5c = 2.87(2) Å) to yield the discrete $[Bi_{12}O_8(cit)_8]^{12-}$ cluster anion (see Figures 2 and 3). In the discrete cluster anion, two crystallographically independent Bi atoms Bi1 and Bi2 have a CN (coordination number) of 7 and 6, respectively (O11, O12, O5, O5c, O1, O7, O7a to Bi1 and O8, O7, O12, O12b, O3, O13 (or disordered O10, O10a) to Bi2). However, when the Bi−O van der Waals contact (3.67 Å)[14] is considered, another long Bi−O contact is present, *i.e.* Bi2−O4f (O4 at 1.3333 − *x*, 1.6667 − *y*, 0.6667 − *z*) = 3.07(5) Å. Thus, if this interaction is considered as a coordination bond, the CN of Bi2 becomes 7, and the compound could even be regarded as a polymeric aggregation of $[Bi_{12}O_8(cit)_8]^{12-}$ anionic clusters. The structure is stabilized by an extensive hydrogen bond network involving $[Bi_{12}O_8(cit)_8]^{12-}$ complex anions, ammonium cations, and water molecules.

Solution Behavior of Compound 1. This compound shows anomalous behavior in its solubility. Although the compound is poorly soluble in water at low concentrations (*e.g.* 6.00 mg/mL, corresponding to 1.25 mM for a Bi_{12} cluster unit), it is very soluble at higher concentrations (*e.g.* 118 mg/mL, corresponding to 25 mM). Once the compound is dissolved, the concentrated solution does not yield any precipitation even after dilution. Since rapid hydrolysis of Bi(III) compounds is quite well-known[8] and the white precipitate isolated from the suspended solution containing **1** (6.00 mg/mL) gives a different infrared spectrum from that of compound **1**, it seems likely that very quick hydrolytic decomposition occurs in the low-concentration solution. In spite of our efforts, the isolated precipitate could not be further characterized.

Since the highly concentrated solutions do not give any precipitate even after dilution, ^1H and ^{13}C NMR spectroscopy was used to observe the dissociation process of the polymeric compound with a decrease in concentration. For the dissociation process, the Bi2−O4f bonds, which are used to connect the Bi_{12} cluster units, are anticipated to be first broken, because the Bi−O interaction is the weakest (the longest Bi−O contact 3.07(5) Å). If this destruction is complete to yield the discrete Bi_{12} anionic cluster $[Bi_{12}O_8(cit)_8]^{12-}$, its ^{13}C NMR spectrum should show sharp signals assignable to each carbon from the coordinating citrates. However, as shown in Figure 5a, very broad peaks as well as many sharp ones from each carbon atom appear in the spectrum (125 mM/$[Bi_{12}]$ in water). The overlap of broad peaks with sharp signals indicates that the dissociation indeed proceeds, while highly aggregated species are still also present in the solution. The spectrum is dependent of the concentration used; *i.e.*, the number of sharp signals increases with decreasing concentration. Furthermore, new peaks whose chemical shifts

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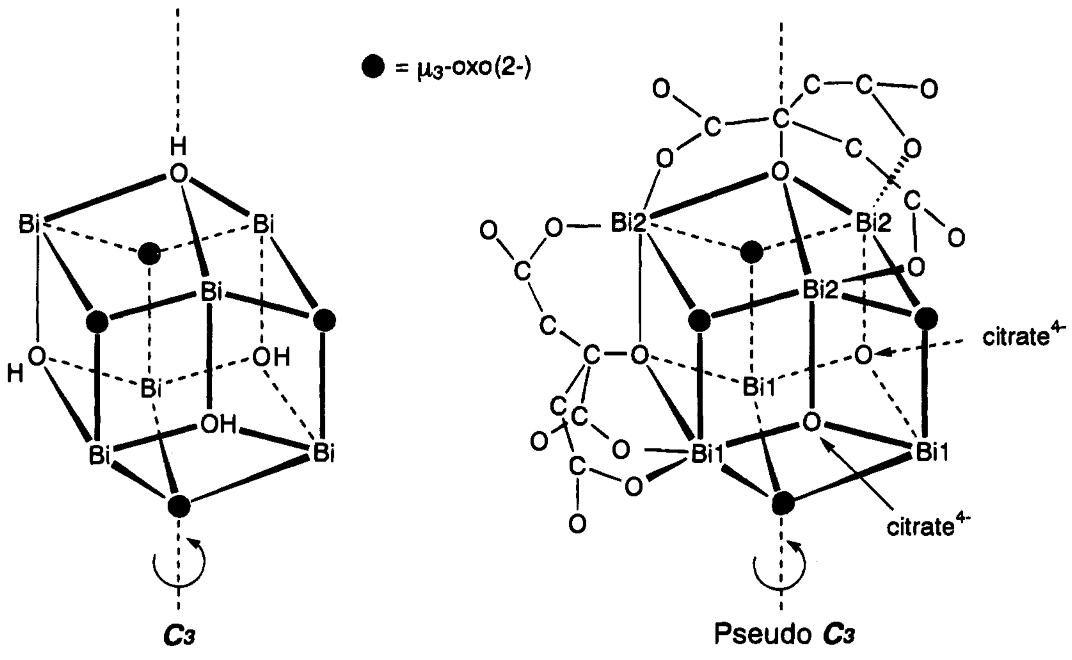
(13) Sundvall, B. *Inorg. Chem.* **1983**, *22*, 1906.

(14) 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.



Two other citrates are omitted for clarity

$[Bi_6O_4(OH)_4]^{6+}$

$[Bi_6O_4(cit^{4-})_4]^{6-}$

Figure 4. Comparison of (part of) the hexanuclear units in well-known bismuth salts (nitrate, perchlorate) and compound **1**.

are practically the same as those of free citrate measured at the same pH appear, and their relative peak intensity also increases with a decrease in the concentration. These results suggest the occurrence of two dissociation processes; *i.e.*, one is the simple dissociation of the polymeric compound to the mixture of anionic Bi_{12}, Bi_{24}, and $(Bi_{12})_n$ ($n > 3$) clusters, and the other is decomposition of the clusters (probably from the Bi_{12} or Bi_6 clusters) to release coordinated citrates. The appearance of not only many sharp peaks but also very broad ones in the spectrum ($[Bi_{12}]$ = 25 mM) shown in Figure 5b clearly indicates the coexistence of highly and poorly aggregated species even in the diluted solution.

The decomposition process to release citrates can be more easily followed with ^1H NMR spectroscopy. The two spectra redrawn in Figure 6 (parts a and b) evidently show that the process becomes dominant as the concentration decreases. Since all citrates in **1** are coordinated to Bi(III) as the tetraionized form (cit^{4-}) in the solid state, released citrates in solutions should function as a proton acceptor to form triionized $Hcit^{3-}$, because of the large pK_a (>11) for the hydroxyl group,[15] finally resulting in a pH increase. In fact, a rapid pH increase was confirmed for the diluted solutions, *e.g.* from pH* 6.96 for 25 mM/$[Bi_{12}]$ to pH* 7.17 for 2.5 mM/$[Bi_{12}]$. In addition, the release of rigidly coordinated citrates in diluted solution can be accelerated by adding free citrate. When a solution of free citrate whose pH* is adjusted to the same pH* (=6.96) as that of the solution of compound **1** is added, the pH* value of the resultant solution rapidly increases and its ^1H NMR spectrum becomes very simple. As an example, the spectrum after addition of free citrate (cit:Bi = 2:1, pH* 7.31 in the resultant solution) is given in Figure 6c. Taking into account the fact that the chemical shifts of the main peaks as an AB pattern are the same as those of free citrate measured at the same pH* (=7.31), most citrates can be regarded as being released (noncoordinated), even though trace amounts of citrate might be still rigidly coordinated. The added citrates may directly attack and coordinate to bismuth or displace the oxo ligands in the cluster species, probably resulting in the destruction of the cluster structure(s). It should be also emphasized that the extra peaks with a very small intensity which appeared after adding free citrate completely vanish at higher pH* (>8.00) and that at lower pH* (<6.50) not only peak disappearance but also broadening of the main peaks as an AB pattern are observed. These results clearly indicate that the cluster units are stable only at pH* 6−8. Also, under weak acidic conditions, all citrates are rapidly exchanged on Bi and averaged on the NMR time scale, just as previously reported[1a,c] bismuth citrate compounds whose citrate:Bi ratio is larger than 1.0 (*vide infra*).

Comparison of Compound 1 with Other Bismuth Citrate Compounds, Including CBS. Since we reported the first example of a detailed chemical investigation on model compounds for CBS in 1991,[1a] thus far six bismuth citrate compounds, $(NH_4)_8[Bi_2(cit)_2(Hcit)_2(H_2O)_4](H_2O)_2$ (**2**),[1a] $K_{4.75}(NH_4)_{0.25}[Bi_2(cit)_2(Hcit)](H_2O)_{13}$ (**3**),[1a] $KBi(cit)(H_2O)_3$ (**4**),[6a] $(NH_4)Bi(cit)(H_2O)_2$ (**5**),[6b] $K(NH_4)Bi_2(cit)_2(H_2O)_4$ (**6**),[1c] and $K(NH_4)Bi_2(cit)_2(H_2O)_6$ (**7**),[1c] have been structurally characterized by X-ray analysis. The most interesting finding from the solid-structural investigation was that a common subunit, (cit)BiBi(cit), shown in Figure 1 was found in the six compounds. In earlier work,[1] including ligand (citrate) titration experiments, we proposed that a citrate coordination behavior in solution is determined by the citrate:bismuth ratio; *i.e.*, when citrate:Bi ≥ 1.0, the ligands rapidly exchange on the metal to be averaged on the NMR time scale under acidic conditions, but hardly coordinate to the metal in alkaline solutions. In fact, the previously reported compounds **2**−**7**, which have a citrate:Bi ratio ≥ 1.0, behave quite similarly in solutions, *i.e.* rapid ligand exchange under acidic conditions and noncoordination of the ligand in alkaline solutions.[1c] Commercially available CBS samples also behave in the same manner as compounds **2**−**7**.[1c]

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[15] Martell, A. E., Ed. *Spec. Publ.—Chem. Soc.* **1964**, *No. 17*, 477−481.

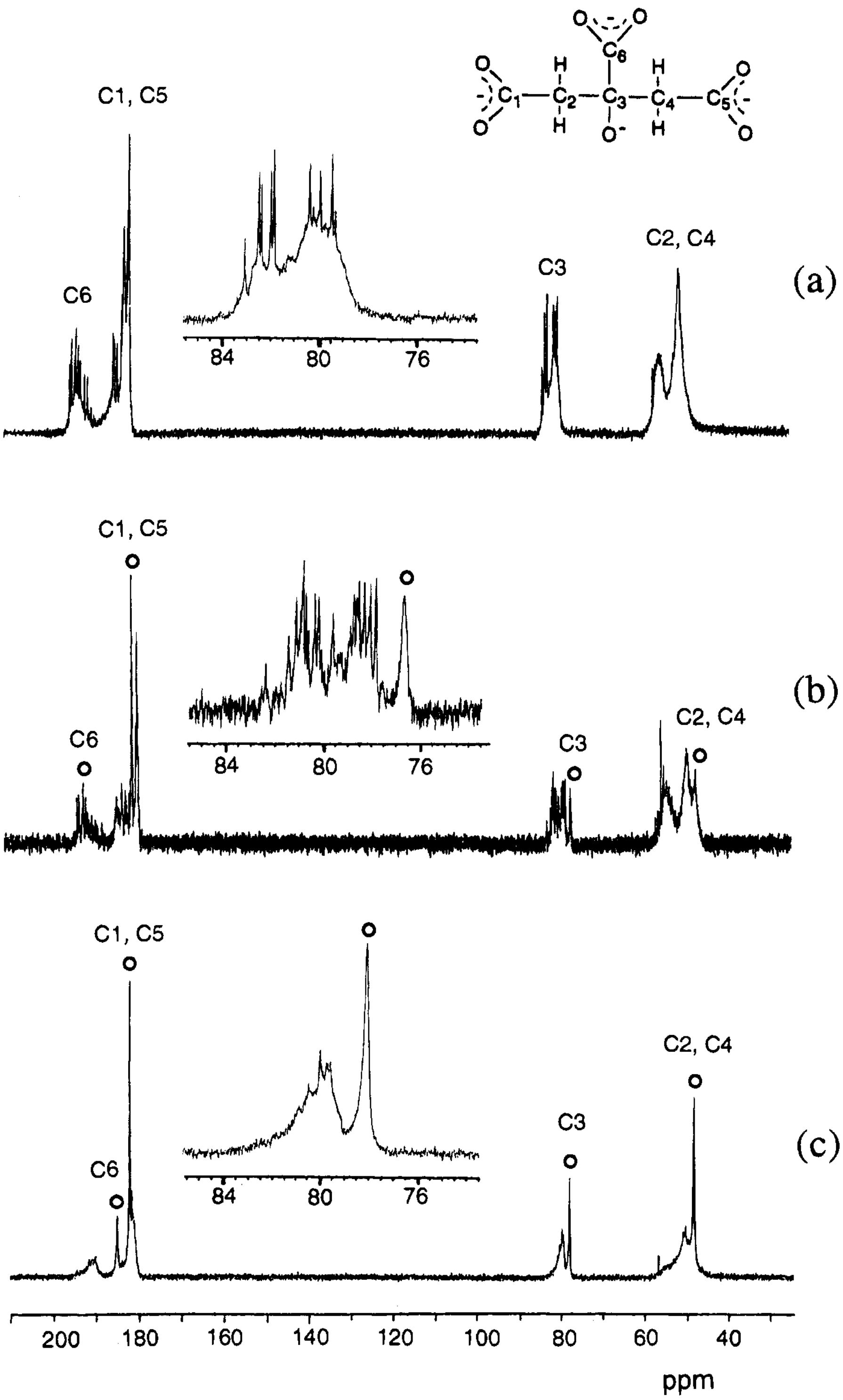

Figure 5. ^{13}C NMR spectra of compound **1** in H_2O: (a) 125 mM/[Bi_{12}] unit at pH 6.96; (b) 25 mM/[Bi_{12}] unit at pH 7.10; (c) 125 mM/[Bi_{12}] unit at pH 9.00. ○: released (noncoordinating) citrate.

It should be noted that the spectrum shown in Figure 5a drastically changes after adding base to the same solution sample. As Figure 5c shows, the spectrum measured at pH 9.00 is significantly different from that shown in Figure 5a and the same as that of a commercially available CBS sample (batch no. 85BC82) measured at the same pH.[1c] This clearly indicates that in basic solutions (>pH 9) compound **1** cannot maintain its feature as anionic cluster(s) and the citrates behave quite similarly to citrates in CBS.

Experimentally estimated cit:Bi ratios in the CBS samples are 1.25–1.30,[11] different from that calculated from $K_3(NH_4)_2[Bi_6O_3(OH)_5(Hcit)_4]$ expressed in the most recent *Merck Index*.[7] As expected from the chemical composition, *i.e.* cit/Bi ≥ 1.0, and the resemblance in NMR behavior between CBS samples and compounds with the citrate:Bi ratio ≥ 1.0 (**2**–**7**), we have already concluded in a previous paper[1c] that solid CBS can be regarded as an aggregated form of the dinuclear [(cit)BiBi(cit)] building blocks. Compared with these compounds, including the CBS samples, **1** is quite unique in its characteristics such that the bismuth–oxo–citrato cluster $[Bi_6O_4(cit)_4]^{6-}$ functions as the smallest building block in the polymeric architecture and that parts of the citrates rigidly coordinate to the metal in solutions even at low concentrations. The rigidity of the citrate coordination can be explained by the presence of

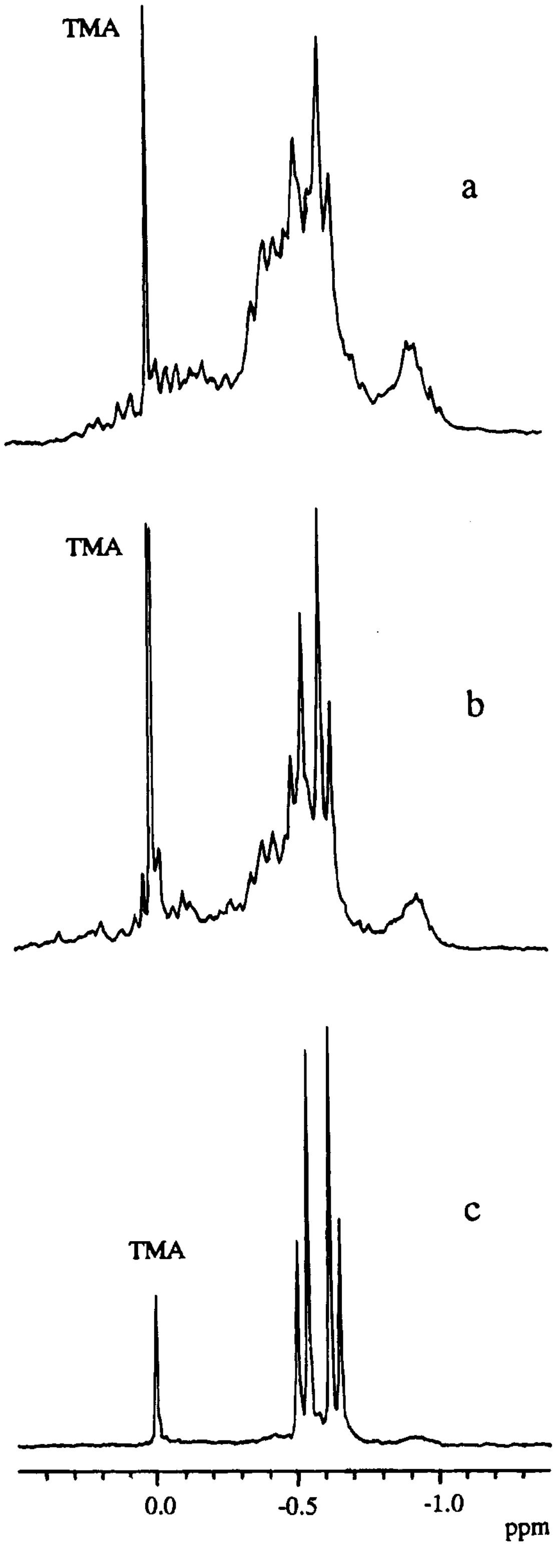

Figure 6. ^{1}H NMR spectra of compound **1** in D_2O: (a) 25 mM/[Bi_{12}] unit; (b) 1.25 mM/[Bi_{12}] unit. Spectrum c is for compound **1** + free citrate (citrate:Bi = 2:1); 1.25 mM/[Bi_{12}] unit.

a μ_3-hydroxo group (alcoholic oxygen of the central carbon in citrate, O7 for the three crystallographically equivalent citrates (citrate 1), and O8 for the apically coordinating disordered citrate (citrate 2)). In compounds **2**–**7**, the hydroxy oxygen always coordinates to the metal in the monodentate fashion, while not being used as the bridging atom. Furthermore, all citrates included in [Bi(cit)(cit)Bi], commonly observed subunits in **2**–**7** (see Figure 1), use didentate carboxylate bridges to connect two Bi atoms in the form of a four-membered chelate, which is generally labile in aqueous solutions. On the other hand, the hydroxy oxygen atoms O7 and O8 in compound **1** strongly coordinate to three Bi(III) atoms (average Bi–O distance: 2.47 Å for μ_3-O7 and μ_3-O8). Thus, since the hydroxo oxygen is rigidly held by three Bi(III) atoms, the rapid ligand exchange behavior observed in **2**–**7** does not seem to easily occur.

Although the charge of −3 has been given to the citrate (as $Hcit^{3-}$) included in CBS in the formula $K_3(NH_4)_2[Bi_6O_3(OH)_5(Hcit)_4]$, the tetraionized form cit^{4-} is more common for citrate coordination to bismuth as observed in **1** and all other structurally characterized bismuth citrate compounds (**2**–**7**). Consequently, the formula seems to be better rewritten as $K_3(NH_4)_2[Bi_6O_3(OH)(cit)_4](H_2O)_4$. According to the *Merck Index* again, its aqueous solution is neutral to litmus,[7] similar to compound **1**. Therefore, we tentatively conclude that if the hexanuclear species is really CBS, an active ingredient of De-Nol and Telen preparations, the original formula is not accurate and should be better represented as $K_{6-x}(NH_4)_x[Bi_6O_4(cit)_4](H_2O)_y$, which can be regarded as the properly mixed cationic derivative of compound **1**. As previously mentioned, however, the experimentally observed citrate:Bi ratio for commercially available CBS samples is 1.25–1.30, *i.e.* significantly different from 0.67 calculated from the formula $K_{6-x}(NH_4)_x[Bi_6O_4(cit)_4](H_2O)_y$. In order to explain the difference in the chemical compositions, we now assume that CBS samples are a physical mixture of **1** with some extra $(NH_4)_pK_q(Hcit)$ ($p + q = 3$). In fact, the NMR behaviors of the CBS samples are the same as those of the physical mixture of **1** with K_3Hcit, whose citrate:Bi ratio is adjusted to be 1.25. However, any IR spectra of mixtures of **1** with K_3Hcit (citrate:Bi ratio = 1.20–1.35) could not be satisfactorily fitted to that of solid CBS samples, therefore not supporting the above mentioned assumption. ^{13}C NMR and IR spectra of a CBS sample (batch no. 85BC82) and those of a mixture of **1** with K_3Hcit (citrate:Bi ratio = 1.25) are compared in Figure S2 and Figure S3, respectively, as supplementary material.

In addition to the difference in chemical composition between compound **1** and commercially available CBS samples, the solution behavior and the thermal properties[1b] of compound **1** (as solid) are quite different from those of the CBS samples, while all other structurally characterized bismuth citrate compounds (**2**–**7**) and CBS samples behave quite similarly in solutions as already mentioned. From these results, we finally conclude that CBS is neither compound **1** as such nor a coprecipitated product of **1** with ammonium potassium citrate $(NH_4)_pK_q(Hcit)$. The CBS solid should best be regarded as a polymeric amorphous material aggregated by very stable $[Bi(cit)(cit)Bi]^{2-}$ building blocks through citrato bridging and hydrogen bond bridging, as suggested in our previous paper.[1c]

Concluding Remarks

The crystal structure of compound **1** has been reinvestigated and found to be a polymerically aggregated form of $[Bi_{12}O_8(cit)_8]^{12-}$ as its ammonium salt. The dodecanuclear unit is further divided into two hexanuclear units $[Bi_6O_4(cit)_4]^{6-}$, each of which uses three carboxylate bridges coming from three crystallographically equivalent citrate ions to cennect the units. One citrate ion per hexanuclear unit, originally not detected by X-ray analysis,[10] could be successfully located in the form of tetraionized cit^{4-} at the apical position of the unit as a disordered coordination.

The solution behavior of compound **1** was studied by using NMR (^{1}H and ^{13}C) spectroscopy and compared with that of CBS and other bismuth citrate compounds already obtained. In solution, **1** dissociates to give a mixture of several anionic clusters with varying nuclearity, likely as $Bi_{12} + Bi_{24} + (Bi_{12})_n$ ($n \geq 3$). Although citrates are released from clusters with decreasing concentration, most citrates remain rigidly coordinated to bismuth. The fact that compound **1** has a chemical composition very close to that of the CBS solid cited in the most recent *Merck Index*[7] tempted us to conclude that compound **1** and CBS are the same. However, the citrate coordination behavior of **1** in solution is quite different from that of commercially available CBS samples. Furthermore, the experimentally estimated citrate:Bi ratio in the commercial samples is different from that in compound **1**, *i.e.* 1.25−1.30 for CBS versus 0.67 for **1**. When free citrate is added to solutions containing **1** to form a citrate:Bi ratio ≥1.0, all citrates are released from the clusters and take part in a rapid ligand exchange process, just as seen in solutions of CBS samples. From these results, it is evident that CBS is not compound **1** as such. The CBS solid is now prepared by a careful spray-drying process.[16] Therefore, it might be possible that a small amount of compound **1** is included in CBS during its production process. Even if this occurs, at least in a solution of CBS, compound **1** cannot maintain its features as anionic cluster(s) because of the citrate:Bi ratio (1.25−1.30) of CBS.

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Supplementary Material Available: Figures showing the unit cell packing diagram of **1** (Figure S1) and ^{13}C NMR (Figure S2) and IR spectral comparisons (Figure S3) of a CBS sample (batch no. 85BC82) with a physical mixture ($\mathbf{1} + K_3Hcit$) and tables of crystallographic data (Table S1), complete bond lengths and bond angles (Table S2), and anisotropic thermal parameters for **1** (Table S3) (7 pages). Ordering information is given on any current masthead page.

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[16] Slikkerveer, A.; de Wolff, F. A. *Med. Toxicol. Adverse Drug Exp.* **1989**, *4*, 303.