DALTON

Solid-state carbon-13 nuclear magnetic resonance investigations of bismuth citrate complexes and crystal structure of $Na_2[Bi_2(cit)_2]\cdot 7H_2O$

Patrick J. Barrie,[a] Milos I. Djuran,[b] Muhammed A. Mazid,[c] Mary McPartlin,*[,d] Peter J. Sadler,*[,b] Ian J. Scowen[d] and Hongzhe Sun[b]

[a] *Christopher Ingold Laboratories, University College London, 20 Gordon Street, London WC1H 0AJ, UK*

[b] *Department of Chemistry, Birkbeck College, University of London, Gordon House and Christopher Ingold Laboratories, 29 Gordon Square, London WC1H 0PP, UK*

[c] *School of Chemistry and Applied Chemistry, University of Wales College of Cardiff, Cardiff CF1 3TB, UK*

[d] *School of Applied Chemistry, University of North London, Holloway Road, London N7 8DB, UK*

The complex $Na_2[Bi_2(cit)_2]\cdot 7H_2O$ (H_4cit = 3-carboxy-3-hydroxypentane-1,5-dioic acid) crystallized during reactions of the antiulcer drug ranitidine bismuth citrate with the tripeptide glutathione (γ-L-Glu-L-Cys-Gly) at low pH. X-Ray analysis showed one $[Bi(cit)]^-$ fragment per asymmetric unit with Bi^{3+} chelated to a terminal carboxylate group; citrate also binds, in tridentate mode, to the bismuth of an equivalent $[Bi(cit)]^-$ unit (related to the first by a C_2 axis) *via* one oxygen donor from each of the remaining two carboxylate groups and the alkoxy group. Both ends of the resultant dimeric anion $\{Bi(\mu\text{-}cit)_2Bi\}^{2-}$ bind to adjacent dimers, related by *n*-glide plane symmetry, *via* double carboxylate bridges, to form a continuous polymeric anionic chain $[\{Bi(\mu\text{-}cit)_2Bi\}_n]^{2n-}$ running throughout the crystal. In this way each bismuth atom achieves six-co-ordination [Bi–O 2.210(10)–2.505(10) Å] with a *nido*-pentagonal-bipyramidal geometry, the vacant axial site providing evidence for a stereochemically active lone pair and the second axial site being occupied by the alkoxy donor. The parallel polyanionic chains are linked by anion–cation interactions [Na · · · O (cit) 2.37–2.50 Å] and by bonds of largely ionic character (Bi · · · O 3.003–3.095 Å) to give the overall three-dimensional solid-state structure which incorporates seven water molecules per dianionic subunit. The solid-state cross-polarization magic angle spinning ^{13}C NMR spectrum of this complex is assigned with the aid of dipolar-dephasing and inversion-recovery cross-polarization experiments, and compared to those of ranitidine bismuth citrate and bismuth citrate Bi(Hcit). The IR and solid-state ^{13}C NMR data suggested that the alkoxy group is protonated in Bi(Hcit) but deprotonated in ranitidine bismuth citrate, and that the latter contains similar dimeric units to $Na_2[Bi_2(cit)_2]\cdot 7H_2O$. The general modes of aggregation of dimeric $[\{Bi(\mu\text{-}cit)_2Bi\}_n]^{2n-}$ units and the relevance to antiulcer activity are discussed.

Bismuth has long been associated with pharmacy and medicine. Various bismuth salts have been used for treating ulcer disorders since 1786, including bismuth carbonate, nitrate and subsalicylate. Some of these are still used today for treating a variety of gastrointestinal disorders.[1] In the past decade, colloidal bismuth subcitrate, an active ingredient of the drug De-Nol,† has been widely used to treat peptic ulcers in many countries; it is an ammonium potassium bismuth citrate complex, with the empirical formula $K_3[NH_4]_2[Bi_6O_3(OH)_5(Hcit)_4]$ (H_4cit = 3-carboxy-3-hydroxypentane-1,5-dioic acid).[2]

Apart from bismuth compounds, some organic histamine (imidazole-4-ethanamine) H_2-receptor antagonists such as cimetidine‡ and ranitidine§ are also effective for the treatment of peptic ulcers. Recently a new adduct of ranitidine with bismuth citrate, **1** (ranitidine bismuth citrate), has been granted a product licence in the UK, and we have shown that the chemical properties of this complex in aqueous solution are different from those of the previously reported ammonium potassium bismuth citrate.[3]

† Registered trade-mark of Gist-Brocades.

‡ *N*-Cyano-*N'*-methyl-*N''*-{2-[(5-methyl-1*H*-imidazol-4-yl)methyl]-sulfanylethyl}guanidine.

§ [*N*,*N*-Dimethyl-5-(3-nitromethylene-7-thia-2,4-diazaoctyl)furan-2-methanamine].

The crystal structures of several bismuth citrate complexes have recently been reported.[4–9] Most of them contain stable dinuclear subunits $[(cit)BiBi(cit)]^{2-}$ with additional O^{2-}, OH^- and H_2O ligands, and these subunits aggregate further *via* citrate bridging and a network of hydrogen bonding involving citrate, ammonium (potassium) and water. Most bismuth citrate complexes have previously been crystallized at high pH > 7, and it is of interest to investigate the structures of such compounds at low pH since this is more relevant to the conditions found in the stomach where bismuth drugs are active.

In this study we have determined the crystal structure of $Na_2[Bi_2(cit)_2]\cdot 7H_2O$ crystallized at pH 4, and have compared it with those of ranitidine bismuth citrate and Bi(Hcit) **2** using cross-polarization magic angle spinning (CP MAS) ^{13}C NMR spectroscopy.

Experimental

Materials

Bismuth citrate Bi(Hcit) and ranitidine bismuth citrate **1**, an amorphous solid consisting of ranitidine, bismuth and citrate in an approximately equimolar ratio, were supplied by Glaxo Wellcome plc. Glutathione (γ-glutamylcysteinylglycine) and *N*-acetyl-L-cysteine were obtained from Sigma.

pH Measurements

These were made using a Corning 145 pH meter equipped with an Aldrich micro combination electrode calibrated with Aldrich standard buffer solutions at pH 4, 7 and 10. The pH-meter readings for D_2O solutions are recorded as pH* values, *i.e.* uncorrected for the effect of deuterium on the glass electrode.

Reaction of ranitidine bismuth citrate (1) with glutathione

A mixture of a D_2O solution of compound **1** (final concentration 50 mmol dm^{-3}) and glutathione (2–2.5 mol equivalents) became yellow within a few minutes at ambient temperature. After raising the pH* from *ca.* 2 to 4.3 with NaOD (0.5 mol dm^{-3}) the solution was deoxygenated by bubbling with argon for *ca.* 10 min to minimize the oxidation of glutathione. Colourless needle-shaped crystals of **3** appeared after standing at ambient temperature for about 36 h (Found: C, 15.00; H, 2.00; Bi, 41.05; Na, 4.90. Calc. for $C_{12}H_{22}Bi_2Na_2O_{21}$: C, 14.90; H, 2.30; Bi, 43.25; Na, 4.75%). Analyses for Na and Bi were carried out using inductively coupled plasma emission spectroscopy. Similar reactions between **1** and *N*-acetyl-L-cysteine also gave rise to crystals of **3**.

Solid-state NMR spectroscopy

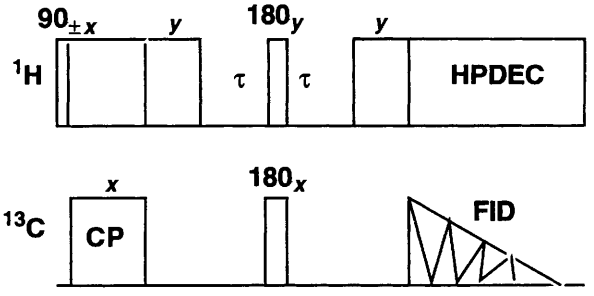
Solid-state ^{13}C NMR spectra were recorded on a Bruker MSL-300 spectrometer at 75.47 MHz, using CP MAS. Sample rotors of 7 mm diameter were used, and spinning speeds of 4.5–5.0 kHz with a 1 ms contact time. Time-domain spectra were collected using 2 K data points, and were zero-filled to 8 K before Fourier transformation. The recycle time between scans was 3–8 s. Typically the 90° pulse length for ^1H was 4.5 μs, and usually 2000–8000 transients were acquired. All spectra were recorded at ambient temperature (296 K). Chemical shifts are quoted relative to external liquid $SiMe_4$ (δ 0.0). The dipolar-dephasing experiments were carried out using the pulse sequence [10] shown in Scheme 1. The important feature of this sequence is that immediately after the cross-polarization period, the proton decoupling power is interrupted for a period 2τ and data acquisition is begun when the proton high-power decoupling (HPDEC) is switched on again. During the interrupted period the magnetization corresponding to carbons having strong dipolar interactions with protons, such as CH_2 and CH groups, dephases rapidly and hence the corresponding signals decay rapidly with increasing interruption time (dephasing time), and finally disappear. In contrast the magnetization corresponding to carbons having weak dipolar interactions, such as quaternary carbons and carboxylate groups, dephases only slowly, and these signals remain almost unchanged unless a long dephasing time is used. A ^{13}C 180° refocusing pulse in the middle of the dephasing period after an integral number of rotor periods removes linear phase distortions and ensures correct phasing of spinning sidebands.

Solution-state ^{13}C-$\{^1H\}$ NMR spectra were acquired on a JEOL GSX 270 spectrometer at 67.5 MHz, using 16 K data points, a relaxation delay of 2 s, and 4000 transients. The chemical shift reference was internal sodium 2,2,3,3-tetradeuterio-3-trimethylsilylpropionate (δ 0.0).

X-Ray crystallography of $Na_2[Bi_2(cit)_2]\cdot 7H_2O$ 3

Crystal data. $C_{12}H_{22}Bi_2Na_2O_{21}$, M = 962.23, monoclinic, space group $C2/c$, a = 15.723(3), b = 13.899(3), c = 10.423(2) Å, β = 94.39(2)°, U = 2271.1 $Å^3$, D_c = 2.662 g cm^{-3}, $F(000)$ = 1680, Z = 4, μ(Mo-Kα) = 150.3 cm^{-1}, Mo-Kα radiation, λ = 0.710 69 Å.

Data collection. Using a PW1100 diffractometer a total of 2211 data were collected at ambient temperature in the range θ 3–25° with a crystal of size 0.46 × 0.10 × 0.08 mm (mounted in a Lindemann tube), using a scan width of 0.80°, by the technique previously described.[11] Equivalent reflections were merged to give 2091 unique reflections (R_{int} 0.0535) and 1401 reflections with $I/\sigma(I) \geqslant 3.0$ of which only 108 had θ > 21°.



Scheme 1 FID = free induction decay

Structure solution and refinement.[12] The structure was solved by direct methods which gave the position of the bismuth and co-ordinated oxygen atoms; the positions of the remaining atoms were located in subsequent Fourier-difference maps. One sodium atom and the oxygen of a water molecule were on the two-fold axis. The second sodium cation, Na(2), was disordered over two sites, related by the C_2 axis, and was readily distinguished from the maxima due to oxygen atoms by its characteristic co-ordination sphere involving Na · · · O (citrate) distances in the range 2.26–2.50 Å; two small but significant maxima, *ca.* 1.7 Å from the cation of half-occupancy, Na(2), were assigned as oxygen atoms O(5w) and O(6w) of half-occupancy, corresponding to two water molecules alternating randomly with Na(2) throughout the crystal. The hydrogen atoms of the citrate ligand were included in calculated positions with a common thermal parameter which refined to a U_{iso} of 0.05 $Å^2$. Absorption corrections (maximum 1.13, minimum 0.94) were applied after refinement with isotropic thermal parameters for all atoms.[13] In the final cycles of heavily damped, full-matrix refinement with weights of $1/\sigma^2(F)$ applied to individual reflections, anisotropic thermal parameters were assigned to the bismuth and the full-occupancy oxygen atoms; the final R was 0.0438 and R' 0.0430, where $R' = [\Sigma w(|F_o| - |F_c|)^2]^{\frac{1}{2}}/\Sigma|F_o|w^{\frac{1}{2}}$. The final Fourier-difference map showed residual peaks of *ca.* 1.5 e $Å^{-3}$ in the vicinity of the bismuth atom.

Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 186/49.

Results and Discussion

Initially we investigated reactions of biologically important thiols such as the tripeptide glutathione (γ-L-Glu-L-Cys-Gly) and *N*-acetyl-L-cysteine with the bismuth antiulcer compound **1** in aqueous solution at acidic pH values, *e.g.* pH 4. When such solutions contained a mol ratio of **1** : glutathione < 1 : 3 (*e.g.* 1 : 2 to 1 : 2.5) white needle-shaped crystals of $Na_2[Bi_2(cit)_2]\cdot 7H_2O$, **3** formed after about 36 h at ambient temperature. These did not form at a mol ratio of 1 : 3 or higher, and ^1H and ^{13}C NMR spectra showed that under these conditions all of the co-ordinated citrate was displaced by the thiol with the formation of $[Bi(SR)_3]$ complexes.[14]

The X-ray crystallographic analysis shows a complicated citrate-bridged polymeric structure for the anion. There is one bismuth citrate fragment per asymmetric unit, the citrate tetraanion bonding to the bismuth atom *via* a terminal bidentate carboxyl group [Bi–O(3) 2.493(11) and Bi–O(4) 2.443(11) Å, Table 1]. The citrate ligand also bonds in tridentate mode to the Bi atom of an equivalent $Bi(cit)^-$ unit, related to

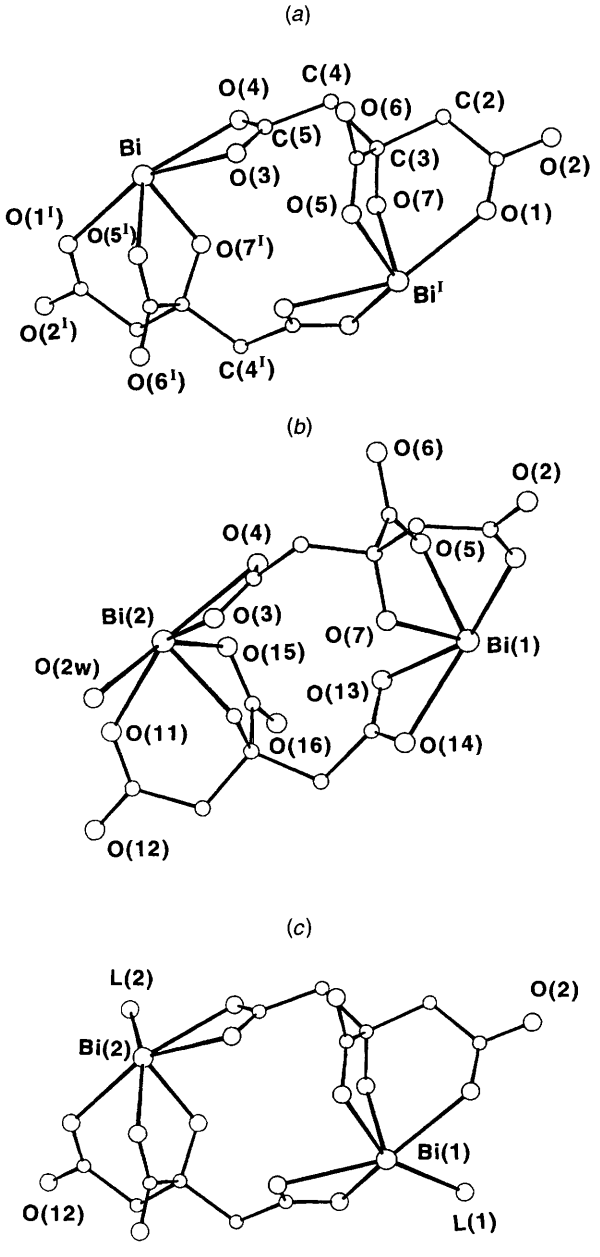


Fig. 1 Structures of the dimeric units of (*a*) compounds **3**, **3a** (ref. 6) and **3b** (ref. 8) which have two co-ordinatively unsaturated bismuth atoms, (*b*) **4a** (ref. 8) and **4b** (ref. 4) which have one bismuth atom co-ordinatively saturated, and (*c*) a simulated structure for a co-ordinatively saturated dimeric unit [LBi(μ-cit)$_2$BiL] (L = H_2O, $Hcit^{3-}$ or other donor)

the first by a C_2 axis, through one oxygen donor from each of the remaining two carboxylate groups [Bi–O(1) 2.485(11) and Bi–O(5) 2.302(11) Å] and the alkoxy group [Bi–O(7) 2.210(10) Å]. The resultant dimeric unit, shown in Fig. 1(*a*), is similar to the dimeric units observed in a number of other citrate compounds [Fig. 1(*a*) and 1(*b*)], and has a characteristic Bi···Bi separation of 6.188 Å. The dimeric unit has two important features: the bismuth atoms both have a vacant co-ordination site, and two unco-ordinated citrate oxygen atoms, one from each of the symmetry-related ligand bridges, directed outwards at the extremities of the dimer. Thus the dimers are ideal preformed units for linear assembly, and in the solid give infinite polymeric chains *via* double *syn-anti* carboxylate bridges [Bi–O(2) 2.505(10) Å] as illustrated in Fig. 2(*a*). The Bi–O(2) bond is not part of a chelate ring and is thus the 'weak link' in the polymeric chain. Severance of this one bond breaks the polymeric chain regenerating the dimeric unit. Adjacent dimeric units in the polymer are related by *n*-glide symmetry so that rows of parallel polyanion chains $[\{Bi(\mu\text{-cit})_2Bi\}_n]^{2n-}$ run throughout the crystal parallel to the long *ac* diagonals. There is an inversion centre in the middle of the double carboxylate bridging unit and the Bi···Bi separation of 4.654 Å is characteristic of this type of bridge.[15]

As a result of ligand bridging, the bismuth atom achieves six co-ordination [Bi–O 2.210(10)–2.505(10) Å] with an irregular *nido*-pentagonal-bipyramidal arrangement of ligands at bismuth. Five donor atoms form the distorted equatorial plane [deviations O(1) −0.14, O(2) 0.26, O(3) 0.20, O(4) −0.34, O(5) 0.02 Å], with the apical alkoxy donor, O(7), situated 1.77 Å above the plane of the best fit, the Bi–O(7) vector intersecting the plane at an angle of 95.6°. The bismuth atom lies in an extremely exposed position, 0.41 Å below the equatorial plane on the opposite side to O(7), so that more than half of the potential co-ordination sphere of the metal is naked, evidence of a marked steric influence of the non-bonding electron pair of the bismuth atom. There is a number of rather long interactions on this side of the molecule (Table 1, Bi···O 3.003–3.095 Å) in the range associated with ionic bonds.

Similar or related dimeric 'building blocks' to those observed in the solid state structure of compound **3** have been characterized in several crystalline products (see below) obtained from colloidal bismuth subcitrate solutions with or without added potassium or ammonium citrate [Fig. 1(*a*) and 1(*b*)]. These have been comprehensively reviewed in a recent paper, and a common feature of aggregation into 'tetrameric' units by long interactions (Bi···O 2.85–3.20 Å) has been discussed in detail.[8] However, there has been no previous discussion of the nature of the aggregate formed by the stronger bonds involved in the primary co-ordination sphere of the bismuth atom. Retrieval of the atomic coordinates of these compounds from the Cambridge Database has allowed a detailed structural comparison with the present observations.

Two of the reported compounds, reformulated as $[NH_4]_2[Bi_2(\mu\text{-cit})_2]\cdot 4H_2O$ **3a**[6] and $K[NH_4][Bi_2(\mu\text{-cit})_2]\cdot 4H_2O$ **3b**,[8] are effectively isomorphous with **3** differing only in the cation and water content. They contain dimeric units virtually identical to that illustrated in Fig. 1(*a*) for **3**, and these aggregate into chain-like polyanions, linked by bismuth primary sphere co-ordination bonds, indistinguishable from those noted for the first time in the structure of **3** [Fig. 2(*a*)].

The related dimeric units present in crystals of two other compounds, reformulated as $K[NH_4][Bi_2(\mu\text{-cit})_2(H_2O)]\cdot 5H_2O$ **4a**[8] and $K_2[Bi_2(\mu\text{-cit})_2(H_2O)]\cdot 5H_2O$ **4b**[4] are shown in Fig. 1(*b*). These have very similar citrate bridges linking the two metal atoms, but differ significantly from the first type of dimeric unit (in **3**, **3a** and **3b**) in that only one of the two bismuth atoms, Bi(1), has a vacancy in the primary co-ordination sphere; the second bismuth atom is six-co-ordinate with the sixth position being occupied by a water ligand [Bi(2)–O(2w) 2.529 **4a** and 2.531 Å **4b**]. Aggregation of these units is therefore by single carboxylate bridges [Bi(1)–O(12) 2.444 Å **4a**] between dimeric units related by a 2_1 axis forming an infinite helical polyanion $[\{Bi(\mu\text{-cit})_2Bi\}_n]^{2n-}$ [parallel to the *b* axis of the unit cell as illustrated in Fig. 2(*b*)]. This type of singly bridged polyanion is particularly interesting as it may be envisaged as a first step in the cleavage of the double carboxylate bridges in **3** in aqueous solution. Breaking the remaining bridge by a second water ligand would give a dimeric unit capable of independent existence with the structure simulated in Fig. 1(*c*). This is supported by the characterization of isolated dimeric units in crystals of $[NH_4]_8[Bi_2(\mu\text{-cit})_2(Hcit)_2]\cdot 5H_2O$,[5] where two centrosymmetrically related bismuth atoms are doubly bridged by citrate tetraanions bonding in tridentate and asymmetric bidentate mode, the primary co-ordination sphere being completed by the extra $Hcit^{3-}$ trianions.

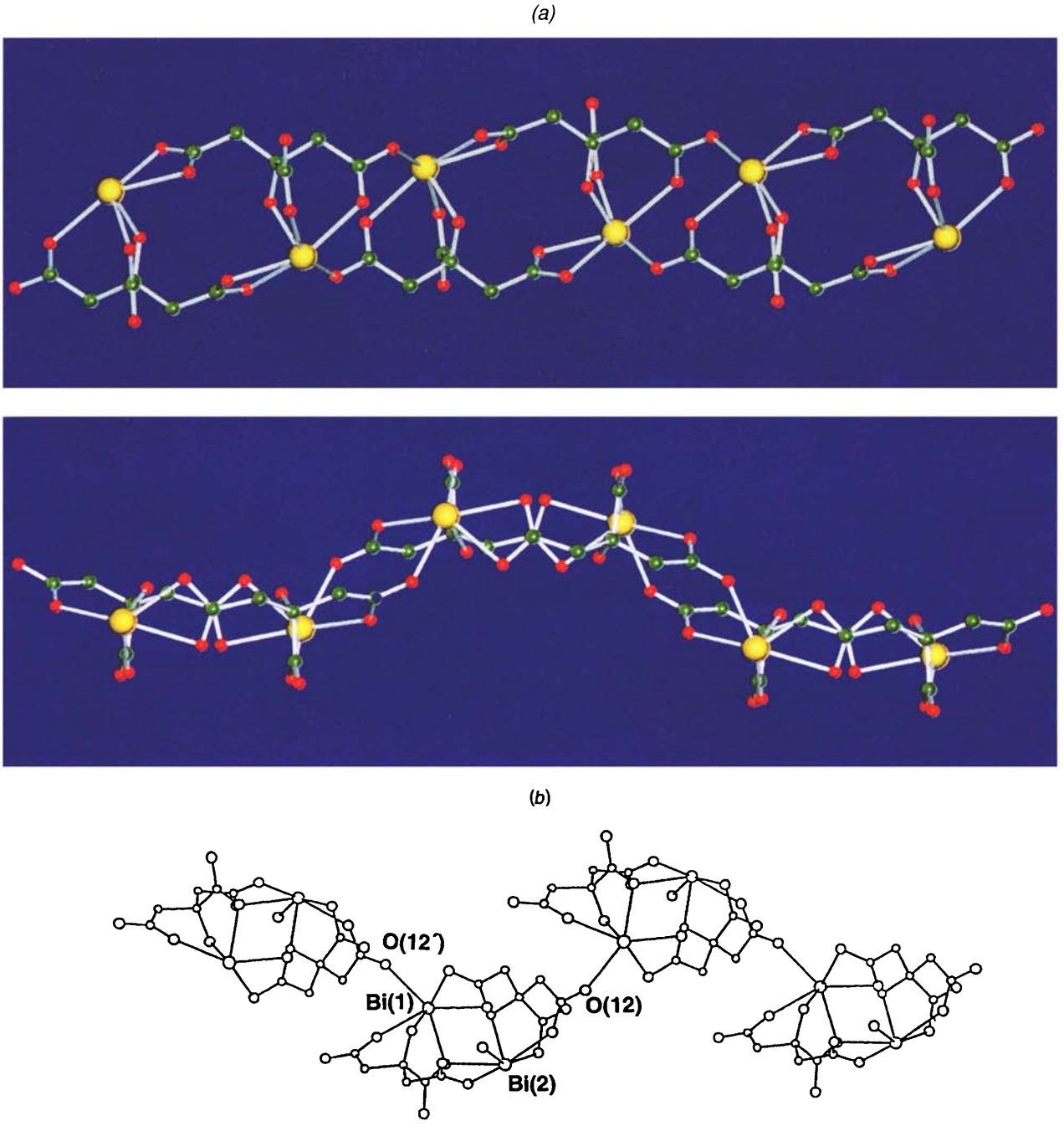


Fig. 2 (*a*) Two approximately orthogonal views of the polyanionic chains of $[\{Bi(\mu\text{-cit})_2Bi\}_n]^{2n-}$ in compound **3** formed from doubly bridged dimers (atom colour code: C, green; O, red; Bi, yellow); (*b*) the helical polyanionic chains in $K[NH_4][Bi_2(\mu\text{-cit})_2(H_2O)]\cdot 5H_2O$ **4a** and $K_2[Bi_2(\mu\text{-cit})_2(H_2O)]\cdot 5H_2O$ **4b** which contain singly bridged dimeric units

The parallel polyanion chains in compound **3** [Fig. 2(*a*)] are cross-linked by anion–cation interaction [Na · · · O(cit) 2.37–2.50 Å] and by interactions of largely ionic character (Bi · · · O 3.003–3.095 Å) to give the overall three-dimensional solid-state structure which also incorporates seven water molecules per dianion subunit.

The range of conditions under which the polyanionic solids have been isolated, both from colloidal bismuth subcitrate and ranitidine bismuth citrate, indicate that dimeric 'building blocks' $[LBi(\mu\text{-cit})_2BiL]^{2-}$ (with the vacant terminal co-ordination sites temporarily 'plugged' by water or other donors L) self-assemble readily in solution, and will be present at the ulcer surface. The solid-state studies demonstrate that these units are preformed to aggregate readily into polyanions (potentially of any length) with very high capacity for secondary co-ordination. It may therefore be readily envisaged that sheets, formed by electrostatic linking of such polyanions (as observed in the solid), might bind to the ulcer surface forming a flexible protective coating.

Infrared and NMR spectroscopy

The IR spectra of compounds **1** and **3** showed the absence of an OH stretch, in contrast to Bi(Hcit) **2** which has a sharp band at 3450 cm^{-1}.[3] In order to investigate further the differences in structure between the bismuth citrate complexes **1**–**3** we compared their solid-state ^{13}C NMR spectra, Fig. 3.

The solid-state ^{13}C NMR spectrum of complex **3** shows six well resolved resonances, three in the high-field region and three in the carboxylate region. In order to aid assignment of these peaks, dipolar-dephasing measurements were made. The dephasing rates are related to the number of nearby hydrogen

Table 1 Selected interatomic distances (Å) for compound **3**

(*a*) The linear anionic polymer

Bi–O(1^{I})	2.485(11)	Bi–O(2^{II})	2.505(10)
Bi–O(3)	2.493(11)	Bi–O(4)	2.443(11)
Bi–O(5^{I})	2.302(11)	Bi–O(7^{I})	2.210(10)
Bi · · · O(3^{III})	3.003	Bi · · · O(6^{III})	3.017
Bi · · · O(1w)	3.095	Bi^{IV} · · · O(1w)	3.095

(*b*) The sodium cations

Na(1) · · · O(1w)	2.41(2)	Na(1) · · · O(2w)	2.48(2)
Na(1) · · · O($2w^{IV}$)	2.48(2)	Na(1) · · · O(2^{V})	2.37(2)
Na(1) · · · O(2^{II})	2.37(2)	Na(2) · · · O(3w)	2.35(4)
Na(2) · · · O(4w)	2.26(4)	Na(2) · · · O($2w^{VI}$)	2.53(4)
Na(2) · · · O(1^{VII})	2.47(4)	Na(1) · · · O(6^{VIII})	2.50(4)

The superscripts refer to atoms at the following equivalent positions: I $-x, y, \frac{1}{2} - z$; II $-\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z$; III $-x, -y, 1 - z$; IV $-x, y, \frac{3}{2} - z$; V $\frac{1}{2} - x, \frac{1}{2} - y, 1 - z$; VI $-x, 1 - y, 1 - z$; VII $\frac{1}{2} - x, \frac{1}{2} - y, -z$; VIII $\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} + z$.

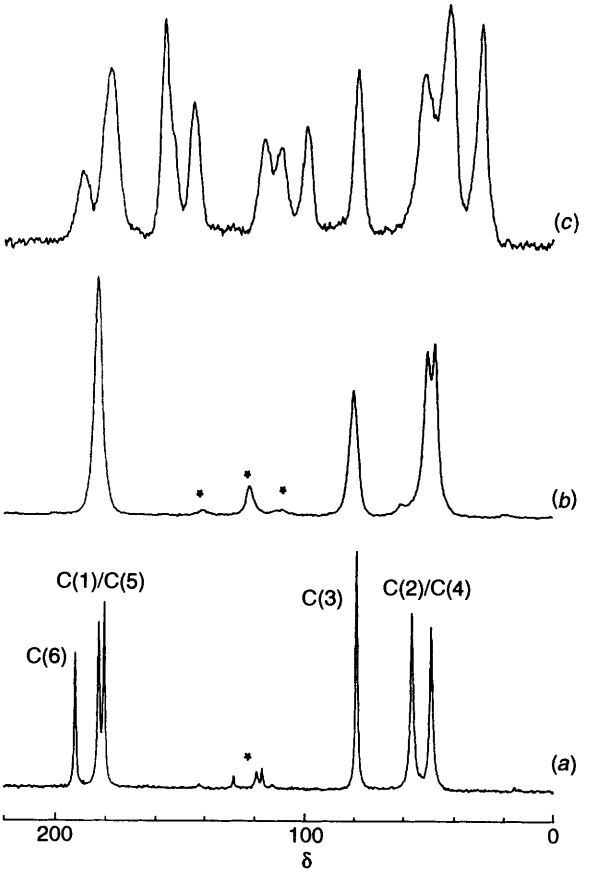


Fig. 3 Solid-state CP MAS ^{13}C NMR spectra of (*a*) $Na_2[Bi_2(cit)_2]\cdot 7H_2O$ **3**, (*b*) Bi(Hcit) **2** and (*c*) ranitidine bismuth citrate **1**. The peaks marked * are spinning side-bands. The spectrum of **1** was acquired using the TOSS sequence to suppress the spinning side-bands

nuclei and their distance away. Fig. 4 shows that the two highest-field peaks disappear first from the dipolar-dephasing spectra with increase in dephasing time and can therefore be assigned to the carbons with directly bonded protons, C(2) and C(4). The next peak to disappear is the peak at δ 79.0 which can be assigned to C(3). The two highest-field carboxylate ^{13}C resonances decrease in intensity before the lowest-field carboxylate peak and the former can therefore be assigned to C(1) and C(5), and the latter to C(6). These assignments were confirmed by inversion-recovery cross-polarization (IRCP) experiments,[16,17] which showed cross-depolarization rates to be C(2,4) > C(3) > C(1,5) > C(6) (data not shown).

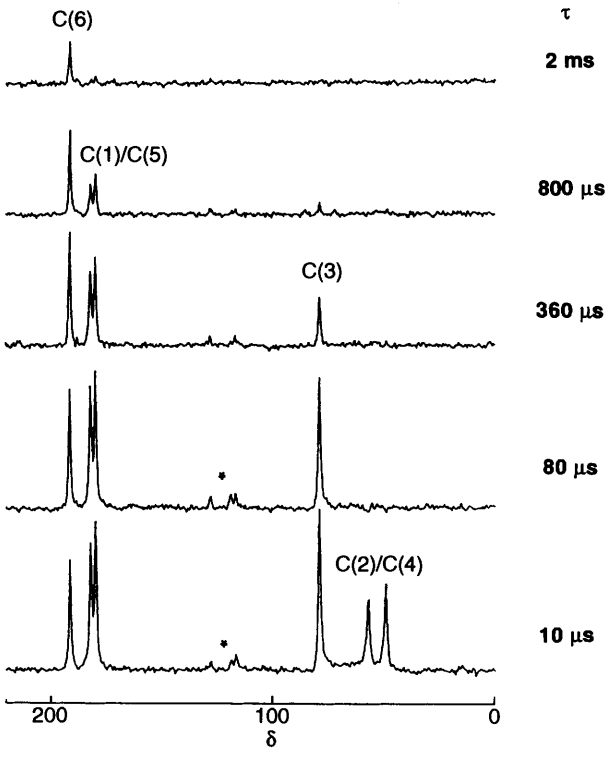


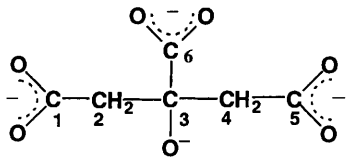
Fig. 4 Dipolar-dephasing solid-state CP MAS ^{13}C NMR spectra of $Na_2[Bi_2(cit)_2]\cdot 7H_2O$ **3** with various delay times (τ). As τ increases the first signals to disappear from the spectra can be assigned to the $C(2)H_2$ and $C(4)H_2$ carbons, followed by C(3), $C(1)O_2^-$ and $C(5)O_2^-$ and finally C(6) which is the most distant from protons

The CP MAS ^{13}C NMR spectrum of Bi(Hcit) **2** shows four separate resonances, of which three are in the high-field region, and only one in the carboxylate region (Fig. 3). By comparison with **3**, we can assign peaks in the high-field region to C(2) (δ 48.0), C(4) (50.9) and C(3) (80.3). It can be assumed that the single peak in the carboxylate region (δ 183.0) arises from all three carboxylate groups in the citrate ligand and that C(6) is not further shifted to low field because the alkoxyl group is not ionized in this complex as it is in **3**.

The spectrum of ranitidine bismuth citrate **1** is much broader due to the amorphous nature of the solid. The signals from the carbon atoms of the bismuth citrate moiety are at δ 52.3, 79.0, 178.0 and 188.9, and the other signals are from ranitidine. We assign the broad highest-field peak at δ 52.3 to C(2) and C(4), and the peak at δ 79.0 to C(3). The low-field peak at δ 178.0 can be assigned to the two terminal carboxylate carbons C(1) and C(5), and that at δ 188.9 to the central carboxylate C(6). All the solid-state ^{13}C NMR chemical shift data for these bismuth citrate complexes are summarized in Table 2 together with solution NMR data of **1** for comparison.

Only one type of citrate anion is observed in the solid-state ^{13}C NMR spectrum of $Na_2[Bi_2(cit)_2]\cdot 7H_2O$ **3**, suggesting that the three kinds of citrate anion group present in the unit cell are symmetry related. This is in agreement with the crystal structure. In contrast, complex Bi(Hcit) **2** exhibits only four distinct ^{13}C signals, including only one signal in the carboxylate region. This suggests a different mode of citrate binding to Bi^{3+} in complexes **2** and **3**. This may be due to the alkoxyl group not being involved in direct binding to bismuth in **2** which would also explain the sharp free OH IR band at 3450 cm^{-1}. Complex **1** (ranitidine bismuth citrate) exhibits much broader signals due to the amorphous nature of the solid, and four signals were observed for bound citrate, as was also found for aqueous solutions. By comparison of ^{13}C NMR spectra of **1** and **3**, we can draw the conclusion that **1** and **3** are similar to some extent, and that solid amorphous **1** may contain the same building

Table 2 Solid-state ^{13}C NMR chemical shifts for complexes **1**–**3**. The shifts for **1** in D_2O are included for comparison



	δ			
Atom	**1** (solid state)	**1** (solution)	**2**	**3**
C(1)	178.0	181.2	183.0 (br)	180.2
C(2)	52.3	52.2	48.0	49.2
C(3)	79.0	81.0	80.3	79.0
C(4)	52.3	52.2	50.9	56.7
C(5)	178.0	181.2	183.0 (br)	182.4
C(6)	188.9	191.9	183.0 (br)	191.6

blocks as **3**. The ^{13}C NMR chemical shifts for **1** in aqueous solution also support this, since they are almost the same as the chemical shifts of **3** in the solid state with the C(2)/C(4) and C(1)/C(5) peaks of **1** having averages of the ^{13}C shifts of C(2) and C(4) and C(1) and C(5) for **3**. The assembly of dimeric units into polymeric chains and sheets in **1** is likely to be determined by second-co-ordination-sphere interactions with cationic ranitidine and we reported previously that such an association can be detected in solutions of **1**.[3]

Conclusion

The crystallization of $Na_2[Bi_2(cit)_2]\cdot 7H_2O$ **3** during reactions of the antiulcer drug ranitidine bismuth citrate with the tripeptide glutathione may be relevant to the biological activity of the drug. As in several other reported bismuth citrate structures, **3** contains highly stable dimeric $[Bi_2(cit)_2]^{2-}$ units in which two Bi^{3+} ions are doubly bridged by citrate ligands. The ions have a *nido*-pentagonal-bipyramidyl geometry with the lone pair of electrons occupying the vacant axial site, *trans* to the strongly bound alkoxy group (Bi–O 2.210 Å). In the solid state these dimeric units are assembled into infinite polymeric chains *via* double *syn-anti* carboxylate bridges. Such polymers formed into sheets by electrostatic cross-links (*e.g.* by Na^+) could be deposited on the surface of the ulcer or on bacteria which can occur in ulcers. Cleavage of the bridges between dimeric units (*e.g.* by water or citrate) can be envisaged to give singly bridged polyanions and eventually independent dimeric units. By comparison of IR and solid-state ^{13}C NMR spectra, it can be deduced that ranitidine bismuth citrate contains similar building blocks to those of **3** arranged into chains, sheets and other aggregates in a manner determined partly by the counter cation, ranitidine. The ability of **3** to form chains and sheets suggests that such a complex may play an important role in activity at the ulcer surface. However citrate can readily be displaced from Bi^{3+} by thiols such as glutathione, and the detailed chemistry of such reactions will be reported elsewhere.[14,18]

Acknowledgements

We thank Glaxo Wellcome plc and the EPSRC for their support for this work, and University of London Intercollegiate Research Service (ULIRS) and MRC for the provision of NMR facilities, and the EPSRC for access to the Cambridge Structural Database at Daresbury. We also thank the Committee of Vice-Chancellors and Principals of the Universities of the United Kingdom for an Overseas Research Student Award for H. S.

References

1 C. F. Baxter, *Chem. Br.*, 1992, **28**, 445.
2 *Merck Index*, 1989, **11**, 197.
3 P. J. Sadler and H. Sun, *J. Chem. Soc., Dalton Trans.*, 1995, 1395.
4 W. A. Herrmann, E. Herdtweck and L. Pajdla, *Inorg. Chem.*, 1991, **30**, 2579.
5 E. Asato, W. L. Driessen, R. A. G. de Graaff, F. B. Hulsbergen and J. Reedijk, *Inorg. Chem.*, 1991, **30**, 4210.
6 W. A. Herrmann, E. Herdtweck and L. Pajdla, *Z. Kristallogr.*, 1992, **198**, 257.
7 E. Asato, K. Katsura, M. Mikuriya, T. Fujii and J. Reedijk, *Chem. Lett.*, 1992, 1967.
8 E. Asato, K. Katsura, M. Mikuriya, T. Fujii and J. Reedijk, *Inorg. Chem.*, 1993, **32**, 5322.
9 E. Asato, K. Katsura, M. Mikuriya, U. Turpeinen, I. Mutikainen and J. Reedijk, *Inorg. Chem.*, 1995, **34**, 2447.
10 R. Fu, S. Ding and C. Ye, *Chem. Phys. Lett.*, 1992, **170**, 159.
11 M. K. Cooper, P. A. Duckworth, K. Henrick and M. McPartlin, *J. Chem. Soc., Dalton Trans.*, 1981, 2357.
12 G. M. Sheldrick, SHELX 76, University of Cambridge, 1976; SHELXS 86, University of Göttingen, 1986.
13 N. Walker and D. Stuart, *Acta Crystallogr., Sect. A*, 1983, **39**, 158.
14 H. Sun, H. Li and P. J. Sadler, *J. Inorg. Biochem.*, 1995, **59**, 190.
15 R. C. Mehrotra and R. Bohra, *Metal Carboxylates*, Academic Press, New York, 1983.
16 N. Zumbulyadis, *J. Chem. Phys.*, 1987, **86**, 1162.
17 D. G. Cory, *Chem. Phys. Lett.*, 1988, **152**, 431.
18 P. J. Sadler, H. Sun and H. Li, *Chem. Eur. J.*, 1996, **2**, 185.

Received 23*rd November* 1995; *Paper* 5/07647A