

Synthesis, crystal structure and chemical stability of bismuth(III) complexed with 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid (H₈DOTMP)

Sindre Hassfjell,^a Kjell Ove Kongshaug^b and Christian Rømming^b

^a Department for Reservoir and Exploration Technology, Institute for Energy Technology,

P.O. Box 40, N-2027 Kjeller, Norway

^b Department of Chemistry, University of Oslo, P.O. Box 1033 Blindern, N-0315 Oslo, Norway

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The potential use of the α -particle emitting compounds ^{212/213}Bi–DOTMP and ²¹²Pb–DOTMP in therapy of bone-associated cancers, and medical interest in bismuth compounds, motivated this study. Syntheses of the Bi(III) and Pb(II) complexes of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid (H₈DOTMP) are reported. Extensive pH-stability was found for both complexes, in the pH range 0–13 for Bi–DOTMP and pH 4–14 for Pb–DOTMP. Furthermore, both complexes formed within 1 min in the pH range 6–10 at 10 μ M metal-ion and 15 μ M DOTMP. Single crystals of [NaBi(H₄DOTMP)] and polycrystalline [Bi(H₅O₂)(H₄DOTMP)] were formed and characterized by single crystal and powder X-ray diffraction methods, respectively. The structure of the anion was found in both salts to exhibit a square antiprismatic eight-coordination with a four-fold axis of symmetry.

Introduction

The α -particle emitting radionuclides ²¹³Bi ($t_{1/2}$ = 46 min), ²¹²Bi ($t_{1/2}$ = 61 min) and ²¹²Pb ($t_{1/2}$ = 10.6 h) (precursor for ²¹²Bi) have been suggested as means for effective therapy of disseminated cancers due to their high cell toxicity and the short range of the α -particles.^{1–3} The α -particle emitting compounds ²¹²Bi–DOTMP[†] and ²¹²Pb–DOTMP[†] have been proposed for therapy of bone cancer such as osteogent sarcoma and bone metastases, a frequent complication from breast, prostate and lung cancer.⁴ It has been shown that ²¹²Bi–DOTMP and ²¹²Pb–DOTMP rapidly targets bone in general and especially areas with high bone turnover as in the above-mentioned malignancies.⁴ High stability of the radiometal complexes is important to minimize irradiation of healthy tissue and ensure a high therapeutic efficacy. Furthermore, to achieve high yields of ²¹²Bi–DOTMP, ²¹²Pb–DOTMP, or alternatively ²¹³Bi–DOTMP, rapid radiometal chelation is desirable owing to the short half-life of the radionuclides. Thus, for a thorough evaluation of the potential of these radiopharmaceuticals, knowledge of stability and formation kinetics of Bi–DOTMP and Pb–DOTMP is warranted. Besides the applications of radiobismuth in cancer therapy, stable bismuth compounds are also receiving interest as antiulcer, antibacterial and anti-HIV drugs among others.⁵ Thus, knowledge of the chemical and structural properties of Bi–DOTMP may be of general interest.

This paper reports the preparation of bismuth and lead complexes of H₈DOTMP (also known as H₈DOTP). The BiH₄DOTMP[−] complexes, with Na(H₂O)₄⁺ and H₅O₂⁺ as counter ions, have been characterized by single crystal X-ray crystallography and powder X-ray diffraction, respectively. The thermal stability of the latter was investigated by thermogravimetric methods. The stability and formation rates in acid and alkaline solutions of the Bi–DOTMP and Pb–DOTMP complexes have been investigated by spectrophotometry.

[†] When the exact protonation state and net charge of Bi(III) and Pb(II) complexes with H₈DOTMP are not known, they are simply referred to as Bi–DOTMP and Pb–DOTMP. Solutions of H₈DOTMP at pH > 0 will, by the same argument, be referred to as DOTMP solutions.

Experimental

Preparation of Bi–DOTMP and Pb–DOTMP

All reagents were of analytical grade and the water was ultra-purified (Milli Q, 18 M Ω , Millipore, Bedford, MA, USA). All pH adjustments of stock solutions were made with NaOH and HNO₃. 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid (H₈DOTMP) (Fig. 1) was purchased from Macrocyclics (Richardson, TX, USA). Both Bi–DOTMP and Pb–DOTMP are 1 : 1 complexes. Pb–DOTMP was made by adding a solution of Pb(NO₃)₂ (J.T. Baker, Deventer, Holland) in slight molar excess (~1%) to a DOTMP solution at pH = 9. After allowing a day for complete reaction, [Na₂Pb(H₄DOTMP)] was precipitated with ethanol, washed extensively with water–ethanol mixtures, and dried over silica gel at reduced pressure. Bi–DOTMP was made by adding small portions of a 2 M Bi(III) solution at pH = 0, to a 20 mM DOTMP solution at pH = 4–5. The Bi(III) solution was made by dissolving Bi₂O₃ (J.T. Baker, Deventer, Holland) in HNO₃. During complex

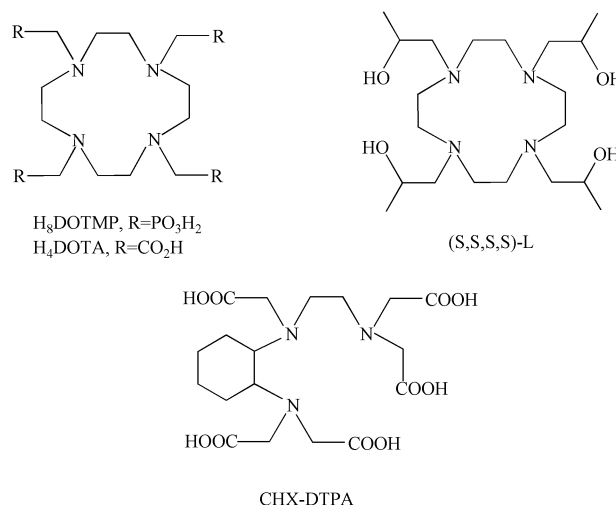


Fig. 1 Structures of DOTMP, DOTA, (S,S,S,S)-L, CHX-DTPA (removal of the cyclohexyl group on the ethylene bridge gives DTPA).

formation the DOTMP solution was kept at approximately 60 °C and under magnetic stirring. The added portions of Bi(III) precipitated at first, but then dissolved in a few minutes. When 95% of equimolar amounts of Bi(III) had been added, [NaBi(H₄DOTMP)] was precipitated at pH = 3–4, washed extensively with water–ethanol mixtures to remove surplus DOTMP and NaNO₃, and dried over silica gel at reduced pressure. Stock solutions of 10.0 mM Bi–DOTMP and Pb–DOTMP at pH 9 were made from the precipitates. The pH was adjusted with NaOH or KOH solutions. Although no M(OH)_n precipitate was observed, the stock solutions were finally filtered through 0.45 µm filters. Stock solutions of 1.00 mM Bi(III) (in 1 M HClO₄), Pb(NO₃)₂ and DOTMP (both at pH = 8) were also made. The purity of the DOTMP, the Pb–DOTMP and the Bi–DOTMP stock solutions were found to be satisfactory (>99%) after UV-analysis on a Hitachi 2000 spectrophotometer, and separation on a HPLC system coupled to a diode array UV detector⁴ (both 190–600 nm). The only contaminant found was very small amounts of nitrate. λ_{max}/nm (Bi–DOTMP): 195 (ε/dm³ mol⁻¹ cm⁻¹ 94 000) and 303 (6950). λ_{max}/nm (Pb–DOTMP): 200 (ε/dm³ mol⁻¹ cm⁻¹ 37 000) and 263 (6400). λ_{max}/nm (DOTMP): 190 (ε/dm³ mol⁻¹ cm⁻¹ 10 000). No absorbance from DOTMP, Pb(II) and Bi(III) was detected above 250 nm. Single crystals of NaBiH₄DOTMP, were formed by allowing slow diffusion of *n*-propanol to a 0.10 ml solution of 40% (v/v) *n*-propanol at pH = 5 containing 45 g l⁻¹ of Bi–DOTMP. After a few days crystals started forming. ¹H and ³¹P NMR spectra were obtained with a Varian 500 MHz instrument. δ_p (500 MHz, solvent D₂O, reference H₃PO₄): DOTMP, 20.6; Bi–DOTMP, 21.6; Pb–DOTMP, 17.1 (4P, t, 4 CH₂PO₃). δ_H (500 MHz, solvent D₂O, reference H₂O): DOTMP, 3.1 (16H, s, 4 N(CH₂)₂N), 2.9 (8H, d, 4 NCH₂P); Pb–DOTMP, 2.9 (br s); Bi–DOTMP, 3.9 (t), 3.3 (t), 3.2 (br t), 3.1 (quartet), 2.9 (d), 2.8 (d). All multiplets from the ¹H NMR of Bi–DOTMP had equal integrals. MS spectra (ES) were obtained on a FT-ICR Apex 47E. *m/z* 753 (BiH₄DOTMP⁻, ²⁰⁸PbH₃DOTMP⁻), 775 (NaBiH₃DOTMP⁻, Na²⁰⁸PbH₄DOTMP⁻), 797 (Na₂BiH₂DOTMP⁻, Na₂²⁰⁸PbH₃DOTMP⁻), 819 (Na₃BiHDOTMP⁻, Na₃²⁰⁸PbH₂DOTMP⁻). These complexes were also observed doubly charged. All peaks of any significance (>99%) were determined to be complex ions of either Pb–DOTMP or Bi–DOTMP. The identities of the complexes were established on double charged ions with high-resolution MS. *m/z* 376.0182 (BiH₃DOTMP²⁻) (calc. 376.0191), 387.0064 (NaBiH₂DOTMP²⁻) (calc. 387.0100), 376.0201 (²⁰⁸PbH₄DOTMP²⁻) (calc. 376.0211), 387.0107 (Na²⁰⁸PbH₃DOTMP²⁻) (calc. 387.0121). The DOTMP complexes with ²⁰⁶Pb and ²⁰⁷Pb were also observed in the spectrogram with the expected isotopic abundances.

pH Stability and formation kinetics

The pH stability and formation kinetics experiments were performed with a Perkin Elmer 55B spectrophotometer at 303 nm for Bi–DOTMP, and for Pb–DOTMP at 263 nm at pH < 7 and 275 nm at pH > 7 (Pb–DOTMP shifted its maximum peak slightly towards 275 nm in basic solutions). At these wavelengths, absorbance from uncomplexed Pb(II), Bi(III), DOTMP, solvents and counter ions was negligible, unless otherwise mentioned. The actual complex was considered stable when the absorbance readout for a solution remained constant over time (>4 weeks) and was in accordance with the values calculated from the molar extinction coefficients. In the pH stability and formation rate experiments 0.090–0.15 mM and 0.005–0.10 mM solutions of the complexes were used, respectively. The buffers used for the pH range 2.7–11 were 50 mM and made from formic, acetic, boric and carbonic acids and pH was adjusted with NaOH. For pH ≥ 12 and pH ≤ 2 solutions of NaOH and HClO₄ (≥0.010 M) were used. All solutions were 1.0 M in NaClO₄ except for the

solutions that were ≥1 M in either NaOH or HClO₄. In the formation rate experiments, the buffer solution and DOTMP were mixed thoroughly before addition of either Pb(II) or Bi(III). The solutions were then mixed thoroughly for 1 min prior to the first absorbance measurement to ensure homogeneity. The solutions used for measuring pH stability were followed for 1–2 months and stored in capped transparent vials on a laboratory benchtop. All experiments were carried out at room temperature (~22 °C).

Thermogravimetric analysis (TGA) of [Bi(H₅O₂)(H₄DOTMP)]

TGA was performed on a Rheometric Scientific STA 1500. The sample was heated in a nitrogen gas flow at a rate of 5 K min⁻¹. The TGA revealed a two-step weight loss curve. The first weight loss of 4.47% between 100 and 140 °C is consistent with the loss of two water molecules (calculated 5.88%). The second weight loss between 300 and 500 °C is due to the loss of the organic component.

Single crystal X-ray crystallography on [Bi(H₄DOTMP)-(Na(H₂O)₄)]

X-Ray data were collected on a Siemens SMART CCD diffractometer⁶ using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Data collection method: ω-scan, range 0.3°, crystal to detector distance 5 cm. Data reduction and cell determination were carried out with the SAINT and XPREP programs.⁶ Absorption corrections were applied by the use of the SADABS program.⁷ The structure was determined and refined using the SHELXTL program package.⁸ The structure was refined assuming the space group *P4/n*, the cation Na(H₂O)₄⁺ was found to be highly disordered. The lower symmetric space group *P4* was also tried, but one had to assume a racemic twinning and the result was much the same as in the centric space group. Attempts to obtain the structure of the cation were not successful. Non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen positions for the anion were found from difference Fourier maps and refined with isotropic thermal parameters. Crystal and refinement data are given in Table 1, and selected geometrical data are listed in Table 3.

CCDC reference numbers 191713 and 191714.

See <http://www.rsc.org/suppdata/dt/b3/b300282a/> for crystallographic data in CIF or other electronic format.

Powder X-ray diffraction analysis of [Bi(H₅O₂)(H₄DOTMP)]

Powder X-ray diffraction data were collected with a Siemens D5000 diffractometer equipped with a Ge primary monochromator giving Cu-Kα₁ radiation. The detector was a Brown PSD. The data was obtained in transmission geometry using a 0.5 mm rotating borosilicate capillary.

Table 1 Crystal data and structure refinement for [Bi(H₄DOTMP)-(Na(H₂O)₄)]

Empirical formula	BiC ₁₂ H ₂₄ N ₄ (HPO ₃) ₄ Na(H ₂ O) ₄
Formula weight	848.29
<i>T</i> /K	150
Crystal system	Tetragonal
Space group	<i>P4/n</i> (no. 85)
Unit cell dimensions	
<i>a</i> /Å	14.717(1)
<i>c</i> /Å	6.886(2)
<i>V</i> /Å ³	1491.49(6)
<i>Z</i>	2
<i>μ</i> /mm ⁻¹	6.215
Reflections collected	30660
Independent reflections (<i>R</i> _{int})	4647 (0.0236)
Reflections observed (>2σ)	4395
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> 1 = 0.0176, <i>wR</i> 2 = 0.0453
<i>R</i> indices (all data)	<i>R</i> 1 = 0.0196, <i>wR</i> 2 = 0.0456

Table 2 Experimental conditions and relevant data for Rietveld refinements of $[\text{Bi}(\text{H}_5\text{O}_2)(\text{H}_4\text{DOTMP})]$

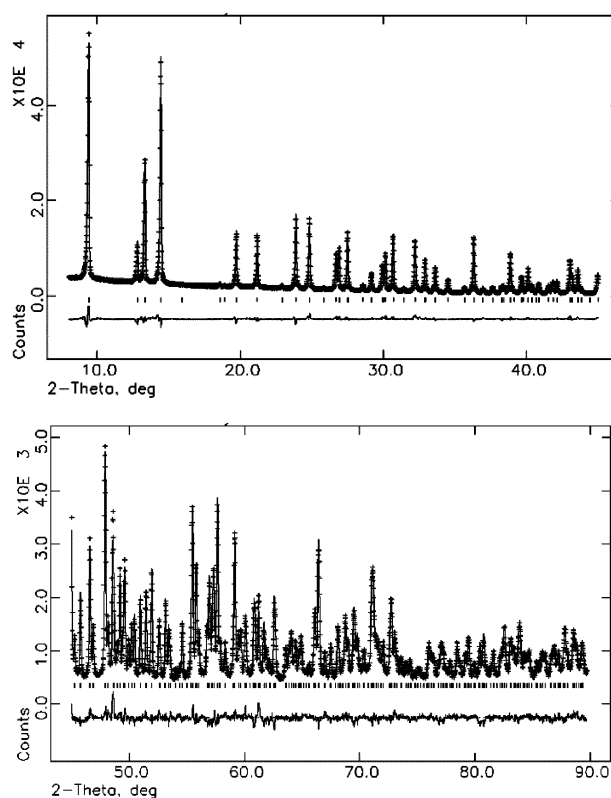
Formula	$\text{BiC}_{12}\text{H}_{24}\text{N}_4(\text{HPO}_3)_4\text{H}_5\text{O}_2$
Formula weight	790.28
Pattern range $2\theta/^\circ$	8–90
T/K	298
Step size $\Delta 2\theta/^\circ$	0.0155517 ^a
$\lambda/\text{\AA}$	1.540598
Crystal system	Tetragonal
Space group	$P4/n$ (no. 85)
$a/\text{\AA}$	13.24204(8)
$c/\text{\AA}$	6.89488(6)
$V/\text{\AA}^3$	1209.02(2)
Z	2
No. observations	5257
No. reflections	513
No. refined params.	66
R_{wp}	0.0484
R_F^2	0.0501

^a Defined by the PSD setting.**Table 3** Selected bond lengths (\AA) and angles ($^\circ$) for $\text{Bi}(\text{H}_4\text{DOTMP})^-$ as determined from the single crystal X-ray diffraction study of $[\text{Bi}(\text{H}_4\text{DOTMP})(\text{Na}(\text{H}_2\text{O})_6)]$ (A) and from the Rietveld refinement of $[\text{Bi}(\text{H}_5\text{O}_2)(\text{H}_4\text{DOTMP})]$ (B)

	A	B
Bi(1)–O(1)	2.4481(9)	2.443(5)
Bi(1)–N(1)	2.6261(10)	2.791(6)
P(1)–O(1)	1.509(10)	1.523(3)
P(1)–O(2)	1.5152(11)	1.518(3)
P(1)–O(3)	1.5747(11)	1.530(7)
P(1)–C(3)	1.8265(13)	1.831(3)
O(3)–H(3)	0.99(5)	
N(1)–C(3)	1.4830(17)	1.485(3)
N(1)–C(1)	1.4898(16)	1.481(3)
N(1)–C(2)	1.4899(17)	1.496(10)
C(1)–C(2)	1.5091(19)	1.523(3)
O(1)#1–Bi(1)–O(1)#2	124.01(5)	122.5(2)
O(1)#1–Bi(1)–O(1)#3	77.27(2)	76.6(1)
N(1)#2–Bi(1)–N(1)#1	107.19(5)	104.7(5)
N(1)#2–Bi(1)–N(1)#3	69.37(2)	68.1(2)
O(1)–P(1)–O(2)	117.36(6)	109.8(4)
O(1)–P(1)–O(3)	109.11(6)	113.3(4)
O(2)–P(1)–O(3)	108.82(6)	110.2(4)
O(1)–P(1)–C(3)	106.64(6)	106.9(4)
O(2)–P(1)–C(3)	107.19(6)	110.4(4)
O(3)–P(1)–C(3)	107.26(6)	106.3(4)

Symmetry transformations used to generate equivalent atoms: #1 $y, -x + 3/2, z$; #2 $-y + 3/2, x, z$; #3 $-x + 3/2, -y + 3/2, z$.

The powder diffraction pattern was autoindexed by means of the TREOR-90 program⁹ using the first 20 Bragg reflections. The best solution gave a tetragonal cell: $a = 13.2471$ and $c = 6.8967$ \AA ($M_{20} = 89$). Inspection of the powder pattern indicated systematic absences $0k0$ for $k = 2n + 1$ and $hk0$ for $h + k = 2n$ consistent with the space groups $P4/n$ (no. 85) and $P4/nmm$ (no. 129). The crystal structure could be solved in space group $P4/n$ by help of the EXPO program,¹⁰ which integrates the program EXTRA¹¹ for the extraction of intensities with SIRPOW92,¹² a direct methods program specially designed for powder data. All Bi, P, O, N and C atoms in the structure could be located from the E-map with the highest figure-of merit. These atomic positions were then used as a starting model for Rietveld refinement using the GSAS program.¹³ Initial refinements included scale, background, zero point, unit cell parameters and profile parameters. The atomic coordinates were refined by adding soft distance constraints: $d(\text{P}–\text{O}) = 1.53(2)$, $d(\text{N}–\text{C}) = 1.48(2)$ and $d(\text{C}–\text{C}) = 1.52(2)$ \AA . Isotropic displacement parameters were introduced for Bi and P, while common isotropic displacement parameters were adopted for

**Fig. 2** Observed, calculated and difference powder X-ray diffraction profiles for $[\text{Bi}(\text{H}_5\text{O}_2)(\text{H}_4\text{DOTMP})]$.

C, N and O atoms, respectively. No hydrogen positions were located. The refinement converged to satisfactory residual factors $R_{\text{wp}} = 0.0484$ and $R_F^2 = 0.0501$ for a total of 66 refined parameters. The weight on the soft constraints could not be removed without unrealistic bond distances emerging in the structure. Further details on the refinement are given in Table 2, and selected bond distances and angles are presented in Table 3. Fig. 2 shows the observed, calculated and difference diffraction profiles from the Rietveld analysis.

Results and discussion

pH stability and formation kinetics

The stability of Bi–DOTMP and Pb–DOTMP as a function of pH is shown in Fig. 3. The absorbance of Bi–DOTMP fell approximately 15% in 5 M HClO_4 , indicating that the stability limit in acidic environment had been reached. Dissociation of Bi–DOTMP was also seen in 1.0 M HCl , probably due to chloride competing more effectively for Bi(III) than perchlorate. In 1.0, 2.0 and 3.0 M NaOH , Bi–DOTMP showed 5, 50 and 90% dissociation of the complex, respectively. In 5.0 and 6.0 M NaOH , Pb–DOTMP showed 40 and 50% dissociation of the complex, respectively.

The extensive range of pH stability of Bi–DOTMP and Pb–DOTMP indicate high thermodynamic stability constants of the complexes. The pH stability in the acidic region is similar to what has been reported for Bi(III) and Pb(II) complexes with 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene acetic acid (DOTA) and Bi(III) complexed with diethylenetriamine-pentaacetic acid (DTPA),^{14–16} (Fig. 1) but extend further into the basic region. The postulated relations between acid stability and $\log K$ values^{17–19} and the very low solubility of Bi(III) in basic solutions^{20,21} indicate a $\log K > 30$ for Bi–DOTMP. Based on the pH stability results, a $\log K$ for Pb–DOTMP similar to the $\log K$ of 24 determined for Pb–DOTA could be expected.¹⁵ It may be anticipated from the literature^{22,23} that Pb–DOTMP has a structure similar to Bi–DOTMP. The rigidity, the high

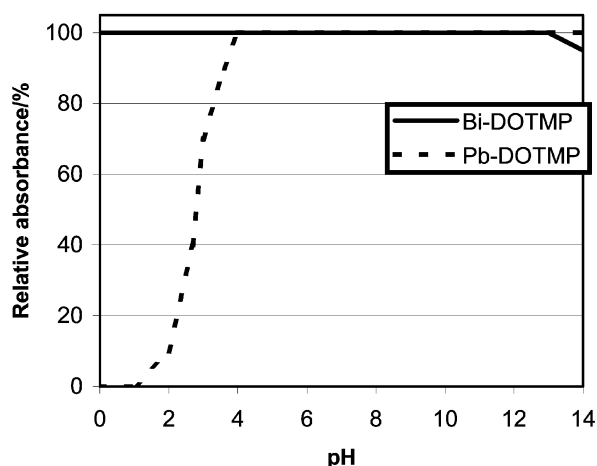


Fig. 3 Relative absorbance values for Bi–DOTMP and Pb–DOTMP are shown as a function of pH.

basicity and the large activation barrier for interconversion between ethylene chelate ring conformations have been postulated as reasons for the high stability of Ln–DOTMP complexes.²⁴ The extensive stability observed in basic solutions in this study may partly be explained by increased charge repulsion (8 vs. 4 acidic protons). The absence of a lone pair coordination (the bismuth atom is only eight-coordinated in contrast to nine as found for other complexes) in Bi–DOTMP (Fig. 4 and 5) should also contribute to the stability by making the complex less exposed for proton or hydroxide mediated dissociation. The high pH stability observed for Bi–DOTMP indicates that ^{212/213}Bi–DOTMP should have the necessary complex stability for α -particle therapy. ²¹²Pb–DOTMP should also be resistant towards dissociation at physiological pH, possibly with the exception of the most acidic conditions inside cells and in the digestive compartments. It may also be anticipated from the stability data that *trans* chelation with biomolecules such as transferrin is unlikely.⁵ These results confirm the *in vivo* stability observed for ²¹²Bi–DOTMP and ²¹²Pb–DOTMP.⁴

The formation rate experiments at pH 6–10 showed that Bi–DOTMP and Pb–DOTMP formed completely within the 1 min mixing time for all applied concentrations, the lowest being 10 μ M Pb(II) or Bi(III) and 15 μ M DOTMP. Although DOTMP is a rigid preorganized chelator, the relatively fast formation rate might be explained by the open conformation observed for DOTMP, where two of the opposite phosphonate groups are positioned above the plane of the ring, and the other two phosphonate groups are oriented away from the ring.²⁵ The fast formation rate is favourable considering the short half-life of ^{212/213}Bi. At pH 12 the formation kinetics were slower. Formation of Bi–DOTMP was also observed in 1.0 M HClO₄. The formation rate experiments confirmed the 1 : 1 formation stoichiometry of Bi–DOTMP and Pb–DOTMP.

Structure description of [Bi(H₅O₂)(H₄DOTMP)]

Fig. 4(a) shows the crystal packing of [Bi(H₅O₂)(H₄DOTMP)]. The complexes are perfectly ordered with a four-fold axis of symmetry. The bismuth atoms have a square antiprismatic cubic eight-coordination to four nitrogens of the cyclen ring and four oxygens from the four phosphonate groups. The phosphonate groups contain two terminal P–O bondings (O2 and O3). Most probably one of these oxygens is an OH group, while the other is double bonded to P. However, the bond distances (Table 3) do not give a clear indication to distinguish between the two oxygens. The two groups are involved in a complex hydrogen-bonding scheme, which also includes the oxonium monohydrate ions in the channels. The interactions are very strong ($d(\text{O}2 \cdots \text{O}3) = 2.517$, $d(\text{O}2 \cdots \text{O}4) = 2.550$

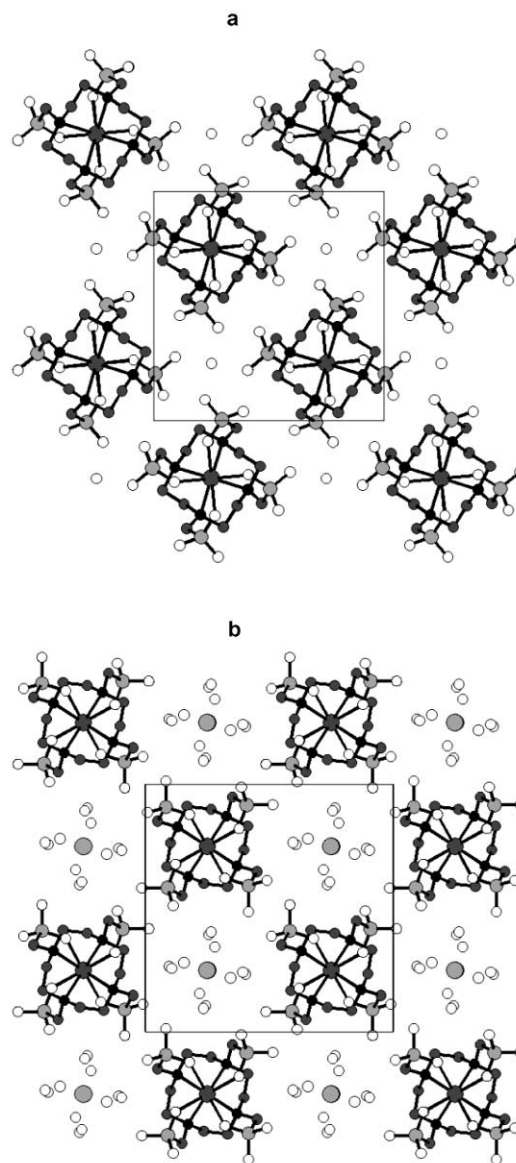


Fig. 4 Crystal packing of [Bi(H₅O₂)(H₄DOTMP)] (a) and [Bi(H₄DOTMP)(Na(H₂O)₄)] (b).

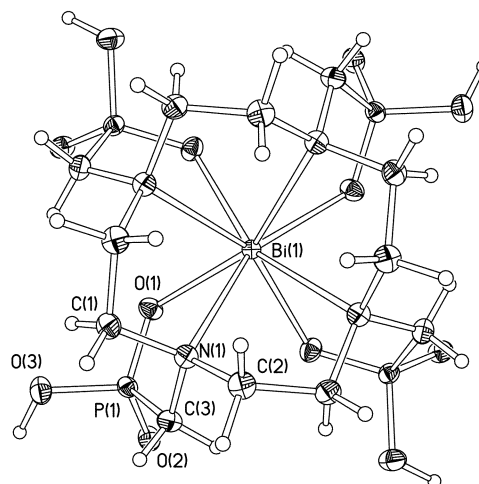


Fig. 5 ORTEP plot of the BiH₄DOTMP⁻ ion as determined for the sodium salt.

and $d(\text{O}4 \cdots \text{O}4') = 2.404$ Å). One additional proton is needed for complete charge neutralization.

In the oxonium monohydrate the anion is hydrogen bonded to four other anions through O3H–O2' bonds in a tetragonal

arrangement. The central hydrogen atom of the cation is probably situated at the inversion centre of the four-fold inversion axis; the four remaining hydrogen atoms are engaged in hydrogen bonds (2.550 Å) to O2 atoms of the surrounding anions.

Single crystal structure of the sodium salt

A list of selected bond lengths and bond angles of $[\text{Bi}(\text{H}_4\text{DOTMP})(\text{Na}(\text{H}_2\text{O})_4)]$ are shown in Table 3. An ORTEP plot of the anion complex is presented in Fig. 5. The complex is perfectly ordered with a four-fold axis of symmetry. The eight-coordination of the Bi atom is antiprismatic cubic with the four nitrogen atoms from the cyclen ring and four acidic oxygen atoms, one from each of the four phosphonate groups as coordinating atoms. All the phosphonate groups are positioned on one side of the cyclen ring. No lone pair coordination was seen. The chelate rings are five-membered, a preferred conformation for larger ions. The bond lengths of P1–O1 and P1–O2 (1.509(1) and 1.515(1) Å, respectively), indicate conjugation of the double bond after deprotonation of one of the acidic protons. Based on the longer bond length of the P1–O3 bond (1.575(1) Å) four acidic protons were assigned to the complex. Complete charge neutralization is achieved with one loosely coordinated counter ion, which displayed disorder. The counter ion, a sodium ion, is coordinated to water molecules, possibly also a disordered propanol molecule at the inversion centre of the four-fold inversion axis. The highly ordered and regular structure in Bi–DOTMP has, to the authors knowledge, not been observed in a Bi(III)-chelate before. This indicates low strain in the complex, which along with the above-mentioned structure implies high complex strength.^{5,14,26}

The crystal structure of the sodium salt is illustrated in Fig. 4(b). The anions are doubly hydrogen bonded (2.519 Å) to four other anions through $\text{O3H} \cdots \text{O2}'$ bonds about centres of symmetry in a tetragonal arrangement forming a rigid two-dimensional structure. The cations, probably $\text{Na}(\text{H}_2\text{O})_4^+$ ions, are disordered in the channels formed by the anions. They have various possibilities to form hydrogen bonds from the water molecules to different O2 and O3 atoms of the anions, hence the disorder observed.

The square-antiprismatic coordination observed for $\text{BiH}_4\text{-DOTMP}^-$ is a common motif found for several Bi-chelates of linear polyaminocarboxylates^{27–29} and for the one cyclen-based macrocycle (*S,S,S,S*)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra-*(S)*-2-hydroxypropyl (L) (Fig. 1) found in the literature.²² Those Bi-chelates have irregular Bi–N and Bi–O bond lengths, with the shortest average values found for *trans*-cyclohexyl-DTPA (CHX-DTPA) (Fig. 1) of approximately 2.53 and 2.48 Å, respectively.²⁸ A loosely conjugated water molecule in the lone pair direction was observed in the Bi–DTPA and Bi–L complexes. Average values for Bi–N and Bi–O bond lengths for Bi–L were reported to be 2.53 and 2.58 Å, respectively. All these complexes are eight-coordinated with five-membered chelate rings, similar to $\text{Bi}(\text{H}_4\text{DOTMP})^-$. The Bi–N bond length in $\text{Bi}(\text{H}_4\text{DOTMP})^-$, is longer than the typical Bi–N bond length found in the above mentioned Bi-chelates, and the Bi–O bond length in $\text{Bi}(\text{H}_4\text{DOTMP})^-$ is shorter than the typical Bi-chelate Bi–O bond length. However, the average bond length for all Bi bonds in $\text{Bi}(\text{H}_4\text{DOTMP})^-$ is 2.54 Å, close to the averages of the above-mentioned eight-coordinated Bi-chelates. All these Bi-chelates possess high complex stability.

Due to the scarcity of published Bi–cyclen based chelates it might be interesting to compare the $\text{Bi}(\text{H}_4\text{DOTMP})^-$ crystal data with literature data of Ln(III) chelates of DOTMP. Ln(III) chelates of DOTMP are reported to have a very rigid structure

with a 101 kJ mol^{–1} inversion barrier, considerably higher than that for DOTA systems.³⁰ All the Ln–DOTMP complexes are isostructural and eight-coordinate with the metal ion. It has been estimated that Ln–DOTMP would have average Ln–N and Ln–O bond lengths of 2.70 and 2.35 Å, respectively,²⁴ somewhat different from the Bi–N and Bi–O bond lengths found for $\text{Bi}(\text{H}_4\text{DOTMP})^-$. The average metal ion bond length for Ln–DOTMP would however be similar to what has been found for $\text{Bi}(\text{H}_4\text{DOTMP})^-$.

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