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Synthesis and crystal structure of an unprecedented bismuth porphyrin containing ester pendant arms

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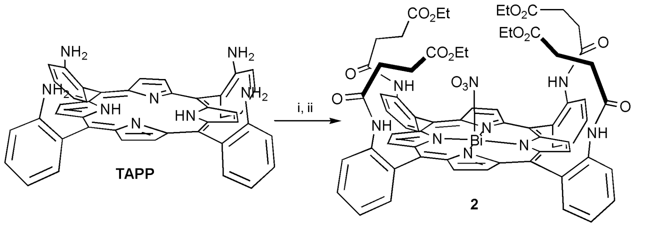
An easily prepared porphyrin with pendant arms is shown to form a stable complex with bismuth(III) ion; the complex is eight coordinate with a square antiprismatic coordination geometry; the solid-state structure exhibits the formation of a dimer assembled *via* mutual coordination of a terminal ester group.

The chemistry of bismuth has been somewhat neglected until recently when bismuth complexes have become of interest in the treatment of gastric ulcers[1] and cancer therapy.[2] In this context, the coordination of bismuth with several types of ligands has been developed in the last ten years. The synthesis of bismuth(III) complexes with nitrogen-donor macrocycles[3,4] has been investigated and it appears that the bismuth(III) ion has a high affinity for these ligands. The promising interest of ^{212}Bi as an α-emitter for radioimmunotherapy has induced studies concerning the complexation[5,6] of this ion with polyaminoacid ligands derived from diethylenetriaminepentaacetic acid, in these types of complexes, the metal exhibits a coordination with carboxylate groups and nitrogen atoms. This background about the coordination of the Bi(III) ion has led us to consider with a new point of view our studies with porphyrins acting as ligands. The literature concerning the metallation of porphyrin with bismuth salts is not very widespread.[7,8] In a recent publication,[9] we have described the structure of (OEP)Bi(SO_3CF_3) as a dimer with a seven coordination geometry in which the bismuth lies 1.07 Å from the plane formed by the four nitrogen of the porphyrin. To quote Brechbiel,[10] 'An important ligand property that increases metal complex stability is preorganization, the tendency of the free ligand to assume the conformation necessary for metal ion complexation'.[11] On the basis of this particular structural feature, we have designed porphyrins with pendant arms as potentially oxygen-atom donors. It is worth noting that in our case, and in contrast with tetraazamacrocycles such as DOTA, the four pickets are not coplanar with the four-nitrogen macrocycle but pre-oriented in a perpendicular direction, as a result of their grafting to *ortho* positions of the meso phenyl ring. Ligand 4ESH$_2$ **1**[†] (the free-base analogue of **2**) was synthesized by reaction of *meso*(tetra-*o*-aminophenyl)porphyrin (atropisomer $\alpha\alpha\alpha\alpha$, TAPP)[12] with ethylsuccinyl chloride (Scheme 1) and isolated in high yield (93%). The Bi(III) complex was prepared under mild conditions with metallation occurring in pyridine at 50 °C during 2 h. The yield of the reaction was almost quantitative (85%) and no demetallation was observed during the purification of the product. Indeed, in contrast to unfunctionalized porphyrins such as (OEP)Bi(SO_3CF_3), chromatography of coumpound **2** does not afford any free base analogue. Crystals[‡] suitable for X-ray study were obtained by a slow diffusion of H_2O–MeOH onto a saturated THF solution of **2**. The ORTEP[13] plot of the X-ray structure is shown in Fig. 1. As depicted in Fig. 2, the Bi(III) is eight coordinate with an approximate square antiprismatic geometry. The four nitrogen atoms of the macrocycle form a square, the other distorted square being formed by four oxygen atoms described as follows: two oxygen atoms of the nitrate anion, the oxygen atom of a water molecule and a carbonyl oxygen atom of the terminal ester group belonging to an arm attached to a



Scheme 1 *Reagents and conditions*: i, ClCO(CH$_2$)$_2$CO$_2$Et, NEt$_3$, THF; ii, pyridine, Bi(NO$_3$)$_3$·5H$_2$O, 50 °C.

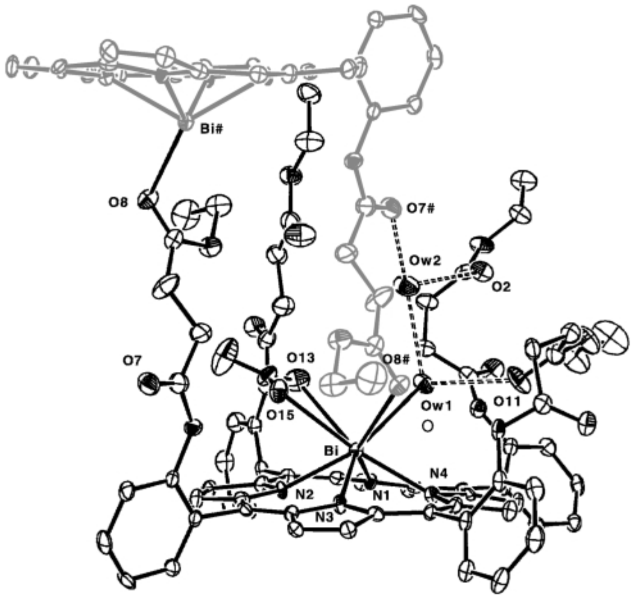


Fig. 1 ORTEP view of the Bi(III) complex (4ES)Bi(NO$_3$) **2**. For clarity, only the relevant part of one symmetrically related molecule forming the dimer is shown (shaded); the labeling # refers to the symmetrical related molecule.

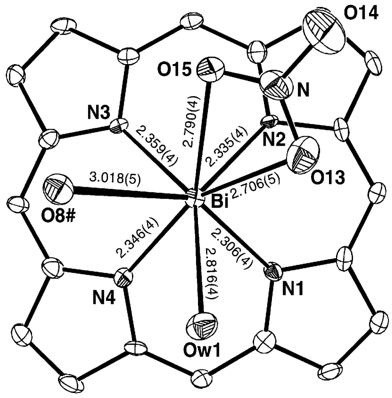


Fig. 2 Polyhedron coordination view of the bismuth in (4ES)Bi(NO)$_3$ **2**.

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symmetrically related macrocycle, thus forming a centrosymmetric dimer in the solid state (Fig. 1). The Bi atom lies 1.125 Å above the N_4 plane and the mean Bi–N bond length is 2.34(2) Å, similar to those observed in (OEP)Bi(SO_3CF_3)[9] which also adopts a centrosymmetric dimeric form [ΔN_4 = 1.07 Å and $<$Bi–N$>$ = 2.31(1) Å]. The Bi–O bond lengths [2.706(5) and 2.789(4) Å] are larger than the sum of their ionic radii (1.13 + 1.40 = 2.53 Å)[14] for the bonds with the nitrate anion O13 and O15, respectively), 2.816(5) Å with the oxygen of the water molecule (Ow1) and 3.018(5) Å with the oxygen atom of the carbonyl group (O8#). This later value is large but, to the best of our knowledge, this type of bond between a Bi atom and an ethoxycarbonyl group is unprecedented, however such a large distance is observed in the (OEP)Bi(SO_3CF_3) dimer[9] where a Bi–O distance of 2.98(2) Å was found between the Bi atom and a triflate oxygen atom. A second water molecule (Ow2) is present in the cage and as shown in Fig. 1, both water molecules are engaged in an intra- and inter-molecular hydrogen bond net, contributing to the stability of the dimer. One arm of the molecule does not participate in any interaction and thus exhibits a regular conformation. As reported above, one arm participates to the coordination sphere of the Bi atom, belonging to the second molecule of the dimer, and the two remaining arms involved in the hydrogen bond net with Ow1 and Ow2, adopt folded conformations.

As it is of interest to know if this particular structure is also plausible in solution, the complex **2** has been studied by NMR spectroscopy. A previous variable temperature ^{1}H NMR study[8] has been made on the compound [Bi(TTP)]NO_3 investigating the aromatic protons of the tolyl groups. The slow rotation of aryl groups of this complex induced broadened signals at room temperature, whereas at low temperature the signal of the tolyl protons were split. In our complex, at 300 K, the methylene protons of the ester groups appear at δ 3.37 as a broad singlet whereas at 290 K, these protons become magnetically non-equivalent, as two singlets at δ 3.31 and 3.39, the same observation being made for the methyl group. It is of note that a 1 : 3 intensity ratio is observed instead of the 1 : 2 : 1 expected. When the temperature decreases, we can clearly see that the pendant arm of the porphyrin is not in the same magnetic environment as the three others, as shown by the integration of the signal. The same temperature dependence is observed for the aromatic protons of the phenyl rings, with the exception of the apparent triplet at δ 7.90 ppm.[15] These observations suggest an unsymmetrical geometry around the Bi(III) ion involving one arm of the porphyrin, which is plausible with the radiocrystallographic structure of 4ESBi(NO_3) **2**. However, the geometry of the molecule is not exactly the same in solution as in the solid state. It seems that the dimer is broken in solution. Indeed, the protons of the pendant arm if bonded to the bismuth *via* the carbonyl, would be strongly upfield shifted because of their localization in the anisotropic current of the porphyrin. As all the aliphatic protons are normally shifted between 0.5 and 3.5 ppm, the ^{1}H NMR spectrum is in accord with a monomer complex in which one of the ‘picket’ groups is able to interact with the metal.

In conclusion, this new bismuth(III) porphyrin demonstrates that the metal can be stabilized by the presence of a suitable coordination sphere, and particularly by oxygen-donor groups. Indeed, in the reported complex, even if the ethoxycarbonyl groups are not ideal in stabilizing the complex, their spatial arrangement seem to be sufficient to increase the rate of metallation and the stability of the complex. Work is now in progress to characterize corresponding analogues with carboxylate picket groups and to study their coordination around Bi(III).

Notes and references

† *Selected data* for 4ESH$_2$ **1**: yield 93%. Anal. Calc. for $C_{68}H_{66}N_8O_{12}\cdot CH_3OH$: C, 67.97; H, 5.79; N, 9.19. Found: C, 68.25; H, 5.44; N, 9.33%. MS (FAB): *m/z* 1187.8 [$(M+H)^+$, 100%]. UV–VIS (CH_2Cl_2): λ_{max}/nm (log ε/dm^3 mol^{-1} cm^{-1}): 419 (5.52), 514 (4.3), 546 (3.76), 588 (3.83), 643 (3.58). δ_H(500 MHz, $CDCl_3$, 323 K): 8.86 (s, 8H, β-pyr), 8.59 (d, *J* 7.09 Hz, 4H, arom.), 8.00 (d, *J* 5.75 Hz, 4H, arom), 7.86 (t, *J* 7.58 Hz, 4H, arom), 7.55 (t, *J* 7.21 Hz, 4H, arom), 7.19 (s, 4H, –NHCO), 3.47 (br s, 8H, CH_2CH_3); 2.18 (t, *J* 6.72 Hz, 8H, CH_2CH_2), 1.65 (br s, 8H, CH_2CH_2), 0.82 (br s, 12H, CH_2CH_3), −2.59 (s, 2H). For (4ES)Bi(NO_3) **2**: yield 85%. Anal. Calc. for $C_{68}H_{64}BiN_9O_{15}\cdot 2H_2O$: C, 54.73; H, 4.59; N, 8.45. Found: C, 55.16; H, 4.47; N, 8.27%. MS (FAB): *m/z* 1393.8 [$(M - NO_3)^+$, 100%]. UV–VIS (CH_2Cl_2): λ_{max}/nm(log ε/dm^3 mol^{-1} cm^{-1}): 354 (4.62), 472 (5.25), 598 (3.99), 644 (3.92). δ_H(500 MHz, $CDCl_3$, 300 K): 9.24 (s, 8H, β-pyr), 8.68 (br s, 4H, arom), 8.22 (br s, 3H, –NHCO), 8.13 (br s, 1H, –NHCO), 7.89 (m, 4H, arom); 7.90 (t, *J* 7.7 Hz, 4H, arom); 7.56 (br s, 4H, arom), 3.46 (br s, 2H, CH_2CH_3), 3.32 (br s, 6H, CH_2CH_3), 2.04 (br s, 8H, CH_2CH_2), 1.92 (br s, 8H, CH_2CH_2), 0.96 (br s, 3H, CH_2CH_3); 0.87 (s, 9H, CH_2CH_3).

‡ *Crystal data*: $C_{68}H_{64}BiN_9O_{15}\cdot 2H_2O$, M = 1492.3, triclinic, space group $P\bar{1}$, a = 14.3980(4), b = 14.9790(4), c = 16.5670(4) Å, α = 116.205(1), β = 97.2490(11), γ = 92.6720(12)°, V = 3159.02(14) Å^3, Z = 2, D_c = 1.569 g cm^{-3}, $F(000)$ = 1516. Data were collected at 110 K on a Nonius Kappa CCD diffractometer with Mo-Kα radiation (λ = 0.7173 Å). The structure was solved by the mean of a Patterson search program[16] and refined by full-matrix least squares on F^2 (14 332 unique reflections, 1054 parameters). The anisotropic refinement led to final residuals $wR2$ = 0.101 for all data and $R1$ = 0.055 for 10 533 intensities with $I > 2\sigma(I)$, and GOF = 1.028. The largest $\Delta(\rho)$ residual densities are 1.36 and −1.69 e Å^{-3}.

CCDC 182/1715. See http://www.rsc.org/suppdata/cc/b0/b004394j/ for crystallographic files in .cif format.

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