

Synthesis, characterisation and properties of bismuth(III) ester pendant arm picket porphyrins †

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A series of porphyrins bearing ester pendant arms has been synthesised. The number of potential coordinating groups was varied from one to four. In the case of the four-picket compounds, the arm length was also investigated. Structural properties towards the coordination of the bismuth(III) cation were studied. In the particular case of the two-picket molecules, the substitution isomers (5,10 or 5,15) were also prepared. An improvement of the rate of metallation was detected in the case of the single-picket porphyrin.

Introduction

Bismuth is commonly used in antiulcer¹ and antibacterial drugs and it has recently revealed potential interest in cancer therapy.² ²¹²Bi and ²¹³Bi isotopes, which have short half-lives of 61 and 46 min, respectively, are α and β -particle and γ -ray emitters. Due to its high linear energy transfer, α -particle decay is particularly promising for tumour destruction. ²¹³Bi produces α and β -particles along with low energy γ -rays and this latter property makes ²¹³Bi a rather preferred element in radiotherapy.³

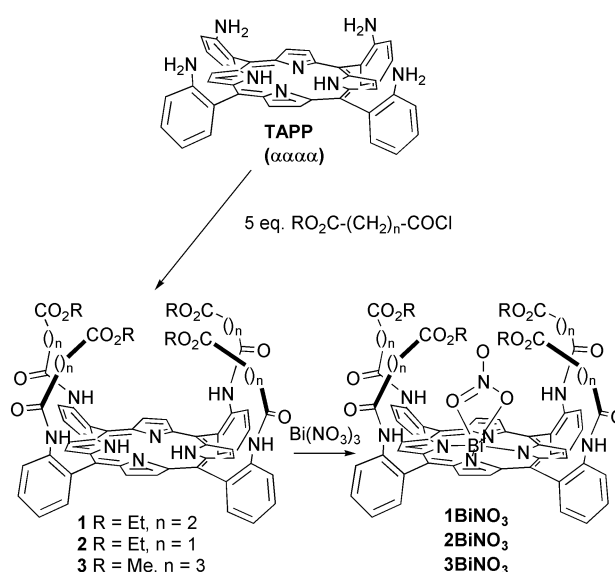
Bi^{III} and Bi^V are the two common oxidation states of the element. The chemistry of Bi^{III} has been largely more developed and has led to synthesis of numerous complexes with coordination number varying from three to nine.⁴ Its affinity with nitrogen and oxygen atoms makes bismuth a good candidate for complexation with chelators and macrocycles such as diethylenetriaminepentaacetic acid (DTPA) and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA).⁵ The high thermodynamic constants obtained for these complexes have led us to investigate the reactivity of bismuth with porphyrins.

Bismuth porphyrins are not very widespread but a few exist and have been fully characterised. First examples reported were from Treibs in 1969 and Buchler in 1974.⁶ Since then, Brothers and co-workers⁷ as well as Guillard and co-workers⁸ have investigated the complexation of bismuth with numerous porphyrins. In parallel to the work of Brothers and co-workers, we have developed a route with porphyrins bearing potentially coordinating pendant arms.⁹ These arms are directed in a perpendicular fashion with respect to the porphyrin macrocycle and offer the possibility of bending in order to satisfy the metal coordination sphere. In a recent communication we discussed the crystal structure of a four-ester arm bismuth porphyrin in which one carbonyl oxygen belonging to an identical neighbouring porphyrin binds to the bismuth atom. Herein we report the synthesis and characterisation of a series of ester arm porphyrins along with their bismuth derivatives.

Results and discussion

This study was originally motivated by a report from Buckingham *et al.* dealing with the rapid insertion of different metals such as copper in a porphyrin.¹⁰ This publication described the reaction of *meso*(tetra-*o*-aminophenyl)porphyrin (atropisomer *aaaa*, TAPP) with maleic anhydride, leading to a

four-picket porphyrin, although no full characterisation of the product was supplied. We reasoned on that if we were able to obtain comparable increase in metallation rate with the bismuth(III) cation, the porphyrin could become a compatible ligand for a use in α -radiotherapy; reminding that the half-life time of ²¹³Bi is only of 46 min.³ Study of the same type of porphyrins was therefore investigated, with ours bearing ester pendant arms as depicted in Scheme 1. Assuming that if the pickets were indeed flexible enough, they could coordinate and presumably stabilize the bismuth within the macrocycle. It is evident that the picket length is a decisive structural parameter. Thus, we prepared three different porphyrins by the reaction of commercially available acyl chlorides with *aaaa*-TAPP. The acylation reagents were the single acyl chloride of ethyl malonyl (EM) acid, ethyl succinyl (ES) acid and methyl glutaryl (MG) acid. Such compounds are readily synthesised and the yields almost quantitative. Metal insertion was achieved by heating with a solution of bismuth nitrate (10 equiv.) in pyridine at 50 °C for 2 h. It is worth noting that these conditions are relatively gentle compared to the usual preparation of bismuth porphyrins, *e.g.* overnight reflux in pyridine or benzonitrile. The different complexes were purified by chromatography on silica-gel and eluted with MeOH-CH₂Cl₂. During this process, formation of free-base porphyrin was scarcely observed from bismuth release unlike previously reported for unfunctionalized porphyrins.⁷



Scheme 1 Bismuth coordination to the four-ester porphyrins.

† Electronic supplementary information (ESI) available: characterisation data for the remainder of the compounds. See <http://www.rsc.org/suppdata/dt/b3/b308776j/>

Additionally, as shown by the proton NMR data, the C_4 symmetry of the different complexes is retained as no atropisomerisation occurred. The metallation rate was monitored by UV-visible spectroscopy. The Soret band of the bismuth porphyrin appears around 470 nm as shown on Fig. 1 for the formation of 1BiNO_3 , the latter possessing four pickets of the ES type. After 90 min, metal insertion is complete as indicated by the loss of free-base Soret band at 420 nm. Although certainly not sufficient for an effective use in therapy as 75% of the activity would be lost after such a period, this result represents a significant improvement compared to porphyrins such as tetraphenylporphyrin (TPP) which requires elevated temperatures and 6 h of stirring.

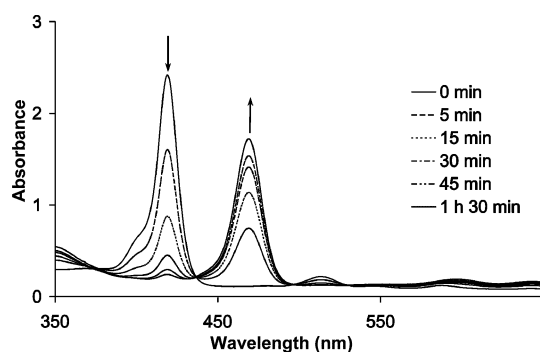


Fig. 1 Monitoring of bismuth insertion in 1.

On the other hand, the same study applied to **2** and **3** did not lead to significant variation in time of metallation. This observation seems inconsistent with our first hypothesis that folding of the pickets helps to stabilize the metal. In the case of the ethyl succinyl picket, we were able to obtain single crystals suitable for X-ray study. These were obtained by slow diffusion of H_2O – MeOH onto a saturated THF solution of 1BiNO_3 . The ORTEP¹¹ plot of the X-ray structure is shown in Fig. 2.⁹

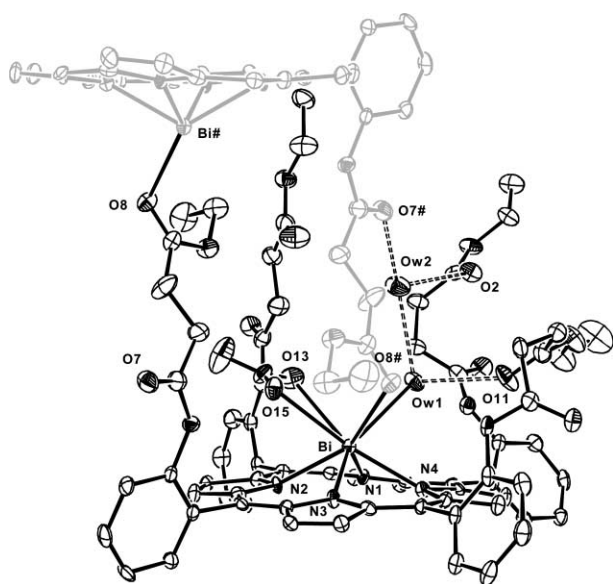


Fig. 2 Molecular structure of the 1BiNO_3 dimer showing the two macrocycles related to each other by the coordination of their respective ester arm. The dotted lines illustrate the hydrogen bonding mode between coordinated and inclusion water molecules. Hydrogen atoms have been omitted for clarity.

The Bi^{III} is eight-coordinate with a slightly distorted square-antiprismatic geometry, Fig. 3. The four nitrogen atoms of the macrocycle form a square, with 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

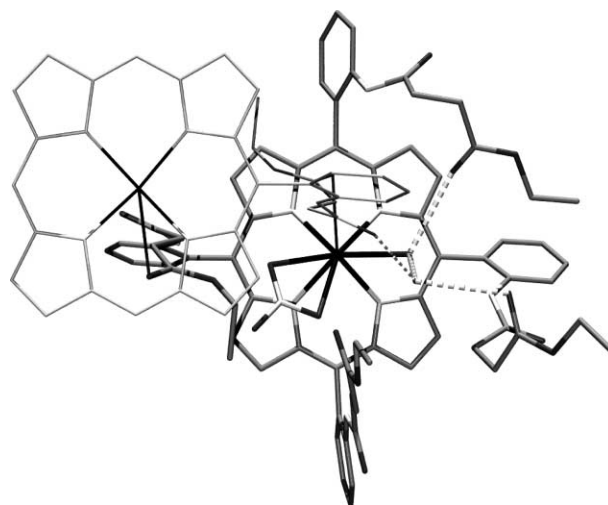


Fig. 3 Top view of the 1BiNO_3 dimer illustrating clearly the antiprismatic conformation around the bismuth centre and also the displacement of the two macrocycles to each other.

belonging to an arm attached to a symmetrically related macrocycle, forming in this way, a centrosymmetric dimer in the solid state. In contrast to the previously reported X-ray structure of $(\text{OEP})\text{Bi}(\text{SO}_3\text{CF}_3)_3$,⁸ the bridge between the two porphyrins is not built by coordination of the counter-anion but by the intramolecular coordinating group, namely the carbonyl of the ester group. The Bi atom lies 1.125 Å above the four-nitrogen plane and the mean Bi–N bond length is 2.34(2) Å; these values are similar to those observed in $(\text{OEP})\text{Bi}(\text{SO}_3\text{CF}_3)_3$ which also adopts a centrosymmetric dimeric form ($\Delta 4\text{N} = 1.07$ Å and $\langle \text{Bi}-\text{N} \rangle = 2.31(1)$ Å). The Bi–O bond lengths are larger than the sum of their ionic radii ($1.13 + 1.40 = 2.53$ Å);¹² 2.706(5) and 2.789(4) Å for the bonds with the nitrate anion (respectively with O13 and O15), 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#). A second water molecule (Ow2) is present in the cage and as shown in Fig. 2, both water molecules are engaged in an intra- and inter-molecular hydrogen bonding network, 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 mentioned 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 bonding network with Ow1 and Ow2, adopt folded conformations. The porphyrin core is not planar and adopts a dome distortion and this is especially reflected by the deviation of the eight β -pyrrolic carbon atoms.¹³ These can be separated by up to 0.312 Å from the porphyrin mean base plane, with an average deviation of 0.138 Å. This is the result of the out-of-plane coordination of the metallic cation.

Fig. 3 illustrates the displacement of the two macrocycles relative to one another. Reported X-ray structures of bismuth porphyrins have always shown dimers with close superimposition of the macrocycles.⁷ In our case the rings are horizontally separated by a significant 7.240 Å. The figure shows also the coordinating ester arms are positioned right through the anisotropic current of the porphyrin. The natural edged position of the ester arms on each porphyrin undoubtedly favours this displacement.

In an attempt to uncover the possibility for this dimeric assembly to exist in solution, ^1H NMR spectroscopy for 1BiNO_3 was studied. Variable-temperature NMR spectra are shown in Fig. 4. At 300 K, the methylene protons of the ester groups appear at 3.37 ppm as a broad singlet whereas at 290 K, they become magnetically non-equivalent with two singlets at 3.31 and 3.39 ppm. The same observation is

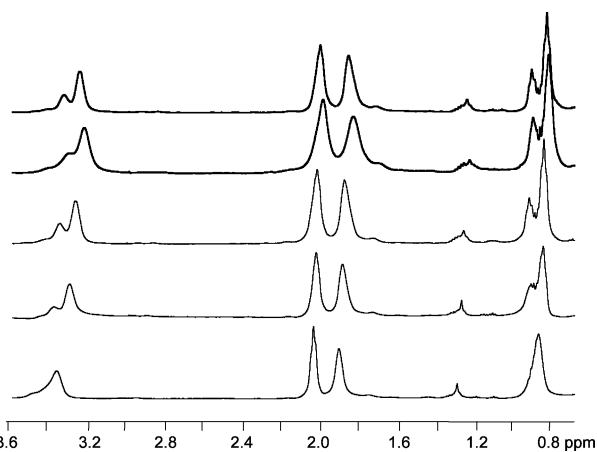


Fig. 4 Variable-temperature ^1H NMR for 1BiNO_3 in the 0–4 ppm region.

made for the methyl group at 0.85 ppm. It is worth mentioning that a 1 : 3 intensity ratio is observed instead of an expected 1 : 2 : 1.

As the temperature decreases, one can clearly assess that a single pendant arm of the porphyrin is in a different magnetic environment than 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 7.90 ppm.¹⁴ These observations have led us to suspect an unsymmetrical geometry around the Bi^{III} ion involving one arm of the porphyrin. This is somewhat compatible with the X-ray crystallographic structure of 1BiNO_3 , although it is not clear whether or not geometries are identical in solution and in solid state. However, it seems more probable that the dimer does not exist in solution. Indeed, the protons of the pendant arm bound to the bismuth *via* the carbonyl oxygen, would be expected to be strongly shifted upfield because of their localization in the anisotropic current of the porphyrin and this shift is not observed. All the aliphatic protons are normally shifted between 0.5 and 3.5 ppm and therefore the ^1H NMR spectrum is in agreement with a monomeric complex in which only one of the picket is capable of interacting with the metal.

As mentioned earlier, the length of the pickets has no notable effect on both the metallation rates by $\text{Bi}(\text{NO}_3)_3$ and the stability of the complex. It was therefore then logical to investigate the influence of the number of ester pickets.

To do so, we have undertaken the synthesis and characterization of four other picket porphyrins **8–11** bearing respectively three, two, two and one ester picket on the same side of the porphyrin plane (Scheme 2). The synthesis is preceded by one step consisting of the protection of the undesired amino functions. Thus, *ααα*-TAPP was allowed to react with 1.8 equiv. acetyl chloride and all possible products were obtained, from the single acetylated to the three acetylated. The four-acetylated porphyrin is only present as a trace on TLC plates. The problem with this synthesis is that the two acetylated porphyrins **5** and **6** are not isolable separately at this stage and acylation by the ethyl succinyl chloride is needed in order to be able to separate products. Unfortunately, even on a 500 MHz ^1H NMR spectrum, the expected patterns for the 5,15 and 5,10 isomers **9** and **10** are not observed. Indeed, for the 5,15 diacetylated ligand **9**, one would expect to obtain two doublets, each integrating for 4H and in the case of the 5,10 disubstituted porphyrin **10**, four doublets integrating for 2H each.

In order to clarify the ambiguity surrounding the two isomers, porphyrin **9** was synthesized by an alternative route depicted in Scheme 3. This route is unambiguous as the ^1H NMR spectrum of **13** exhibits two expected doublets at 8.99 and 8.84 ppm with the typical β -pyrrolic coupling constant of 4.7 Hz.¹⁵

The metal insertion in these four new compounds was achieved using the same procedure to that of the preparation of 1BiNO_3 . Products were also purified by chromatography on silica gel with MeOH–methylene chloride and this occurred without any significant demetallation. This indicates that the stabilities of these bismuth picket porphyrins are not seriously affected by the number of ethyl succinyl pickets although isomer 10BiNO_3 seems slightly more stable than the other complexes during chromatography. Metallation kinetics were followed by UV-visible spectroscopy and again, we applied the same strategy to that of 1BiNO_3 . For all ligands but one, the metal insertion was found to be complete after 2 h in pyridine at 50 °C. Surprisingly, the reaction was found to be faster in the case of porphyrin **11** bearing one picket only, Fig. 5. In the same conditions of solvent and temperature, the metallation reaction was complete after only 45 min. This increase in rate may be attributed to the lack of steric hindrance above the macrocycle making metal insertion faster. Indeed, in the X-ray structure of 1BiNO_3 , only one picket binds directly to the bismuth. If we assume that the same binding mode exists also in 11BiNO_3 , the same stabilization of the metal occurs but with much faster rates.

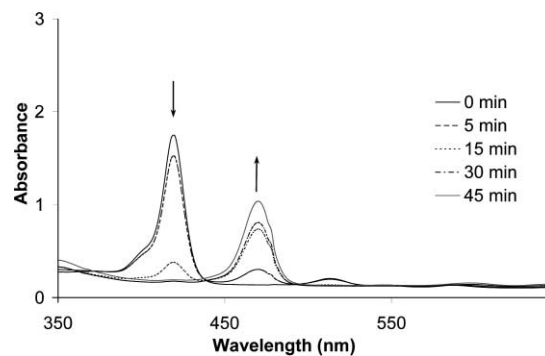
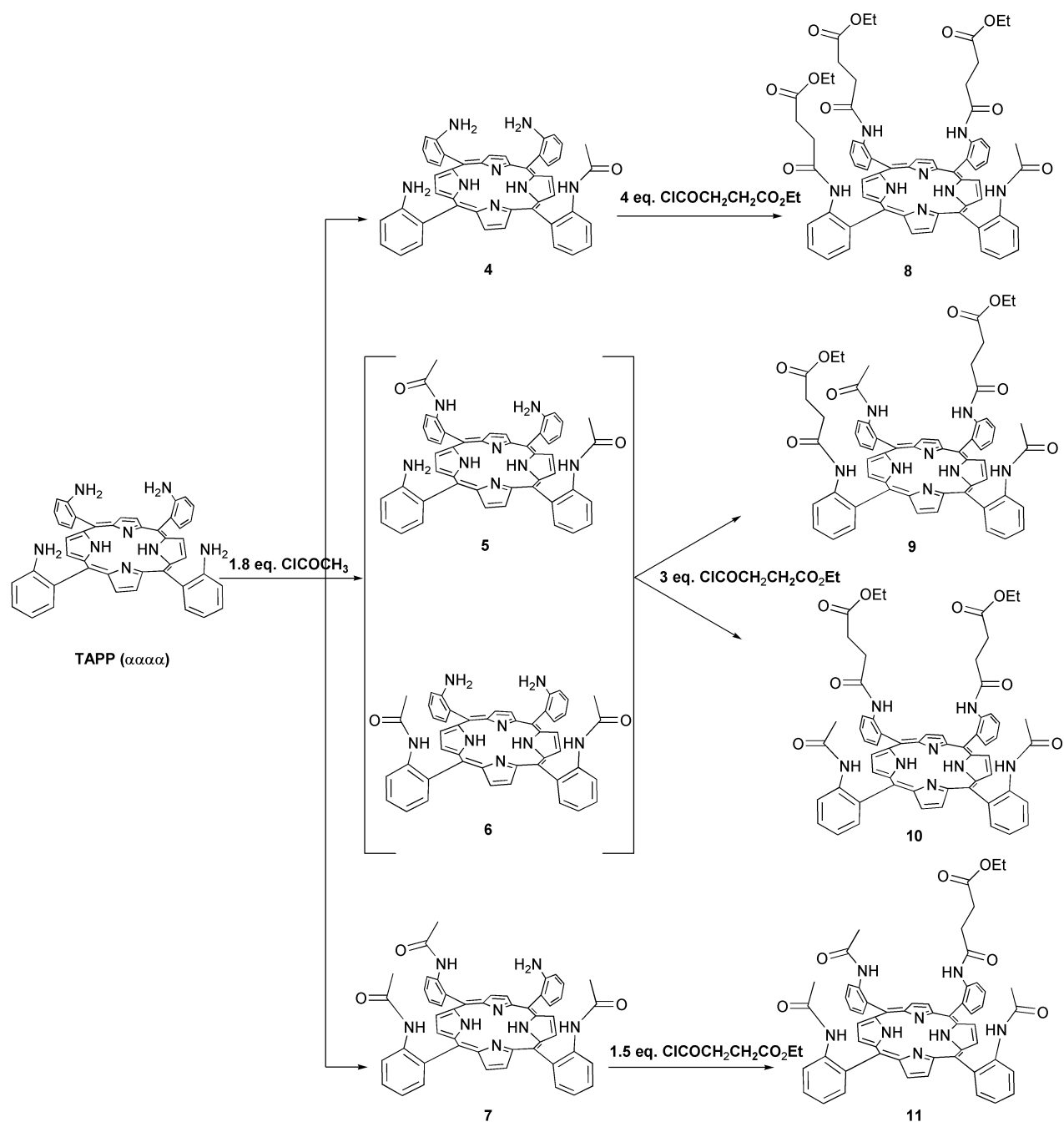


Fig. 5 Monitoring of bismuth insertion in **11**.

In conclusion, we have explored possibilities of bismuth complexation by ester arm picket porphyrins. We have shown that tethering at least one ester picket above the porphyrin plane stabilizes the complex enough and enables us to fully characterise products. For the four-picket porphyrin, this stabilization may be explained by the dimeric edifice in which a reciprocal coordination of the metals is ensured by one carbonyl from an ester function. In the case of the two-picket porphyrins, without an X-ray structure, it is more difficult to rationalise the greater stability of the 5,10 isomer. Additionally, the rate of metallation is neither affected by the length of the picket nor by their relative positions but most certainly by the lack of steric hindrance. With the one-ester arm porphyrin **11**, it seems that we have found a good balance between the thermodynamic stability and the rate of bismuth insertion.

Experimental

General considerations. ^1H (500.13 MHz, 300.13 MHz) NMR spectra were recorded on Bruker Avance spectrometers and referenced to the residual protonated solvent. Mass spectra were performed on a MS/MS ZABSpec TOF spectrometer at the University of Rennes I (C.R.M.P.O.). UV-visible spectra were recorded on a Varian Cary 1E and an Uvikon XL spectrometers. Infrared spectra were recorded on Bruker IFS 66 and 28 spectrometers. All solvents (ACS for analysis) were purchased from Carlo Erba. THF was distilled from potassium metal whereas methanol was distilled from magnesium turnings; CH_2Cl_2 was used as received. Triethylamine was distilled from CaH_2 . The starting materials were generally used as received (Acros, Aldrich) without any further purification. All reactions were performed under an argon atmosphere and monitored by



Scheme 2 Synthetic pathway to the desired acetyl-ester porphyrins.

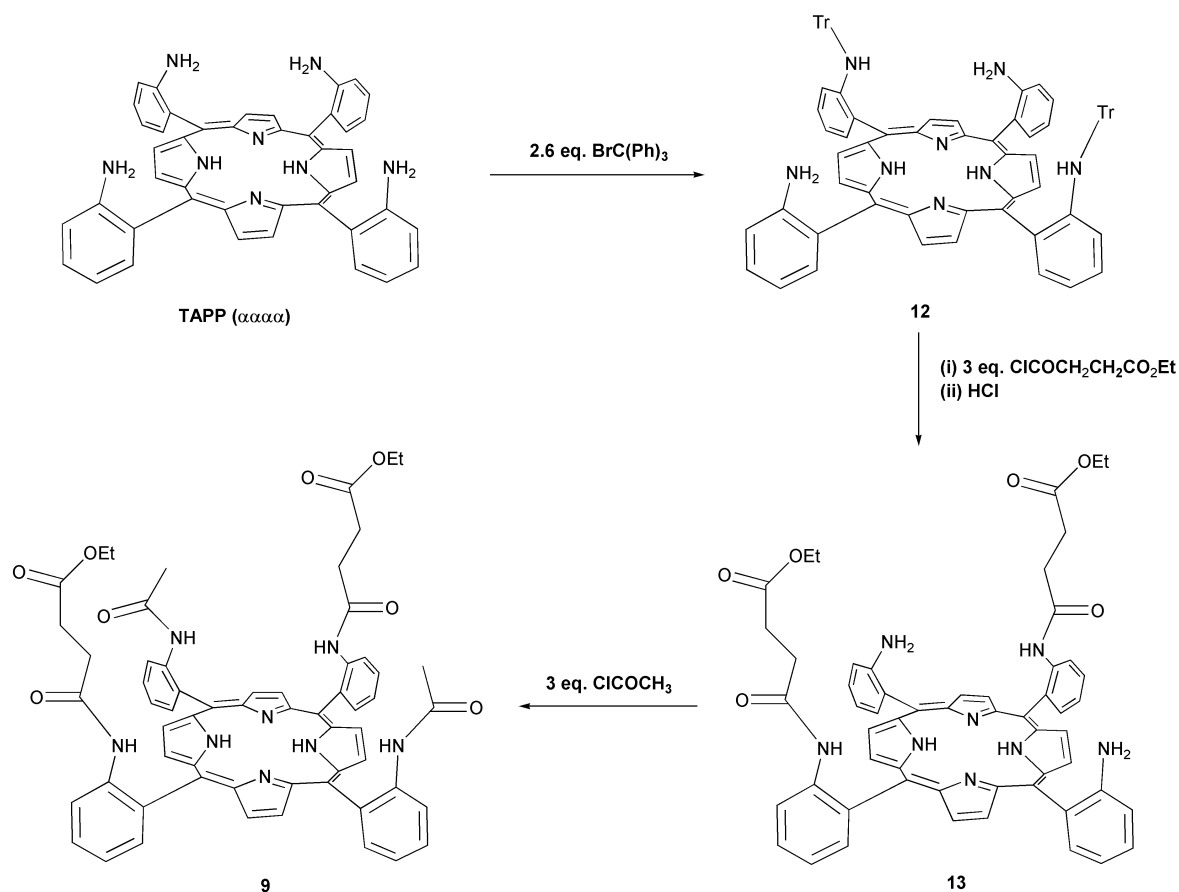
TLC (silica, CH_2Cl_2 -MeOH). Column flash chromatography was performed on silica gel (Merck TLC-Kieselgel 60H, 15 μm). Elemental analyses were obtained on an EA 1108 Fisons Instrument.

Typical procedures

α -5,10,15,20-Tetrakis{2-[3-(ethoxycarbonyl)propionylamido]-phenyl}porphyrin 1. TAPP (0.2 g, 0.3 mmol) was dissolved in 20 mL freshly distilled THF under argon. 10 equivalents anhydrous Et_3N were added and the mixture was cooled to 0 °C. Ethyl succinyl chloride (5 equiv.) was then added and the solution stirred overnight. The solvent was evaporated to dryness and the residue dissolved in a minimum of CH_2Cl_2 to be poured on a silica gel chromatography column. The product was eluted with 0.1% CH_3OH - CH_2Cl_2 and obtained in 93% yield (330 mg, 0.28 mmol). Microanalysis: $\text{C}_{68}\text{H}_{66}\text{N}_8\text{O}_{12} \cdot \text{CH}_3\text{OH}$, found (calc): C, 68.25 (67.97); H, 4.44 (4.79); N, 9.33 (9.19)%. FAB-MS: $m/z = 1187.8$ [$\text{M} + \text{H}$] $^+$. FTIR (KBr, cm^{-1}): 1731 (CO)_{ester}, 1694 (CO)_{amide}. UV-VIS (CH_2Cl_2 , λ/nm , 10^{-3}e/l

$\text{M}^{-1} \text{cm}^{-1}$): 419 (337), 514 (20.9), 546 (5.8), 588 (6.7), 643 (3.7). ^1H NMR (CDCl_3 , 323 K, 500 MHz): δ_{H} 8.86 (8H, s, β -pyr), 8.59 (4H, d, $J = 7.1$ Hz, arom), 8.00 (4H, d, $J = 7.5$ Hz, arom), 7.86 (4H, t, $J = 7.6$ Hz, arom), 7.55 (4H, t, $J = 7.2$ Hz, arom), 7.19 (4H, s, -NHCO), 3.44 (8H, br s, $-\text{CH}_2\text{CH}_3$), 2.18 (8H, t, $J = 6.7$ Hz, $-\text{CH}_2\text{CH}_2$), 1.70 (8H, br s, $-\text{CH}_2\text{CH}_2$), 0.79 (12H, br s, $-\text{CH}_2\text{CH}_3$), -2.59 (2H, s, -NH pyr). ^{13}C NMR (CDCl_3 , 300 K, 125 MHz): δ_{C} 172.6, 170.1, 138.7, 135.4, 132.1, 130.3, 123.9, 122.9, 115.5, 60.7, 31.5, 29.0, 14.1.

1BiNO_3 . In a 50 mL flask, **1** (26 mg, 0.02 mmol) was dissolved in 7 mL pyridine. This was warmed up to 55 °C before $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ (100 mg, 0.2 mmol) was added. We note here that 10 equivalents of the bismuth salt were necessary for all the following metallation reactions. After 2 h heating, the solvent was evaporated and dissolved in a minimum of CH_2Cl_2 to be poured on a silica gel chromatography column. The product was eluted with 1.2% CH_3OH - CH_2Cl_2 and obtained in 85% yield (25 mg, 0.017 mmol). Microanalysis: $\text{C}_{68}\text{H}_{64}\text{BiN}_9\text{O}_{15} \cdot 2\text{H}_2\text{O}$, found (calc): C, 55.16 (54.73); H, 4.47 (4.59); N, 8.27



Scheme 3 Alternative route to porphyrin 9.

(8.45)%. FAB-MS: $m/z = 1393,8$ $[\text{M} - \text{NO}_3]^+$. UV-VIS (CH_2Cl_2 , λ/nm , $10^{-3}\epsilon/\text{M}^{-1}\text{cm}^{-1}$): 354 (42.4), 472 (176.9), 598 (9.8), 644 (8.3). FTIR (KBr, cm^{-1}): 1732 (CO)_{ester}, 1695 (CO)_{amide}, 1384 (NO_3), 991 (Bi–N(por)). ^1H NMR (CDCl_3 , 300 K, 500 MHz): δ 9.24 (8H, s, β -pyr), 8.68 (4H, br s, arom), 8.22 (3H, br s, $-\text{NHCO}$), 8.13 (1H, br s, $-\text{NHCO}$), 7.89 (4H, m, arom), 7.90 (4H, t, arom), 7.56 (4H, br s, arom), 3.46 (2H, br s, $-\text{CH}_2\text{CH}_3$), 3.32 (6H, br s, $-\text{CH}_2\text{CH}_3$), 2.04 (8H, br s, $-\text{CH}_2\text{CH}_2$), 1.92 (8H, br s, $-\text{CH}_2\text{CH}_2$), 0.96 (3H, br s, $-\text{CH}_2\text{CH}_3$), 0.87 (9H, s, $-\text{CH}_2\text{CH}_3$). ^{13}C NMR (CDCl_3 , 300 K, 125 MHz): δ_{C} 173.5, 170.8, 149.3, 140.4, 134.9, 133.5, 131.3, 130.6, 123.6, 123.1, 122.7, 119.3, 60.8, 31.5, 29.5, 14.1.

Crystallography for 1BiNO_3

Crystallographic details for 1BiNO_3 have already been reported in ref. 9. Crystal data: $\text{C}_{68}\text{H}_{64}\text{BiN}_9\text{O}_{15}\cdot 2\text{H}_2\text{O}$, $M = 1492.3$, triclinic, space group $P\bar{1}$, $a = 14.3980(4)$, $b = 14.9790(4)$, $c = 16.5670(4)$ Å, $\alpha = 116.205(1)$, $\beta = 97.2490(11)$, $\gamma = 92.6720(12)^\circ$, $V = 3159.02(14)$ Å³, $Z = 2$, $D_{\text{c}} = 1.569$ g cm⁻³, $F(000) = 1516$. Data were collected at 110 K on a Nonius Kappa CCD diffractometer with Mo-K α radiation ($\lambda = 0.71073$ Å). The structure was solved by a Patterson search program and refined by full-matrix least-squares method on F^2 (14332 unique reflections, 1054 parameters). The anisotropic refinement led to final residuals $wR2 = 0.101$ for all data and $R1 = 0.055$ for 10533 intensities with $I > 2\sigma(I)$, and $\text{GOF} = 1.028$. The largest $\Delta(\rho)$ residual densities are 1.36 and -1.69 e Å⁻³.

CCDC reference number 149483.

See <http://www.rsc.org/suppdata/dt/b3/b308776j/> for crystallographic data in CIF or other electronic format.

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