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Functionalization of Porphyrins: Mechanistic Insights, Conformational Studies, and Structural Characterizations[‡]

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The condensation of 3-chloromethylbenzoyl chloride with three atropisomers of *meso*-5,10,15,20-tetrakis(2-aminophenyl)porphyrin (TAPP) is reported, followed by the reaction of the anion of diethyl malonate to prepare various strapped porphyrins. According to two different geometries of the straps, the resulting preorganization of the hanging ethoxycarbonyl groups is more or less adapted to the coordination of cations such as lanthanides. The conformational study, as well as the X-ray structures of three strapped porphyrins, demonstrate that among the three atropisomers investigated in this work, only two of them lead to strapped porphyrins in which an ethoxycarbonyl group is directed towards the centre of the porphyrin. Additionally, we were able to explain some peculiar reactivities observed for single-strapped porphyrins, as the 5–15 strapped geometry is shown to be favoured.
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Introduction

The coordination chemistry of various elements plays a crucial role in the chemistry of life, and metal complexes have been used in medicine for more than a century.[1] For instance, various chelates[2] have been discovered and applied in clinical use as diagnostic[3] or therapeutic agents in the domain of radiopharmaceuticals, or in chelation therapy for the control of several elements.[4–8] Among these metal complexes, cisplatin is one of the most widely used anticancer drugs, along with the second-generation drug, carboplatin. Several gadolinium complexes have been clinically approved and widely used, such as Magnevist or Dotarem. These drugs are based on the well known ligands [(2-{(2-[bis(carboxymethyl)amino]ethyl)carboxymethylamino}-ethyl)carboxymethylamino]acetic acid (DTPA) and [4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetic acid (DOTA), respectively. In the area of radioimmunotherapy, where the use of β-emitter elements is clinically approved, for instance, with yttrium DOTA-type complexes,[9,10] the application of α-emitter elements against isolated cell diseases is still to be validated.[11–13] In our continuing interest to develop new preorganized macromolecules to coordinate and stabilize different elements, we have focused our attention on the coordination of α-emitter elements. Indeed, because of its very short range in tissues (70 μm) and to its high linear energy transfer (200 keV/μm), α-emission becomes attractive in nuclear medicine.[14,15] Among the three plausible candidates for such a therapy (At, Ac and Bi), we began to explore the coordination chemistry of bismuth inside porphyrins.[16–19] We have shown that picket porphyrins bearing ester groups lead to stable bismuth dimers, thereby carrying two metal atoms at a time.[20] We report in this work the synthesis and structural characterization of highly preorganized strapped porphyrins bearing hanging ethoxycarbonyl groups.

Results and Discussion

We have reported that the reaction of 3-(chloromethyl)-benzoyl chloride with the atropisomers ααββ, αααα and αααβ of TAPP,[21] followed by the nucleophilic attack of either the anion of diethyl malonate or imidazole/benzimidazole lead, among others, to porphyrinic architectures **1**, **2**, and **7**.[22] Therefore, we have reinvestigated the synthesis of

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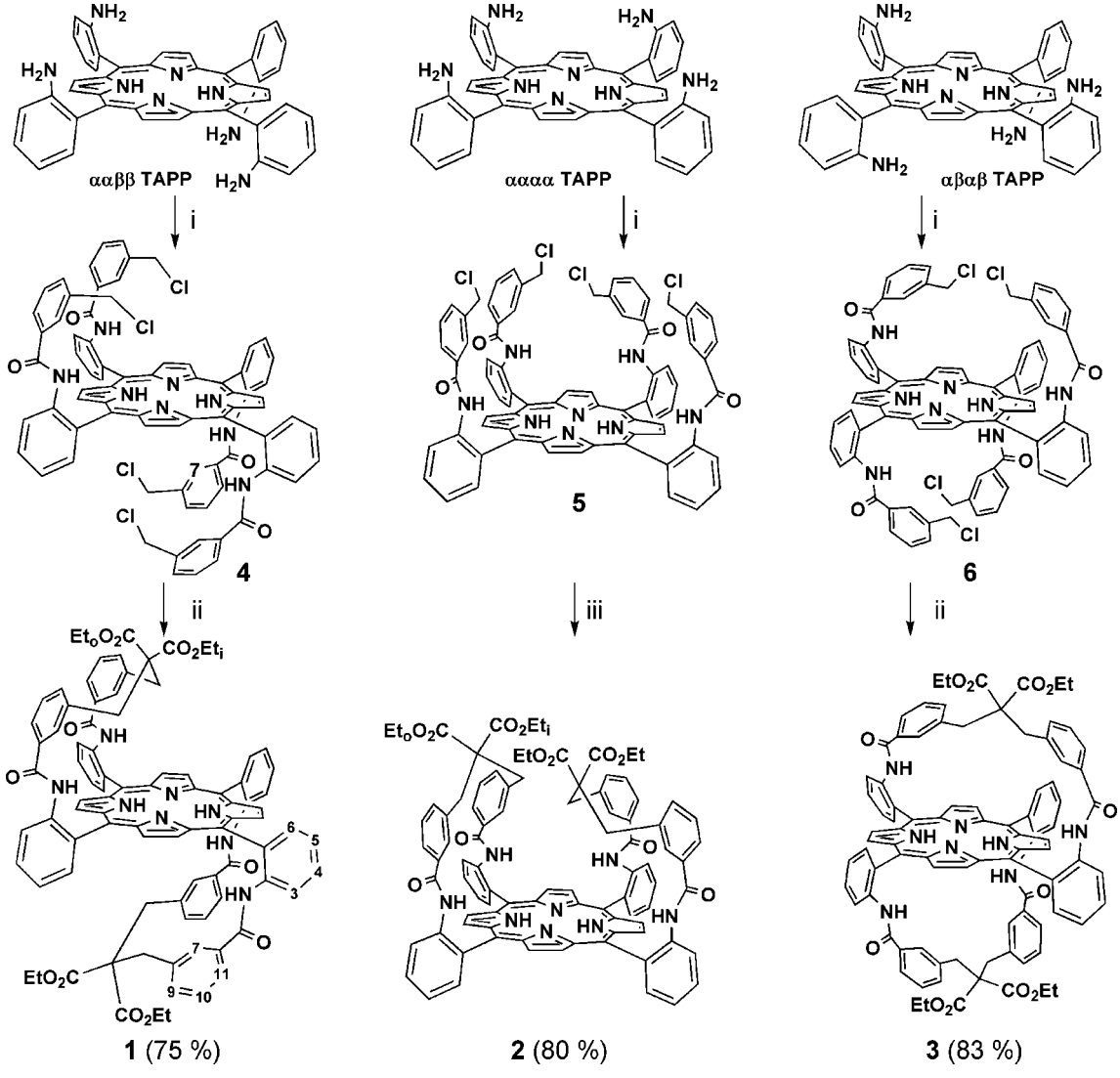
the porphyrins resulting from the reaction of diethyl malonate with the 3-(chloromethyl)benzoylamino-phenyl picket porphyrins, and we also extended this reaction to the αβαβ atropisomer to obtain the bis-strapped porphyrin **3** (Scheme 1). In our first publication,[22] the peculiar reactivity that we initially observed with the αααα atropisomer led to two compounds, **2** and **7**, differing by the geometry of the strap(s). For instance, when 20 equiv. of sodium diethyl malonate was allowed to react at room temperature with **5**, the single-strap porphyrin **7** was the main product of the reaction (74%). On the other hand, if a large excess of sodium diethyl malonate was used (1000 equiv.), the bis-strapped porphyrin **2** was obtained, almost exclusively, in 80% yield. The X-ray structure of **5** indicates that among the four [3-(chloromethyl)benzoyl]aminophenyl pickets, only one is oriented outside the picket-fence of the porphyrin;[23] thus it was not surprising to observe both geometries. As we and others have shown, these "U-shaped" pickets were preorganized.[24,25] Additionally, being able to control the reaction, according to the experimental conditions, towards the preferential production of either **2** or **7** represented for us an additional advantage. Nevertheless, this intriguing observation prompted us to extensively study this reaction. We already knew that the same reaction with the ααββ atropisomer **4** led exclusively to the bis-strapped porphyrin **1**, as in this atropisomer, the formation of a 5–15 strap is geometrically ruled out.[26] Thus, it was important to elucidate the various factors, presumably steric, which could influence this reaction, as the two geometries are expected to exhibit different properties and efficiency towards the stabilization of a large cation in the porphyrin cavity.

Our first investigation concerned the reactivity of the new "U-shaped" acceptor **6** resulting from the reaction of 3-(chloromethyl)benzoyl chloride with the αβαβ atropisomer of TAPP (Scheme 1). As we had performed the reaction on the ααββ atropisomer **4** to avoid the formation of



Scheme 1. Synthesis of three bis-strapped porphyrins bearing two diethyl malonate units, starting from different atropisomers of TAPP. Left: ααββ, middle: αααα, right: αβαβ. i) 3-(chloromethyl)benzoyl chloride (5 equiv.)/THF/Et_3N/0 °C; ii) $CH_2(CO_2Et)_2$ (20 equiv.)/THF/EtONa/room temperature/2 h; iii) $CH_2(CO_2Et)_2$ (1000 equiv.)/THF/EtONa/room temp./2 h. The subscripted letters, i and o, of the ethyl groups refer to in and out positions.

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the 5–15 strap, we needed a system where we could avoid the competitive formation of the 5–10 and 15–20 straps. Where the atropisomer **5** allows the formation of both geometries of strap, the two other atropisomers **4** and **6** lead to the exclusive formation of the 5–10 strap and 5–15 strap, respectively. Thus, to obtain the bis-strapped porphyrin **3**, 20 equiv. of sodium diethyl malonate were allowed to react with the four-picket porphyrin **6**. The reaction proceeds through the slow addition of porphyrin **6** dissolved in THF to sodium diethyl malonate in ethanol. As only one compound is formed, the yield of isolated porphyrin **3** is relatively high (83%). Unlike what is observed for all the other strapped porphyrins described in this work, the ^{1}H NMR spectrum of **3** remains very simple. The latter is mainly characterized by a broad signal at 1.3 ppm and a triplet at –0.45 ppm in the aliphatic domain, corresponding to the four ethoxy groups, which are equivalent in this compound (Figure 1). The chemical shift of the ethoxy methyl group can be compared with its counterpart in other compounds bearing a 5–15 strap, namely **7**, **8** and **9** (Scheme 2). The main difference between these compounds and porphyrin **3** is the mobility of the strap, as the mobility is expected to increase in the series **7**, **9**, **8** and **3**. Indeed, in **7**, **8** and **9**, the strap is pinched between two pickets, and its mobility is more restrained as the size of the picket increases, see 3-[2,2-bis-(ethoxycarbonyl)ethyl]benzoylamino vs. 3-(chloromethyl)-benzoylamino. In the case of **3**, the swinging motion of the strap can never be hindered by any picket. However, the chemical shifts of the methyl groups from the ester functions in **7**, **8**, **9** and **3** are –0.63, –0.65, –0.77/–0.55[27] and –0.45 ppm, respectively. This data leads to two pieces of clear structural information. First, the change in steric hindrance between the two pickets is not significant. Second, the possibility of oscillation of the 5–15 strap does exist in strapped porphyrin **3** but not in picket-strapped porphyrins **7**, **8**, and **9**. Nevertheless, having analysed this slight difference, we can assume that the 5–15 strap in **3**, for which an X-ray structure was obtained and will be discussed here, is an accurate structural model of its analogue in porphyrins **7**, **8** and **9**.

The two new porphyrins **8** and **9** were easily prepared from picket porphyrin **5** by adding, in one portion, 10 equiv. of sodium diethyl malonate and stopping the reaction after 2 h. The novelty of this procedure consists of being able to obtain mixed porphyrins such as **8** and **9** which bear one or two reactive picket(s), and for which the shape of the binding pocket is known by analogy with porphyrin **3**. One can easily conceive a further functionalization of the 3-(chloromethyl)benzoylamino picket of **9** to link the porphyrin to a monoclonal antibody or to a fluorescent probe. This would lead either to a bifunctional chelate or to a fluorescent ligand.

The major difference in reactivity from the previously described synthesis of bis-strapped porphyrin **2** is that to synthesise exclusively porphyrin **2**, 1000 equiv. of NaCH-$(CO_2Et)_2$ were employed, and the precursor porphyrin **5** was added slowly over a 2 h period. It should be noticed that the same exclusive synthesis could not be extended to the preparation of porphyrin **7**. Indeed, when only 20 equiv. of $NaCH(CO_2Et)_2$ were employed, the synthesis of **7** pro-

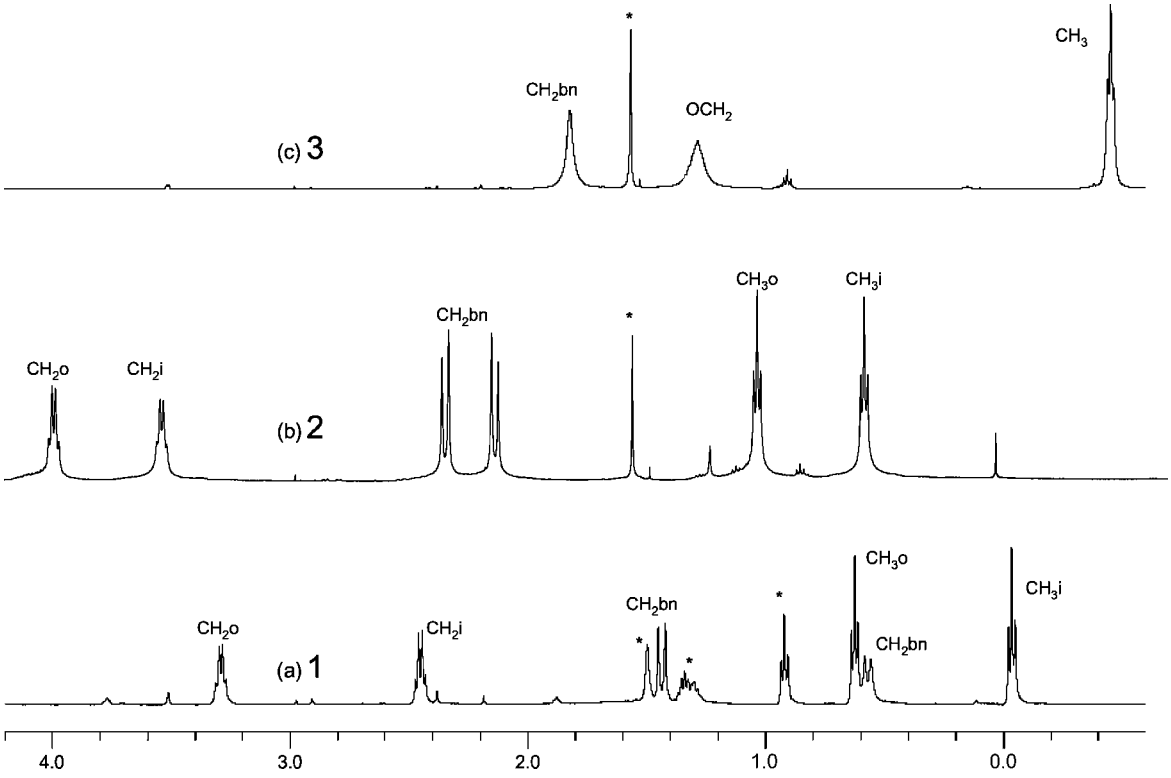

Figure 1. Aliphatic domain of the 500-MHz ^{1}H-NMR spectra (300 K) of (a) **1**, (b) **2**, (c) **3**; * = impurities.

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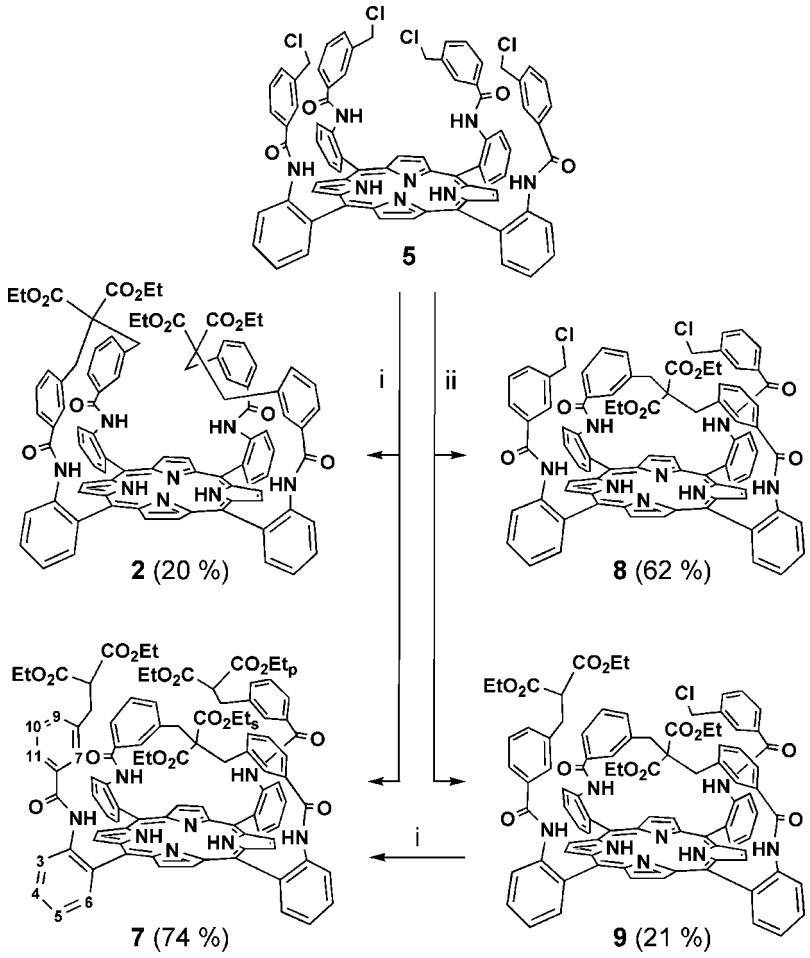

Scheme 2. Synthetic route to strapped porphyrins bearing a variable number of "U-shaped" pickets, starting from the αααα atropisomer of TAPP. i) $CH_2(CO_2Et)_2$ (20 equiv.)/THF/EtONa/room temperature; ii) $CH_2(CO_2Et)_2$ (10 equiv.)/THF/EtONa/room temperature/2 h; the subscripted letters, s and p, of the ethyl groups stand for strap and picket.

ceeded with a decent yield of 74% but **2** was also obtained (20%). We can rationalize this peculiar reactivity by two different explanations. The first one is that the 3-(diethylmalonylmethyl)benzoylamino picket is bulky. Although the second $NaCH(CO_2Et)_2$ to be added on **5** is statistically favoured in an adjacent position (10 or 20), due to steric hindrance, an excess of reagent favours the 15 position. Then, once the 5 and 15 positions are substituted, the straps can be linked only on an adjacent position leading to porphyrin **2**. As a final proof, the synthesis of **7** from **9** still requires 20 equiv. of $NaCH(CO_2Et)_2$ under the usual conditions! The second explanation is that the resulting 2,2′-[3,3′-[2,2-(diethoxycarbonyl)propane-1,3-diyl]dibenzoylamino]diphenyl strap is more adapted, both in terms of length and shape, to link the 5 and 15 *meso* positions than to link two adjacent *meso* positions. In fact, if this was not true, under the reaction conditions by which the single-strapped porphyrin **8** is obtained, the single-strapped porphyrin bearing two 3-(chloromethyl)benzoylamino pickets in adjacent positions should also be isolated.

From the coordination point of view, our synthesis allows the preparation of three types of pre-shaped architectures. In these ligands, one or two ethoxycarbonyl groups are located around the centre of the porphyrin.[28] We know from previous work that, 1: An ethoxycarbonyl group can participate to the stability of bismuth complexes, for instance,[19] and that it is the precursor of a carboxylate group; 2: Cations such as bismuth(III), and also lanthanides,[29] lie about 1.2 Å above the mean porphyrinic plane.[18] If we consider that the average bond length between a bismuth cation and a carboxylate group is 2.75 Å, it means that the oxygen of the carbonyl of an ester group should be delivered at least 3.90 Å away from the centre of the porphyrin. On the other hand, according to the element coordinated in the porphyrin, the out-of-plane coordination can vary in terms of distance, and hence, a versatile ligand should be able to adapt its shape to several elements. However, on the basis of proton NMR spectroscopic data, we had predicted that the strap linked between two adjacent positions should be closer to the porphyrin in **1** than it is in **2**. Obviously, as opposed to **3**, the two ethoxycarbonyl groups of each strap in **1** and **2** are in two very different locations relative to the ring current of the porphyrin, and the terminal methyl group of the ester represents a real and efficient probe of the distance to the centre of the porphyrin. Thus we have labelled them "in" (i) and "out" (o). For

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instance, the closest ester methyl to the porphyrin centre (Me_i) exhibits a signal at δ = 0.65 ppm in **2** but is shielded at 0 ppm in **1**, and the Me_o resonates at δ = 1.10 ppm in **2** but at δ = 0.63 ppm in **1**. This observation simply means that in **1**, the "out" ester is almost as close to the porphyrin centre as is the "in" ester in **2**. We have explained this phenomenon by a reciprocal repulsion of the two straps in **2**. In fact, as the strap possesses a "U" shape conformation, the relaxed position of the strap locates the ester groups just above the centre of the porphyrin. But this relaxed conformation can be achieved only in compound **1**, in which each strap is located on one face of the porphyrin. Interestingly, in compound **3**, the ester groups are even closer to the centre of the porphyrin, as revealed by their chemical shift of –0.45 ppm. This result is expected, as the straps are bridged across the anisotropic ring current of macrocycle **3**. On the other hand, the flexibility of the 5–15 strap is lower than that of the 5–10 strap. This implies that the chelating agents related to **3** or **7** should be less adaptable to the change in size of the element to be complexed than the chelates related to **1**.

In order to evaluate in a reliable way the conformation of the handles, we have also used another probe in proton NMR spectroscopy, which is the proton labeled H-7 (Scheme 1 and Scheme 2). This proton will be very sensitive to the smallest change of conformation of the handle, particularly if the handle is leaning above the plane of the porphyrin. As a result, we can compare the chemical shift of H-7 in **1** and **2** (Figure 2), as well as in **3** and **7**. The signal of H-7 appears at δ = 4.84 ppm in **1** and at δ = 6.60 ppm in **2**; this result is evidently in favor of a straight-up conformation of the straps in **2** and is consistent with a flat conformation of the straps in **1**. The difference between **3** and **7** is less evident, but the comparison is quite as precise. Indeed, H-7 resonates at 4.9 ppm in the case of **7** whereas it is downfield-shifted to 5 ppm in the case of **3**. Thus, the strap in the 5–15 conformation, which on its own is less flexible than in the 5–10 conformation, is not very sensitive to the two other *meso* positions, whether substituted or not.

Fortunately, we were able to verify our conclusions from the conformational studies by means of X-ray structural analysis for the three porphyrins **1**, **2** and **3** (Figure 3).[30] Porphyrin **2** must be considered apart from the two other ligands when observing the corresponding ORTEP view (b). It is striking that the two straps are rejected from the centre of the porphyrin, and that no ethoxycarbonyl group can be located inside the pocket. Although not linked together, it is clear that the two straps form a cage on one face of the porphyrin, in which is included an acetic acid molecule coming from the crystallisation solvents. The two ethoxycarbonyl groups of each diethyl malonate unit are located almost at the same distance from the centre of the porphyrin. If we consider the O atom [labelled O3, view (e)] from the ester carbonyl as the reference atom to evaluate the distance to the porphyrin centre, this distance was measured to be 7.318 Å for the closest ethoxycarbonyl group in **2**. In this geometry, it becomes clear that no coordination chemistry assisted by "hanging" groups from the strap is expected in **2**, as the straps cannot approach closer to the porphyrin, and a distance of 3.9–4.0 Å between the ethoxycarbonyl group and the centre of the porphyrin is a prerequisite for participation of ethoxycarbonyl groups in coordination chemistry (vide supra). It should also be noticed that among the three ligands of Figure 3 (views d, e, f), **2** is the only porphyrin to exhibit a significant distortion, classified as saddle-shaped, presumably due to the mutual repulsion of the straps. This distortion is evaluated by the out-of-plane location of the two pairs of diametrically opposed pyrrole units. Indeed, if one pair is above the mean porphyrin plane, the second pair is found below the same plane.

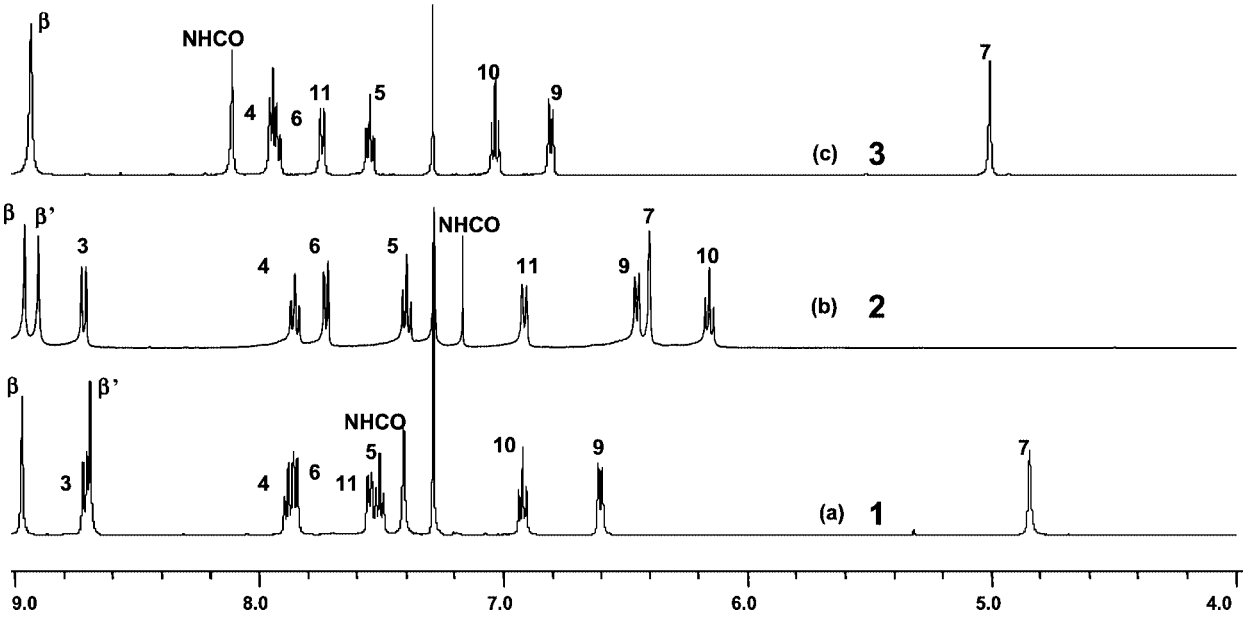

Figure 2. Aromatic region of the 500-MHz ^{1}H-NMR spectra (300 K) of (a) **1**, (b) **2**, (c) **3**.

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Moreover, this saddle-shape distortion is also accompanied by a ruffled distortion which is observable by the twist angle between two diametrically opposed Cβ-pyrrolic to Cβ-pyrrolic bond.[31] In the case of **2**, these two angles were measured to be 9.9° and 10.1°, respectively.

Porphyrin **1** is located on an inversion centre. The molecule results formally from the attachment of the same strap but one on each side of the porphyrin. This means that in this ligand, each strap is free to adopt its more stable conformation (views a, d). One can verify that the two ethoxycarbonyl groups of each diethyl malonate unit are in very different environments. It becomes evident that C30 and C31 represent the "out" branch, where C27 and C28 are attributed to the "in" branch. Therefore, O5 (out) is located 7.359 Å away from the porphyrin centre, while O3 (in) is only 3.347 Å away from this same centre. It should be underlined that we must revise the conclusion drawn on the basis on the proton NMR analysis, namely that the "out" methyl group in **1** is as close as the "in" methyl group in **2**. The distance of 3.347 Å is compatible with a possible interaction between the ethoxycarbonyl – or carboxylic – group and a metal inside the porphyrin. The porphyrin crystallises with eight acetic acid molecules. These molecules give rise to a 2D-infinite network due to intermolecular hydrogen bonds with the porphyrin macrocycle.

The last X-ray structure is of doubly strapped porphyrin **3**, in which the two straps are attached through the diametrically opposed *meso* positions. It is the only porphyrin of this work in which the two ethoxycarbonyl branches of each strap are magnetically equivalent. Therefore, in this case, the solid-state structure represents only one specific conformation rather than an average position in solution. Indeed, in contrast to what is observed in views (c) and (f), the two ethoxycarbonyl groups lead to only one signal in the proton NMR spectrum. This magnetic equivalence points out that in addition to the swinging motion of the strap around the *meso* positions, the diethyl malonate motif has its own motion around the two carbon atoms C116 and C316. It also implies that the two ethoxycarbonyl groups can potentially coordinate a metal in the porphyrin. Furthermore, in this porphyrin, the distance between the centre of the porphyrin and the O atom from the ester carbonyl, namely O419, is the shortest among the three structurally characterized molecules, with a value of 3.111 Å.

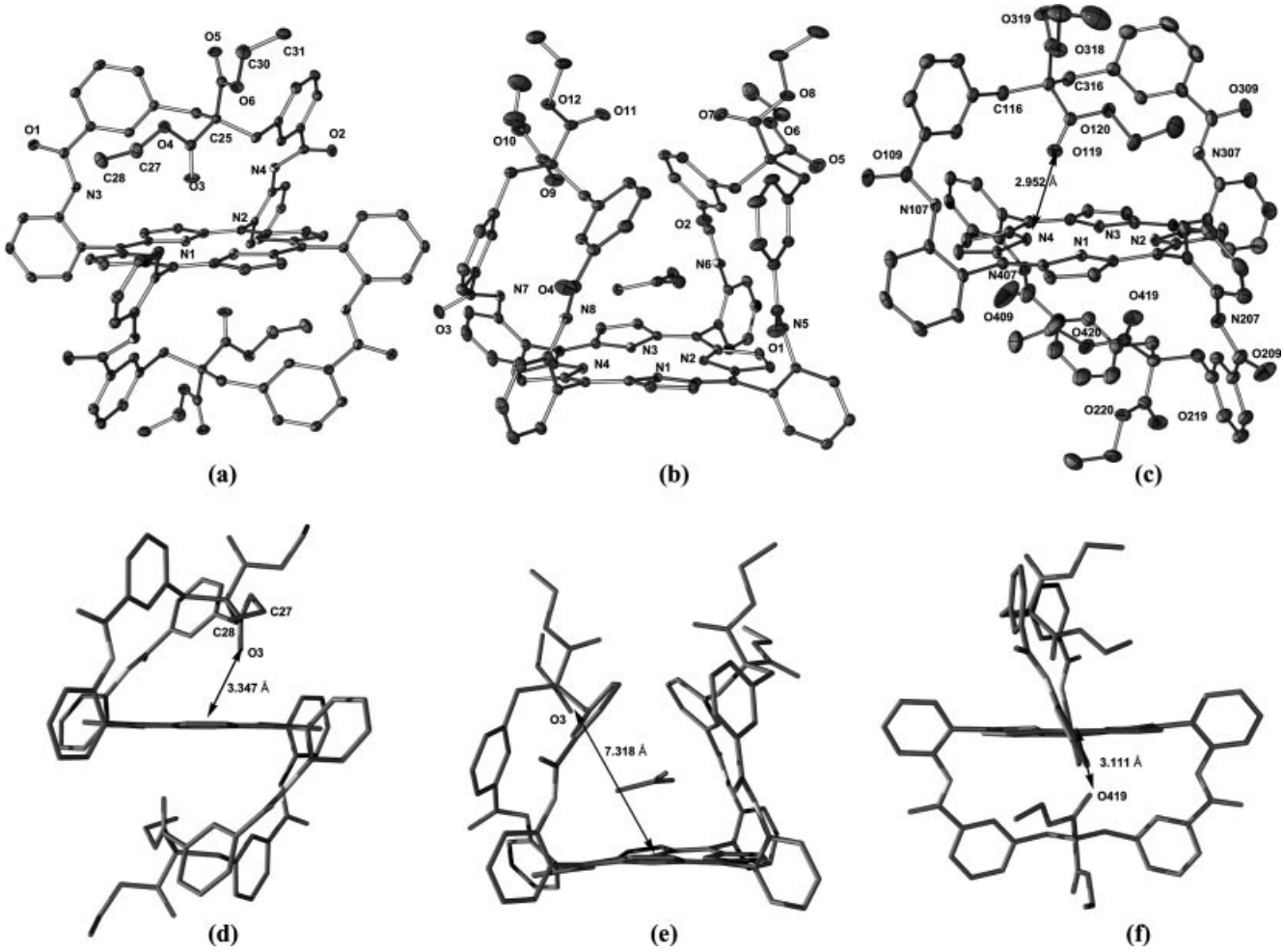

Figure 3. ORTEP view (30% thermal ellipsoid) of the solid-state structures of (a) **1**, (b) **2**, (c) **3**. Stick lateral views of (d) **1**, (e) **2**, (f) **3**. For the sake of clarity, the solvent molecules and the hydrogen atoms are omitted, with the exception of the acetic acid molecule included in **2**.

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Thus, with ligands **1** and **3**, we have synthesized two macromolecules capable of delivering close to the centre of the porphyrin one (or two) ethoxycarbonyl group(s), precursor(s) of a carboxylate function, with a preorganized yet flexible structure. Indeed, in both porphyrins, the motion of the straps should allow the chelate to adapt the size of its cavity to different metal cations.

Conclusion

We have described the synthesis and structural characterization of three typical strapped porphyrins using a simple reaction of the anion of diethyl malonate with various atropisomers of electrophilic "U-shaped" picket porphyrins. We have extensively optimised different reaction conditions to obtain single- vs. bis-strapped porphyrins, or single-strapped chloro-benzoylamino picket porphyrins vs. single-strapped malonate-benzoylamino picket porphyrins. All the reported bis-strapped porphyrins have been further studied and characterized by X-ray crystallography. These studies clearly confirm our hypothesis about the preorganization of these "U-shaped" straps and allow us to rule out the bis-strapped porphyrin in the αααα geometry for coordination purposes. On the other hand, the single-strapped porphyrins in the αααα geometry remain attractive as we are now able to prepare new ligands **8** and **9**, in which the number of ester functions differs, and on which one or two reactive functions are spared for further development of bifunctional chelates. The two other geometries, based on the functionalization of the αβαβ and ααββ atropisomers, lead to adaptable systems with promising coordination properties, which are under current investigation in our laboratories.

Experimental Section

General Remarks: ^{1}H NMR spectra were recorded with a Bruker Avance DRX 500 spectrometer and referenced to the residual proton solvents. Mass spectra were collected with an MS/MS ZAB-Spec TOF spectrometer at the University of Rennes I (C.R.M.P.O.). UV/Vis spectra were recorded with Varian Cary 1E and Bruker IFS 66 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 argon and monitored by TLC (silica, CH_2Cl_2/CH_3OH). Column flash chromatography was performed on silica gel (Merck TLC-Kieselgel 60 H, 15 μm). Elemental analyses were obtained with an EA 1108 Fisons Instruments. Experimental data as well as synthetic procedures have already been published for compounds **1**, **2**, **4**, **5**, and **7**.[22]

α-5,15,β-10,20-Bis{2,2′-[3,3′-[2,2-(diethoxycarbonyl)propane-1,3-diyl]dibenzoylamino]diphenyl}porphyrin (3): The procedure described[22] for **1** was applied to **6**. Compound **3** was purified on a silica gel column, eluted with 0.3% CH_3OH/CH_2Cl_2, and obtained in 83% yield (47 mg). ^{1}H NMR (500 MHz, $CDCl_3$, 310 K): δ = 9.16 (d, J = 8 Hz, 4 H), 8.93 (s, 8 H), 8.11 (s, 4 H), 7.93 (m, 8 H), 7.74 (d, J = 8 Hz, 4 H), 7.55 (t, J = 7.5 Hz, 4 H), 7.03 (t, J = 7.5 Hz, 4 H), 6.80 (d, J = 7.5 Hz, 4 H), 5.01 (s, 4 H, H-7), 1.82 (broad s, 8 H, CH_2CH$_3$), 1.05 (large s, 8 H), –0.45 (t, J = 5 Hz, 12 H, CH$_2$CH_3), –2.07 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 310 K): δ = 167, 164, 139, 136, 134, 133, 132, 130, 128.4, 127.5, 127, 123, 120, 115, 57, 42.6, 12 ppm. HRMS (ESI-MS): m/z = 1481.5319, calcd. 1481.5323 for $C_{90}H_{74}N_8NaO_{12}$ [M + Na]$^+$. UV/Vis (CH_2Cl_2): λ ($10^{-3}\cdot\varepsilon$, $M^{-1}cm^{-1}$) = 423 (425.1), 515 (24.8), 549 (6.9), 589 (7.7), 648 (3.5) nm.

α-5,15,β-10,20-Tetrakis{2-[(3-chloromethyl)benzoylamino]-phenyl}porphyrin (6): The procedure described[22] for **4** was used on the αβαβ atropisomer of TAPP (1 g), and the desired compound was eluted with CH_2Cl_2 and obtained in 82% yield (1.37 g). ^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 8.99 (s, 8 H), 8.85 (d, J = 8.4 Hz, 4 H), 8.08 (d, J = 7.5 Hz, 4 H), 7.96 (d, J = 7.8 Hz, 4 H), 7.61 (t, J = 7.5 Hz, 4 H), 7.48 (s, 4 H), 6.78 (d, J = 7.5 Hz, 4 H), 6.67 (d, J = 8.0 Hz, 4 H), 6.58 (t, J = 7.8 Hz, 4 H), 6.32 (s, 4 H, H-7), 3.36 (s, 8 H), –2.48 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 300 K): δ = 164.3, 163.9, 138.9, 137.7, 134.4, 132.0, 130.8, 128.4, 126.1, 123.5, 121.2, 44.2 ppm. HRMS (ESI-MS): m/z = 1305.2928, calcd. 1305.2920 for $C_{76}H_{54}Cl_4N_8NaO_4$ [M + Na]$^+$. UV/Vis (CH_2Cl_2): λ ($10^{-3}\cdot\varepsilon$, $M^{-1}cm^{-1}$) = 422 (323.6), 516 (18.2), 549 (4.9), 589 (5.8), 647 (2.7) nm.

α-5,15-{2,2′-[3,3′-[2,2-(Diethoxycarbonyl)propane-1,3-diyl]dibenzoylamino]diphenyl}-α-10,20-bis{2,2′-[(3,3′-chloromethyl)-benzoylamino]phenyl}porphyrin (8) and α-5,15-{2,2′-[3,3′-[2,2-(diethoxycarbonyl)propane-1,3-diyl]dibenzoylamino]diphenyl}-α-10-{2-[(3-chloromethyl)benzoylamino]phenyl}-α-20-{2-[3-[1-(diethoxycarbonyl)ethane-2-yl]benzoylamino]phenyl}porphyrin (9): A 250-mL two-necked round-bottomed flask equipped with a stir bar was charged with sodium (90 mg, 4 mmol) in EtOH (15 mL). After 30 min, diethyl malonate (0.9 mL, 4 mmol) was added, and the mixture was stirred for 1 h. Porphyrin **5** (0.5 g, 0.4 mmol) was dissolved in dry THF (50 mL) and added in one portion to the reaction mixture. After 2 h, the solvent was removed, and the residue was purified on a silica gel column. Compound **8**, eluted with 0.2% methanol/ CH_2Cl_2, was obtained in 62% yield (330 mg), and compound **9**, eluted with 0.4% methanol/ CH_2Cl_2, was obtained in 21% yield (123 mg).

8: ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 9.13 (d, J = 8.5 Hz, 2 H), 9.06 (d, J = 5 Hz, 4 H), 9.1 (d, J = 5 Hz, 4 H), 8.74 (d, J = 8.5 Hz, 2 H), 8.63 (s, 2 H), 8.02 (d, J = 7 Hz, 2 H), 7.94 (m, 4 H), 7.87 (t, J = 7 Hz, 2 H), 7.69 (d, J = 8 Hz, 2 H), 7.60 (m, 4 H), 7.53 (s, 2 H), 7.37 (d, J = 7.5 Hz, 2 H), 6.96 (t, J = 8 Hz, 2 H), 6.87 (d, J = 7 Hz, 2 H), 6.64 (d, J = 7.5 Hz, 2 H), 6.49 (d, J = 7.5 Hz, 2 H), 6.17 (t, J = 7.5 Hz, 2 H), 4.89 (s, 2 H, H-7), 4.02 (s, 4 H, CH_2Cl), 1.24 (large s, 4 H, CH_2CH$_3$), 0.95 (s, 4 H, CH_2C), –0.68 (large s, 6 H, CH$_2$CH_3), –2.35 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 167.4, 165.7, 164.3, 137.3, 136.1, 135.8, 132.5, 131.3, 130.2, 128.4, 127.5, 125.6, 123.7, 123.2, 122.0, 120.4, 115.9, 114.8, 44.7, 42.7, 11.9 ppm. HRMS (ESI-MS) m/z = 1393.4118, calcd. 1393.4122 for $C_{83}H_{64}Cl_2N_8NaO_8$ [M + Na]$^+$. UV/Vis (CH_2Cl_2): λ ($10^{-3}\cdot\varepsilon$, $M^{-1}cm^{-1}$) = 423 (389.9), 517 (21.2), 551 (5.9), 591 (6.5), 647 (2.5) nm. **9:** ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 9.11 (d, J = 9 Hz, 2 H), 8.99 (m, 8 H), 8.76 (d, J = 9 Hz, 1 H), 8.70 (d, J = 9 Hz, 2 H), 8.58 (d, J = 7 Hz, 2 H), 7.94 (m, 8 H), 7.58 (m, 10 H), 6.96 (t, J = 8 Hz, 2 H), 6.71 (d, J = 8 Hz, 1 H), 6.62 (d, J = 7 Hz, 1 H), 6.49 (d, J = 7 Hz, 4 H), 6.13 (t, J = 7 Hz, 1 H), 5.92 (t, J = 7 Hz, 1 H), 4.86 (s, 2 H, H-7), 4.09 (m, 4 H, C$H_{2,p}$CH$_3$), 3.99 (s, 2 H, CH_2Cl), 3.38 (t, J = 7.5 Hz, 1 H, CH$_2$CH), 2.81 (d, J = 7.5 Hz, 2 H, CH_2CH), 1.45 (broad s, 4 H, CH_{2s}CH$_3$), 1.17 (t, J = 7.5 Hz, 6 H, CH$_2$C$H_{3,p}$), 0.92 (broad s, 4 H, CH_2C),

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–0.55 (broad s, 3 H, $CH_2CH_{3,s}$), –0.77 (broad s, 3 H, $CH_2CH_{3,s}$), –2.36 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 166.3, 164.8, 164.3, 138.1, 137.3, 135.7, 135.0, 132.6, 131.7, 131.2, 130.2, 128.4, 127.4, 125.5, 123.7, 122.0, 120.5, 119.1, 116.1, 114.8, 61.6, 59.5, 53.3, 44.8, 41.6, 33.9, 14.0, 12.2 ppm. HRMS (ESI-MS): *m/z* = 1517.5093, calcd. 1517.5091 for $C_{90}H_{75}ClN_8NaO_{12}$ $[M + Na]^+$. UV/Vis (CH_2Cl_2): λ ($10^{-3}\cdot\varepsilon$, $M^{-1}cm^{-1}$) 423 (389.5), 517 (21.2), 551 (5.8), 591 (6.4), 647 (2.4) nm.

X-ray Crystallographic Studies

1: $C_{90}H_{74}N_8O_{12}\cdot 8(C_2H_4O_2)$, M = 1939.99. Enraf–Nonius Kappa-CCD diffractometer, Mo-$K\alpha$ radiation (λ = 0.71073 Å), T = 110 K; monoclinic, $P2_1/n$, a = 13.0618(7), b = 14.959(1), c = 24.364(2) Å, β = 91.196(3)°, V = 4759.5(6) Å^3, Z = 2, d = 1.354 g·cm^{-3}, μ = 0.099 mm^{-1}. The structure was solved by direct methods and refined with full-matrix least-square methods based on F^2 (SHELX-97)[32] with the aid of the WINGX[33] program. All non-hydrogen atoms were refined with anisotropic thermal parameters. H atoms were included in their calculated positions or found in the final difference Fourier maps and refined with a riding model. A final refinement on F^2 with 6530 unique intensities and 644 parameters converged at $wR(F^2)$ = 0.145 [$R(F)$ = 0.058 for 4583 observed reflections with $I > 2\sigma(I)$].

2 and 3: For both, single-crystal data collection has been performed on a 4-circles diffractometer equipped with a CCD detector (Centre de Diffractométrie X, Univ. Rennes 1), with Mo-$K\alpha$ radiation (λ = 0.71073 Å). A Nonius KCCD diffractometer and a APEX2 Bruker-AXS diffractometer were used to collect diffraction data at room temperature and T = 100 K, for **2** and **3** respectively. Structures were solved by direct methods using the SIR97 program,[34] which revealed all the non-hydrogen atoms. The SHELX-97 program[32] was used to refine the structure.

2: $C_{90}H_{74}N_8O_{12}\cdot 4(C_2H_4O_2)\cdot(H_2O)$, M = 1715.78 crystallizes in the centric $P2_1/n$ monoclinic space group [room temperature: a = 13.498(2), b = 24.772(3), c = 27.477(5) Å, β = 102.705(4)°, V = 8963(2), Z = 4, d = 1.272 g·cm^{-3}, μ = 0.090 mm^{-1}]. The asymmetric unit was found to contain one molecule of $C_{90}H_{74}N_8O_{12}$, four molecules of acetic acid (CH_3COOH) from solvent, and a water molecule.

3: $C_{90}H_{74}N_8O_{12}$, M = 1459.57 crystallizes in the centric $C2/c$ monoclinic space group [T = 100 K: a = 32.333(5), b = 12.632(2), c = 38.270(7) A, β = 97.470(11)°, V = 15498(4), Z = 8, d = 1.251 g·cm^{-3}, μ = 0.084 mm^{-1}]. Only the $C_{90}H_{74}N_8O_{12}$ molecule was found to crystallize in this unit cell, which contains no solvent molecule.

Finally, except for those found by Fourier difference in the porphyrin cycle, all the hydrogen atoms were placed geometrically and held in riding mode in the least-squares refinement procedure. Final refinements included atomic positions for all the atoms, anisotropic displacement parameters for all the non-hydrogen atoms and isotropic displacement parameters for all the hydrogen atoms. Thus, 1151 and 997 independent parameters (for 19773 and 14352 reflections) have been refined for the crystals of **2** and **3**, respectively.

Supporting Information (see footnote on the first page of this article) includes ^1H and ^{13}C data of all new compounds.

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