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TEMPLATED SYNTHESIS OF INTERLOCKED MACROCYCLIC LIGANDS, THE CATENANDS. PREPARATION AND CHARACTERIZATION OF THE PROTOTYPICAL bis-30 MEMBERED RING SYSTEM

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Abstract. We describe here the detailed template synthesis of a **copper(I) catenate.** Demetallation leads to the corresponding free ligand, a **catenand.** Both molecules are made of two interlocked 30 membered rings.

The synthesis of more and more sophisticated molecules is a challenge in organic or inorganic chemistry. Topological novelty and complexity adds to the aesthetical appeal of molecular systems. Compounds whose molecular graph cannot be drawn in a plane without crossing points (i.e. having non-planar presentation when embedded in three-dimensional space) are particularly fascinating. The archetypical example of such systems is that of interlocked rings arranged in a chain of two or more cyclic links (catenanes). These have been abundantly discussed in relatively old literature and various synthetic approaches have been reported.[1,2]

Other topologically non trivial systems consist of knots.[3] Besides catenanes and knots, a molecular Möbius strip has been described.[4] It corresponds to the complete bi-partite graph built on two sets of three vertices each, K_{33}. The first topologically non-planar organic molecule, equivalent to the complete graph formed on five vertices (K_5) was reported independantly by two groups in 1981.[5,6] The first hydrocarbon with a K_5 topology was very recently synthesized by a particularly efficient and elegant procedure.[7]

Interesting and detailed discussions forming the basis of modern Chemical Topology applied to non-planar molecular graphs have recently been published.[8-9]

A few years ago, we developed an efficient synthesis of interlocked rings based on the three dimensional template effect of a transition metal, able to gather and predispose coordinating molecular threads so as to lead to interlocked systems after cyclization.[10-11] We now report the detailed synthesis of the compounds briefly discussed in two previous short communications.[10]

Results and discussion

1. The three-dimensional template synthesis of catenates and catenands : principle

Transition metals have only scarcely been used in 3-space as templating species for making cyclic structures. Recent spectacular examples are the cobalt(III) mediated synthesis of sepulchrates by Sargeson et al.[12] and the preparation of a bicyclic ligand around an iron(III) centre, as recently published by Raymond and coworkers.[13] Previous interesting work on the use of hexa-coordinate cobalt(III) complexes as precursors of bicyclic structures can be found in relatively old literature.[14,15]

The principle of our three-dimensional template synthesis of interlocked rings is represented in Figure 1.

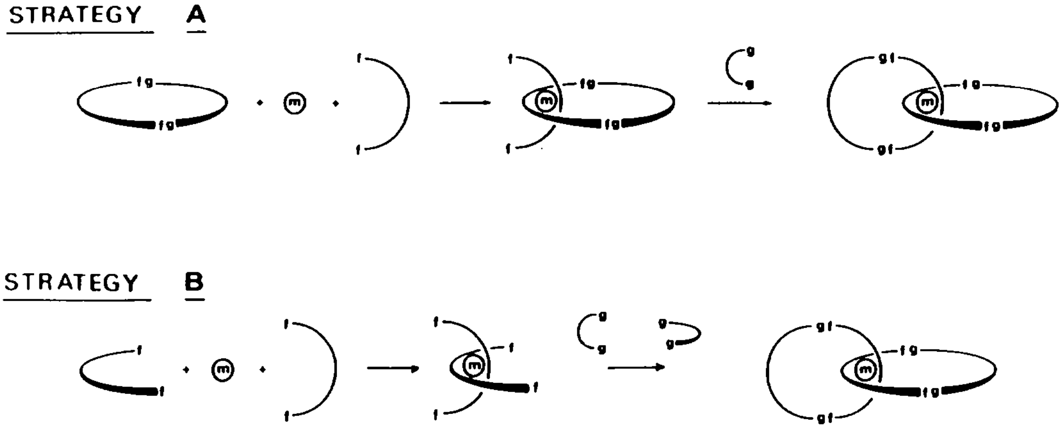

Figure 1

Strategy A is one step longer than strategy B since it requires the preliminary synthesis of a coordinating cycle. However, it involves only four reacting centres to be properly connected (two f points and two g points) in the cyclization reaction whereas strategy B necessitates eight centres (4 f + 4 g) to react in the proper fashion in a one-pot reaction leading to the catenate. Another advantage of Strategy A is that it allows preparation of disymetrical compounds, containing two different interlocked rings, provided the f-f and g-g fragments used for making the monocyclic precursor are different from the f-f and g-g links used in the second cyclization step.

We have proposed the words "catenand" and "catenate" for the free ligands and the complexes respectively, the very general name for molecules containing interlocked cycles being "catenane", as introduced by Schill.[1]

2. The two-step approach to the copper(I) catenate

Applying Strategy A of Figure 1 to 2,9-diaryl-1,10-phenanthroline chelates (f-f subunits), copper(I) (the templating species) and the di-iodo derivative of pentaethylene glycol (the g-g link), we could make the first catenate, as described in Figure 2.

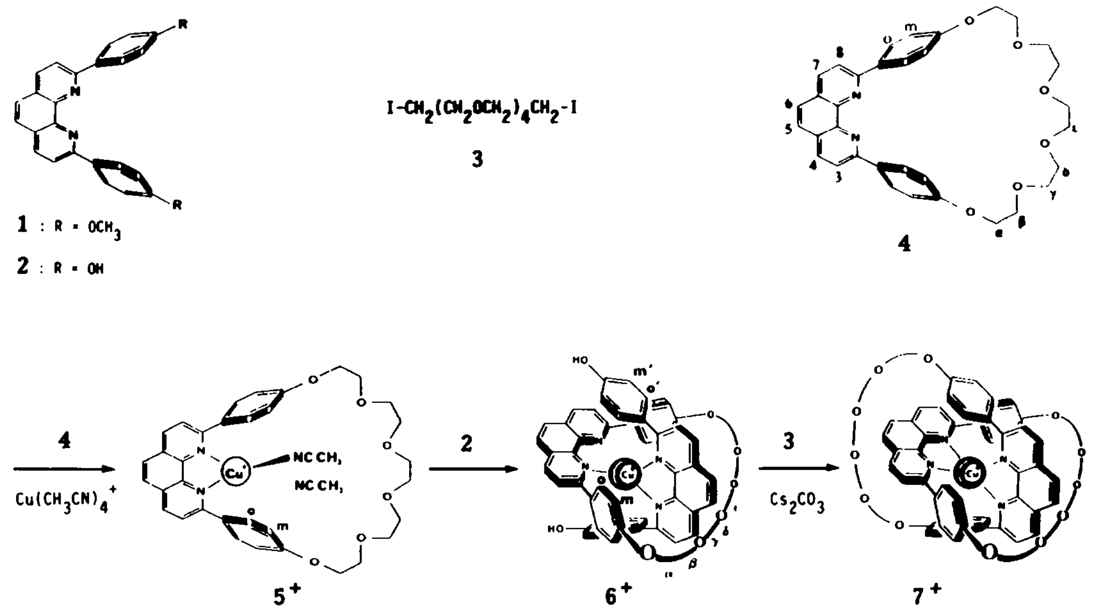

Figure 2

Preparation of **1**, **2** and **4** was reported earlier.[16] The reaction of 4-lithio anisole[17] with 1,10-phenanthroline suspended in toluene at room temperature under argon lead to **1** in 70% yield after hydrolysis and oxidation by MnO_2.[18] The phenolic function was then deprotected under drastic conditions, in analogy with those described previously for cleaving aryl-methyl ethers.[19] **1** was treated by pyridinium chloride at 210° to afford quantitatively the diphenol **2**. By treating this compound by **3**[20] in DMF in the presence of a large excess of Cs_2CO_3[21] at 65°C under high dilution conditions and under argon, a 45% yield of **4** was obtained.

By adding an acetonitrile solution of $Cu(CH_3CN)_4^+.BF_4^-$ to a stoechiometric amount of **4** in CH_2Cl_2 under argon, a yellow air sensitive solution of $\mathbf{5}^+$ was obtained in quantitative yield as monitored by ^1H NMR spectroscopy. Addition of one equivalent of **2** in DMF to the solution of $\mathbf{5}^+$ lead to an immediate colour change, with quantitative formation of the deep red-brown complex $\mathbf{6}^+$.[22] After pumping off the solvents, $\mathbf{6}^+.BF_4^-$ was isolated as a dark red, air stable complex. An equimolar solution of $\mathbf{6}^+.BF_4^-$ and **3** in DMF was slowly added (high dilution) to a vigorously stirred suspension of Cs_2CO_3 in DMF, under argon at 65°C. After work-up and chromatographic separation (on silica with CH_2Cl_2 plus small amounts of CH_3OH as eluant), the catenate 7^+ was isolated as its BF_4^- salt in 42% yield from **4**. $7^+.BF_4^-$ is a deep dark red highly crystalline solid (MP = 274-275°C). It is indefinitely stable in air either in solution or in the solid state. 7^+ contains two interlocked 30 membered rings and it has been amply characterized and studied by various physical methods, including X-ray crystallography.[23]

3. The one-pot synthesis of the copper(I) catenate

By applying the straightforward Strategy B to **2** and copper(I) it was possible to synthesize the catenate 7^+, as represented in Figure 3.

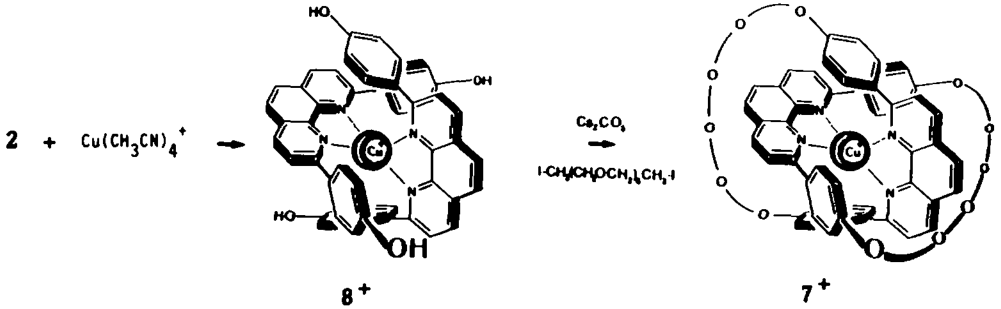

Figure 3

$Cu(CH_3CN)_4^+.BF_4^-$ was added to two equivalents of the diphenol **2** in DMF to form instantaneously and quantitatively the very stable and deep red complex 8^+. This compound was reacted with **3** in DMF, under high dilution conditions, in the presence of an excess of Cs_2CO_3, to afford the catenate 7^+ as its BF_4^- salt in 27% yield after work-up and careful chromatographic separation. Besides 7^+, a 20% yield of the monocyclic compound **4** was obtained. Various open-chained products and possibly cyclic oligomers were also formed and isolated but they were not further characterized.

4. Demetallation reaction to the catenand and characterization

CN^- turned out to be the most convenient decomplexing agent. Indeed, treatment of $7^+.BF_4^-$ by a large excess of KCN in a CH_3CN-H_2O mixture at room temperature leads quantitatively to the catenand **9**. The reaction is relatively slow but it is extremely clean and easy to monitor since the colour of the catenate gradually fades with simultaneous precipitation of the free ligand. It is the pure catenand **9** which can be crystallized in benzene/CH_2Cl_2. The demetallation reaction is represented schematically in Figure 4.

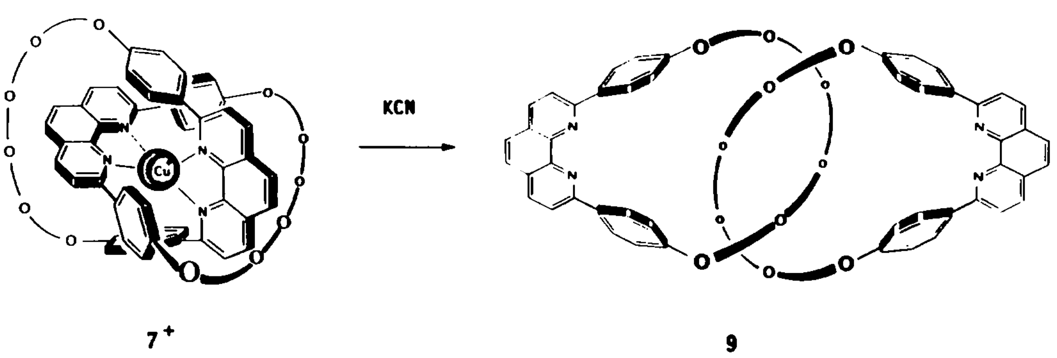

Figure 4

9 has been characterized and studied by numerous techniques. Its molecular structure was solved by X-ray diffraction,[23] showing that the molecular shape of the catenand **9** is indeed very different from that of the catenate 7^+. In particular, the two chelating subunits are completely separate in the free ligand whereas they are intimately entwined in the catenate.

The general topography of each system 7^+ or **9** in solution roughly corresponds to the drawing of Figure 4, as clearly demonstrated by ^{1}H NMR studies.

Conclusion

3D template allows preparation of the first member of a new family of ligands, the catenands ; one pot synthesis is particularly attractive since it is very direct (4 steps from 1,10 phenanthroline). It could be scaled up, allowing preparation of batches of 1 gram **9** per experiment, although the yield was slightly decreased.

Experimental Section

General

Acetonitrile was dried and purified by distillation (normal pressure) over CaH_2. $Cu(CH_3CN)_4.BF_4$ was prepared by the literature method.[24] Alternatively, $Cu(CH_3CN)_4.BF_4$ was prepared by reduction of $Cu(BF_4)_2$ by copper powder (excess) in CH_3CN under argon at room temperature, the mixture being stirred until complete bleaching of the solution was effected. All other chemicals were of the best commercially available grade and were used without further purification.

^{1}H-NMR spectra were recorded with a Bruker WP 200 SY spectrometer. All compounds based on diphenyl-phenanthroline showed similar highly characteristic pattern : a singlet for H_5 and H_6, an AB pattern for H_3 or H_8 and H_4 or H_7 (coupling constant $J \approx 8.5$ Hz) and an AA'XX' system (J ≈ 8.7 Hz) for H_o and H_m.

Electronic spectra were performed with a Varian Cary 118 spectrometer or with a Kontron Unikon 80 one. Mass spectra were recorded on a LKB 9000S or a THOMSON THN 208. Melting points were measured with a REICHERT Micro Melting Point apparatus (uncorrected).

Preparation of 2,9-di(p-anisyl)-1,10-phenanthroline 1

p-Anisyl-lithium was prepared by the direct interaction of freshly cut lithium with p-bromo-anisol in ether under argon and at room temperature.[17] The resulting organolithium solution was titrated by the double titration method described by Gillman and al.[25] In a typical run, 200 ml of a 1,3 M p-anisyl-lithium solution were obtained by reacting 7 g (1 mole) lithium with 56,1 g (0,3 mole) of p-bromo-anisole in 300 ml of dry ether (yield : 86%). 100 ml of the latter solution were added by syringe at room temperature to a degassed suspension of 4.95 g (25 mmol) commercial 1,10-phenanthroline monohydrate in 50 ml toluene. After the resulting dark red solution was stirred for 48 h under argon at room temperature, it was hydrolized at 0°C with water. The bright yellow toluene layer was decanted and the aqueous layer extracted three times with 150 ml portions of CH_2Cl_2. The combined organic layers were thereafter rearomatized by successive additions of MnO_2 under effective magnetic stirring (MnO_2 Merck n° 805958, ∿20 g for each batch). This reoxydation, easily followed by TLC and disappearance of the yellow colour, was ended after addition of 100 g MnO_2. After the mixture was dried over $MgSO_4$, the black slurry could be easily filtered on a sintered glass and the filtrate evaporated to dryness to give crude 1 which after recrystallization from hot toluene was obtained in 43% yield (4.20 g, 10.7 mmol). Further 2.63 g (6.70 mmol) of 1 could be obtained by column chromatography of the filtrate on silica gel (CH_2Cl_2/1% MeOH). Overall yield : 70%.

1. Colourless needles (mp : 179°). ^{1}H-NMR (CD_2Cl_2) : 8.43 (d, 4H, H_o) ; 8.30 (d, 2H, H_4 or H_7) ; 8.11 (d, 2H, H_3 or H_8) ; 7.78 (s, 2H, H_5 and H_6) ; 7.14 (d, 4H, H_m) ; 3.92 (s, 6H, OCH_3). Absorption (CH_2Cl_2, λ_{max} (nm) [log ε]) : 240 [4.46] ; 285 [4.66] ; 323 [4.41] ; 340 [4.39]. Anal. calc. for $C_{26}H_{20}N_2O_2$: C, 79.59 ; H, 5.10 ; N, 7.14. Found : C, 79.58 ; H, 5.21 ; N, 6.79.

Preparation of 2,9-di(p-phenol)-1,10-phenanthroline 2

Technical grade pyridine (16 ml) was placed in a 100 ml three-necked round-bottomed flask fitted with a thermometer and a magnetic stirrer. With rapid stirring concentrated hydrochloric acid (17.6 ml) was added. The flask was equipped for distillation, and water was distilled from the mixture until its internal temperature rose to 210°. After cooling to 140°, 1 (6.27 g, 16 mmol) was added as a solid and the reaction flask was fitted with a reflux condenser connected to a source of argon. The yellow mixture was stirred and refluxed for three hours ($190° < \theta < 220°$). The hot reaction mixture was then diluted with 10 ml warm water and slowly poured into 60 ml hot water. The resulting bright yellow suspension was refrigerated overnight. After cooling, the precipitated solid was filtered by suction, and washed with cold water. Crude acidic diphenol **2** was suspended (it dissolves partially) in an ethanol-water mixture (250/85 ml) and neutralized with a dilute NaOH solution. After this pH-meter monitored neutralization (end-point : pH = 7,32), solution was diluted with hot water (300 ml). Neutral **2** precipitated as a beige solid during cooling down. Filtrated by suction, it was air dried to yield 5.85 g of an ochre solid. Upon further drying (high vacuum in presence of P_2O_5) the latter turned bright red (5.31 g, 92% yield) and could be utilized without further purification.

2. Scarlet red solid (mp > 260°). ^{1}H-NMR (DMF) : 10.14 (s, 2H,-OH) ; 8.56 (d, 4H, H_o) ; 8.55 (d, 2H, H_4 or H_7) ; 8.37 (d, 2H, H_3 or H_8) ; 7.98 (s, 2H, H_5 and H_6) ; 7.14 (d, 4H, H_m). Anal. calc. for $C_{24}H_{16}N_2O_2$: C, 79.12 ; H, 4.40 ; N, 7.69. Found : C, 79.08 ; H, 4.47 ; N, 7.59.

Preparation of macrocycle **4**

A mixture of **2** (1.045 g, 2.87 mmol) and **3** (1.445 g, 3.15 mmol) in DMF (100 ml) was added dropwise within 32 h under efficient stirring to an argon flushed suspension of Cs_2CO_3 (3 g, 9.2 mmol) in 400 ml DMF kept at 55-60°. At the end of addition, stirring and heating was continued for 48 h. DMF was removed under high vacuum and the residue taken up in H_2O-CH_2Cl_2. Decantation, extraction with three 100-ml portions of CH_2Cl_2 and drying over $MgSO_4$ left, after the solvent was removed, 2.00 g of crude yellow glassy product. It was purified by column chromatography on silica gel (eluent CH_2Cl_2 containing 0.5 to 1% MeOH) giving pure macrocycle **4** (731 mg, 45% yield).

4. Pale yellow cristals (mp : 157-158°). ^{1}H-NMR (CD_2Cl_2) : 8.44 (d, 4H, H_o) ; 8.30 (d, 2H, H_4 or H_7) ; 8.10 (d, 2H, H_3 or H_8) ; 7.79 (s, 2H, H_5 and H_6) ; 7.23 (d, 4H, H_m) ; 4.37 (t, 4H, J = 11.7 Hz, $CH_{2\alpha}$) ; 3.86 (t, 4H, J ≈ 11.7 Hz, $CH_{2\beta}$) ; 3.72 to 3.65 (m, 12 H, $CH_{2\gamma,\delta,\varepsilon}$). MS : 567 ($MH^+$). Anal. calc. for $C_{34}H_{34}N_2O_6$: C, 72.08 ; H, 6.00 ; N, 4.95. Found : C, 72.19 ; H, 6.03 ; N, 4.99.

Preparation of precatenate $\mathbf{6}^+$

By the double-ended needle transfer technique, 383 mg (1.21 mmol) of $Cu(CH_3CN)_4.BF_4$ in degassed acetonitrile (30 ml) were added under argon and at room temperature to a stirred degassed solution of **4** (656 mg, 1.16 mmol) in CH_2Cl_2 (50 ml). Instantaneous appearance of a deep orange coloration in the solution was related to the formation of 5^+. Highly air sensitive, 5^+ could not be isolated but it's formation directly in an NMR tube allowed at least spectroscopic characterization (see ^{1}H-NMR below). After 0.5 h at room temperature, a solution of **2** (422 mg, 1.16 mmol) in DMF (50 ml) was added to complex 5^+. The solution turned dark red immediately. After the solution was stirred for 1 h under argon at room temperature, the solvents were evaporated to dryness : dark red needles of crude $\mathbf{6}^+$ were obtained in quantitative yield (1.252 g, 1.16 mmol). $\mathbf{6}^+$ was utilized without further purification.

5$^+$. Orange solid, decomposed in air. ^{1}H-NMR (CD_2Cl_2, CD_3CN) : 8.66 (d, 2H, H_4 or H_7) ; 8.17 (d, 2H, H_3 or H_8) ; 8.08 (s, 2H, H_5 and H_6) ; 7.95 (d, 4H, H_o) ; 7.17 (d, 4H, H_m) ; 4.33 (m, 4H, $CH_{2\alpha}$) ; 3.82 (m, 4H, $CH_{2\beta}$) ; 3.69 to 3.56 (m, 12 H, $CH_{2\gamma,\delta,\epsilon}$).

6$^+$. Dark red needles. ^{1}H-NMR (CD_2Cl_2, CD_3CN, DMF) : 9.05 (s, 2H, -OH) ; 8.46 (d, 2H, H'_4 or H'_7) ; 8.41 (d, 2H, H_4 or H_7) ; 8.07 (s, 2H, H'_5 and H'_6) ; 7.92 (s, 2H, H_5 and H_6) ; 7.73 (d, 2H, H'_3 or H'_8) ; 7.71 (d, 2H, H_3 or H_8) ; 7.31 (d, 4H, H'_o) ; 7.16 (d, 4H, H_o) ; 5.83 (d, 8H, H'_m and H_m) ; 3.65 (s, 4H, H_ϵ) ; 3.56 to 3.26 (m, 16H, $H_{\alpha,\beta,\gamma,\delta}$).

Preparation of catenate 7$^+$. (Strategy A).

A mixture of **6**$^+$ (1.252 g, 1.16 mmol) and **3** (0.599 g, 1.31 mmol) in DMF (100 ml) was added dropwise within 30 h under efficient stirring to an argon flushed suspension of Cs_2CO_3 (1.300 g, 3.98 mmol) in 200 ml DMF kept at 50-55°. The mixture, first orange-yellow, turned progressively dark brown-red. At the end of addition, stirring and heating was continued for 40 h. DMF was removed under high vacuum and the dark red residue taken up in H_2O-CH_2Cl_2. The aqueous layer was extracted three times with 100-ml portions of CH_2Cl_2. In order to eliminate open-chain (oligomers) copper(I) complexes also formed in the reaction, the dark red combined organic layers were treated with 100 ml 34% HBF_4 solution overnight (magnetic stirring, room temperature). The latter procedure allowed uncharacterized decomplexed oligomers to settle down in the flask as a yellow glue which could be easily removed by decantation. After decantation, the remaining dark red CH_2Cl_2 layer was washed twice with water and thereafter treated (3 h) with a large excess of $NaBF_4$ dissolved in a minimum of water. By the means of this exchange reaction, we obtained **7**$^+$, originally formed as carbonate, iodide and tetrafluoborate, exclusively as its BF_4^- salt. The resulting organic layer, washed twice with water, was dried over $MgSO_4$ and evaporated to dryness to yield 977 mg of a dark red solid. Column chromatography on silicagel (eluant CH_2Cl_2) gave 289 mg **4** (45% yield, CH_2Cl_2 containing 0.5 to 1% MeOH) and pure **7**$^+$ (624 mg, 42% yield, CH_2Cl_2 containing 1 to 5% MeOH).

7$^+$. Dark red needles (mp : 274-275°). ^{1}H-NMR (CD_2Cl_2) : 8.66 (d, 4H, H_4 or H_7) ; 8.28 (s, 4H, H_5 and H_6) ; 7.87 (d, 4H, H_3 or H_8) ; 7.37 (d, 8H, H_o) ; 6.02 (d, 8H, H_m) ; 3.82 (s, 8H, H_ϵ) ; 3.70 (m, 8H, H_δ) ; 3.62 (m, 8H, H_α) ; 3.59 (m, 8H, H_γ) ; 3.48 (m, 8H, H_β). Absorption (CH_2Cl_2, λ_{max} (nm) [log ϵ]) : 248 [4.85] ; 275 [4.76] ; 323 [4.68] ; 440 [3.48] ; shoulder near 475 and 600.

Anal. calc. for $C_{68}H_{68}N_4O_{12}$ BF_4Cu : C, 63.65 ; H, 5.30 ; N, 4.37 ; Cu, 4.91. Found : C, 63.46 ; H, 5.39 ; N, 4.41 ; Cu, 4.84.

One-pot synthesis of 7$^+$ (Strategy B)

By the double-ended needle transfer technique, 570 mg (1.81 mmol) of $Cu(CH_3CN)_4.BF_4$ in 30 ml degassed CH_3CN were added under argon at room temperature to a stirred degassed solution of **2** (1.092 g, 3.0 mmol) in 20 ml DMF. The mixture turned dark red instantaneously, indicating the formation of **8**$^+$. After the solution was stirred for 1 h under argon at room temperature, the solvents were evaporated to dryness : dark red solid of crude **8**$^+$ was obtained in quantitative yield (1.318 g, 1.5 mmol). Complex **8**$^+$ was used without further purification.

A mixture of **8**$^+$ (1.318 g, 1.5 mmol) and **3** (1.517 g, 3.31 mmol) in DMF (200 ml) was added dropwise within 20 h under efficient stirring to an argon flushed suspension of Cs_2CO_3 (3.000 g, 9.20 mmol) in 400 ml DMF kept at 60-62°. The mixture, yellow at the beginning, turned progressively to a dark brown colour. Reaction was monitored by TLC which showed that **3** was consumed faster than **8**$^+$. Supplementary **3** (0.550 g, 1.20 mmol) in 50 ml DMF was added over a period of 20 h. After this second addition of **3**, stirring and heating was continued for 24 h. DMF was then evaporated and the dry dark red residue taken up in H_2O-CH_2Cl_2. Work-up similar to that described under strategy A (HBF_4 and $NaBF_4$ treatments) gave 1.242 g of crude **7**$^+$. Column chromatography on silica gel (eluant $CHCl_3$) yielded 340 mg of **4** (20% yield, $CHCl_3$ containing 0.5% MeOH) and pure **7**$^+$ (530 mg, 27% yield, $CHCl_3$ containing 2 to 5% MeOH). An analytical sample of **7**$^+$ was obtained by recrystallization in hot CH_2Cl_2-toluene (1:1).

Demetallation of **7**$^+$ to afford **9**

KCN (1.00 g, 15.38 mmol) dissolved in water (10 ml) were added to **7**$^+$ (0.956 g, 0.745 mmol) in CH_3CN (40 ml). The characteristic dark red colour of the magnetically stirred solution disappeared progressively whereas free ligand **9**, completely insoluble in CH_3CN, precipitated as a pink solid. Addition of 30 ml CH_2Cl_2 dissolved the floculated solid and allowed completion of the demetallation. After 3 h stirring, the resulting pale yellow solution was evaporated to dryness and taken up in H_2O-CH_2Cl_2. The aqueous layer was extracted with three 50-ml portions of CH_2Cl_2 ; combined organic layers were carefully washed three times with water, dried over $MgSO_4$ and evaporated to dryness : crude **9** was thus obtained quantitatively (0.843 g) as a colourless solid. Analytical sample was obtained by recrystallization in CH_2Cl_2-C_6H_6 (0.780 g, 92% yield).

9$^+$. Colourless needles (mp : 183-184°). ^{1}H-NMR (CD_2Cl_2) : 8.49 (d, 8H, H_o) ; 8.29 (d, 4H, H_4 or H_7) ; 8.11 (d, 4H, H_3 or H_8) ; 7.78 (s, 4H, H_5 and H_6) ; 7.11 (d, 8H, H_m) ; 4.20 (t, 8H, $CH_{2\alpha}$) ; 3.70 (s, 8H, $CH_{2\varepsilon}$) ; 3.74 to 3.62 (m, 24 H, $CH_{2\beta,\gamma,\delta}$). MS : 1133 ($MH^+$). Absorption ($CH_2Cl_2$, λ_{max} (nm) [log ε]) : 227 [4.69] ; 240 [4.77] ; 285 [4.88] ; 321 [4.62] ; shoulder at 342 [4.55]. Anal. calc. for $C_{68}H_{68}N_4O_{12}$: C, 72.06 ; H, 6.05 ; N, 4.94. Found : C, 72.08 ; H, 6.15 ; N, 4.73.

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