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Molecular Composite Knots

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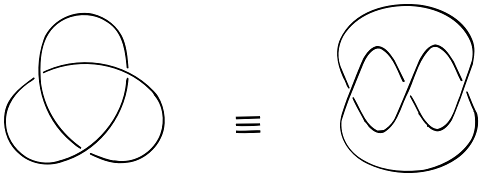
Abstract: Molecular composite knots have been prepared from transition metal-assembled precursors via a Glaser acetylenic coupling reaction. The templating metal is copper(I), and the coordinating fragments incorporated into the final structure are 1,10-phenanthroline-type chelates. The compounds are *composite* knots as opposed to prime knots such as the classical trefoil knot. By combining two tied open-chain fragments in a cyclodimerization reaction, the simplest composite knots are obtained as a mixture of two topological diastereomers. The minimum number of crossing points used to represent the molecules in a plane is six. Due to the complexity of the entangled precursors and to the several cyclization possibilities, the formation yield of composite knots is only modest (~3%). On the other hand, the compound has been fully characterized by ES-MS (molecular weight, 4037.8) and by ^{1}H NMR spectroscopy, including 2D NMR (NOESY).

Knot theory is a very active field of mathematics within the more general area of topology.[1] As real objects, the emergence of knots is mostly due to the recognition of their existence in biology. DNA forms beautiful catenanes and knots, which have been characterized by electron microscopy,[2] the first single-stranded DNA knot being reported in 1976 by Liu et al.[3] Interestingly, knots have also been identified in proteins, by careful screening of X-ray structures.[4] In chemistry, a few landmark papers[5−10] have introduced and developed some essential topology concepts that have been applied to hypothetical molecules, thus bringing closer two scientific fields that appeared *a priori* relatively remote from one another. On the borderline between synthetic chemistry and biology, Seeman and co-workers have created a fascinating family of interlocking ring systems and knots, constructed on single-stranded DNA.[11]

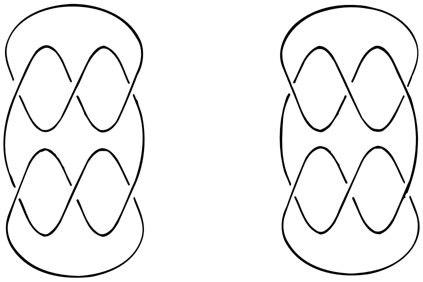
A few years ago, some of us reported the synthesis of a molecular trefoil knot,[12] i.e., the simplest nontrivial prime knot. We now report that our synthetic approach can be extended to the preparation of *composite knots* (composite, as opposed to prime; see Chart 1) consisting of two trefoil knot units. The strategy is represented in Figure 1.

Several important requirements have to be fulfilled for the strategy of Figure 1b to be successful. In particular, the order-creating step (iii) generating (E) will have to be favored over the numerous other possible reactions between (D) and the metal centers. This prerequisite can be reached by careful design of the various fragments to be incorporated in the multifunctional linear thread D and by application of the knowledge acquired in the course of the synthesis of various molecular trefoil knots.[13,14]

Chart 1



A trefoil knot ($\mathbf{3_1}$)



Composite knots from $\mathbf{3_1}$

Results and Discussion

A. Design and Synthesis. (1) Molecular String 1. The design of the multifunctional linear thread D necessary to follow strategy b of Figure 1 toward composite knots F and G was achieved by taking advantage of the knowledge acquired during all of our preceding templated syntheses. Accordingly, by a multistep procedure depicted in Figure 2, we synthesized the molecular string **1**, which appeared suitable for our target. The two 1,10-phenanthroline nuclei of each two-chelate coordinating fragment (intermediate compounds **5** and **6**) are separated by 1,3-phenylene spacers since this linker was revealed to be highly efficient in the elaboration of other double-stranded helical

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(1) Adams, C. C. *The Knot Book*; W. H. Freeman: New York, 1994.

(2) Hudson, B.; Vinograd, J. *Nature (London)* **1967**, *216*, 647. Clayton, D. A.; Vinograd, J. *Nature (London)* **1967**, *216*, 652. Wasserman, S. A.; Cozzarelli, N. R. *Science* **1986**, *232*, 951. Krasnow, M. A.; Stasiak, A.; Spengler, S. J.; Dean, F.; Koller, T.; Cozzarelli, N. R. *Nature (London)* **1983**, *304*, 559.

(3) Liu, L. F.; Depew, R. E.; Wang, J. C. *J. Mol. Biol.* **1976**, *106*, 439.

(4) Liang, C.; Mislow, K. *J. Am. Chem. Soc.* **1994**, *116*, 11189; **1995**, *117*, 4201.

(5) Frisch, H. L.; Wasserman, E. *J. Am. Chem. Soc.* **1961**, *83*, 3789.

(6) Schill, G. *Catenanes, Rotaxanes and Knots*; Academic Press: New York, 1971.

(7) Walba, D. M. *Tetrahedron* **1985**, *41*, 3161.

(8) Sauvage, J. P., Ed. *New J. Chem.* **1993**, *17*, (special issue).

(9) Liang, C.; Mislow, K. *J. Math. Chem.* **1994**, *15*, 35.

(10) *Supramolecular Stereochemistry*; Siegel, J. S., Ed.; Nato ASI Series; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1995.

(11) Seeman, N. C.; Chen, J. *Nature (London)* **1991**, *350*, 631. Seeman, N. C.; Zhang, Y. *J. Am. Chem. Soc.* **1994**, *116*, 1661.

(12) Dietrich-Buchecker, C. O.; Sauvage, J.-P. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 189. Dietrich-Buchecker, C. O.; Guilhem, J.; Pascard, C.; Sauvage, J. P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1154.

(13) Dietrich-Buchecker, C. O.; Sauvage, J. P.; Kintzinger, J. P.; Maltèse, P.; Pascard, C.; Guilhem, J. *New J. Chem.* **1992**, *16*, 931.

(14) Dietrich-Buchecker, C. O.; Sauvage, J.-P.; De Cian, A.; Fischer, J. *J. Chem. Soc., Chem. Commun.* **1994**, 2231.

S0002-7863(96)01459-X CCC: $12.00

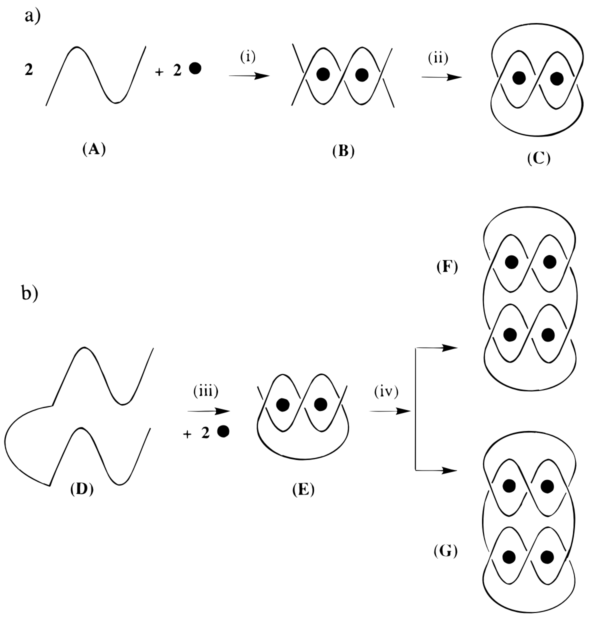
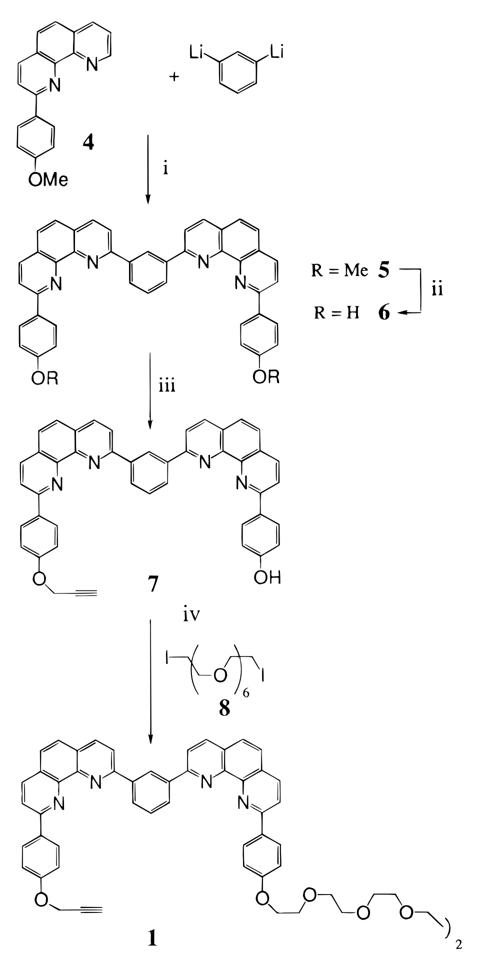


Figure 1. (a) Strategy previously used for making the knot (C) by (i) intertwining two molecular threads (A) around two transition metal centers (black dots) to form a double-stranded helical complex (B), followed by (ii) a double cyclization reaction leading to the knotted structure (C). (b) In the present work, two fragments, each containing two chelating units, are interlinked to afford the long four-coordination site molecular thread D. In a first step (iii) (D) is preorganized by coordination to two metal centers to afford the precursor (E). In a cyclodimerization reaction (iv) involving chemical functions attached to the two ends of the semiknotted thread of (E), (F) and (G) are obtained. (F) is a chiral species, both helical components being left-handed, whereas (G) is the meso species (left- and right-handed double helices present in the molecule). It should be noted that, for the sake of simplicity, in this figure and throughout this paper only one enantiomer for a chiral species is depicted and represents this enantiomer together with its mirror image.

complexes.[14-16] Propargyl ethers were introduced as end-functional groups so that the cyclization step (iv) of Figure 1 can be performed by a Glaser−Eggligton coupling reaction of terminal acetylenes. We selected this latter reaction in the present work because it turned out to be particularly advantageous in previous cyclooligomerization reactions leading to [3]- and [poly]catenates.[17] Finally, in order to allow the system to find its way to the desired precursor by complexation to two metal centers (formation of (E) in Figure 1), we connected the two rigid blocks **7** (expected to become the two strands of the helical core) by a long and flexible linker **8** derived from heptaethylene glycol.

The bridged bis-1,10-phenanthroline **5** was prepared in 62% yield by reacting 1,3-dilithiobenzene[18] with 2 equiv of 2-(*p*-anisyl)-1,10-phenanthroline (**4**) in tetrahydrofuran[22] at room temperature followed by hydrolysis and oxidation by MnO_2. Diphenol **6** was obtained by the drastic pyridinium chloride demethylation procedure described earlier[13,19] and subsequently reacted with 1 equiv of propargyl bromide, thus affording the monoacetylenic subunit **7** in 46% yield after chromatographic purification. Finally, the linear thread **1** was formed in 82% yield by reacting 2 equiv of bis-chelate **7** with 1 equiv of the chain **8**, diiodo derivative of heptaethylene glycol.[20]



i) 45h, MnO_2, RT / ii) Py·HCl, 200°C / iii) K_2CO_3, $BrCH_2C{\equiv}CH$, 50° C
iv) Cs_2CO_3, 60°C

Figure 2. Acyclic precursors and synthetic reactions leading to the four-coordination site molecular thread **1**.

(2) Synthesis of the Helical Precursor Copper Complex. The long flexible tetrachelating compound **1**, corresponding to the molecular thread D of Figure 1, was expected to afford the double-helical precursor E (Figure 1) in the presence of 2 equiv of copper(I). In fact, when **1** was reacted with $[Cu(CH_3CN)_4{}^+][PF_6{}^-]$ in acetonitrile, we obtained a mixture of two copper(I) complexes $\mathbf{2}^{2+}$ and $\mathbf{3}^{2+}$ depicted in Figure 3.

Both complexes appeared very stable (no detectable ligand exchange or equilibration even after 1 h heating at 60 °C in DMSO). Unfortunately, they could not be separated by chromatography since they displayed identical deep red color and absolutely identical polarity. Nevertheless, ^1H NMR and mass spectroscopy studies allowed us to determine the precise nature as well as the respective proportions of $\mathbf{2}^{2+}$ and $\mathbf{3}^{2+}$. The two complexes, formed in a 1/3−7/3 ratio, had both helical structures as clearly evidenced by the highly characteristic chemical shift of their H_3; $H_{3'}$ protons (see Figure 7)[12,13] and corresponded to complexes of the type one ligand/two copper-

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(15) Rüttiman, S.; Piguet, C.; Bernardinelli, G.; Bocquet, B.; Williams, A. F. *J. Am. Chem. Soc.* **1992**, *114*, 4230.

(16) Constable, E. C.; Hannon, M. J.; Tocher, D. A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 230. Constable, E. C.; Hannon, M. J.; Tocher, D. A. *J. Chem. Soc., Dalton Trans.* **1993**, 1883.

(17) Dietrich-Buchecker, C. O.; Khemiss, A. K.; Sauvage, J.-P. *J. Chem. Soc., Chem. Commun.* **1986**, 1376. Bitsch, F.; Dietrich-Buchecker, C. O.; Khemiss, A. K.; Sauvage, J.-P.; Van Dorsselaer, A. *J. Am. Chem. Soc.* **1991**, *113*, 4023.

(18) Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847.

(19) Curphey, T. J.; Hoffman, E. J.; McDonald, C. *Chem. Ind.* **1967**, 1138.

(20) Crude heptaethylene glycol was obtained by distillation of commercially available PEG 300. The heptaethylene glycol containing fraction was transformed into the corresponding ditosylate, which was purified by chromatography according to: Fenton, D. E.; Parkin, D.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 449. Finally, the ditosylate was reacted with NaI in refluxing acetone to afford quantitatively the diiodo derivative **8**.

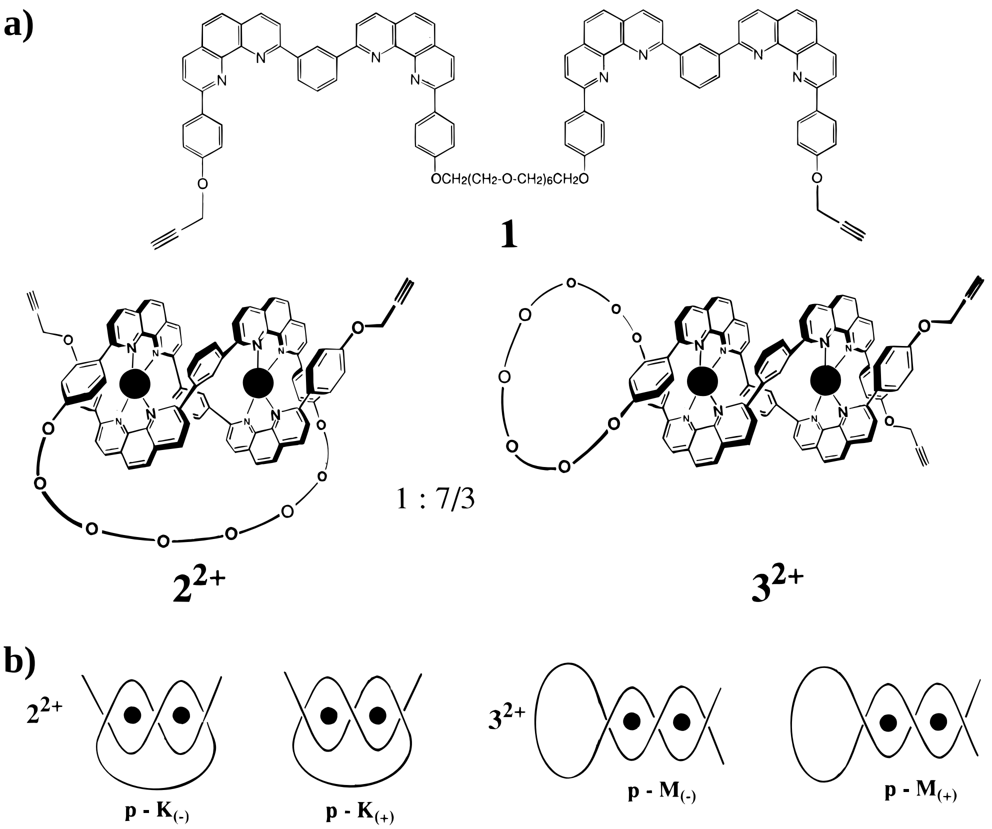
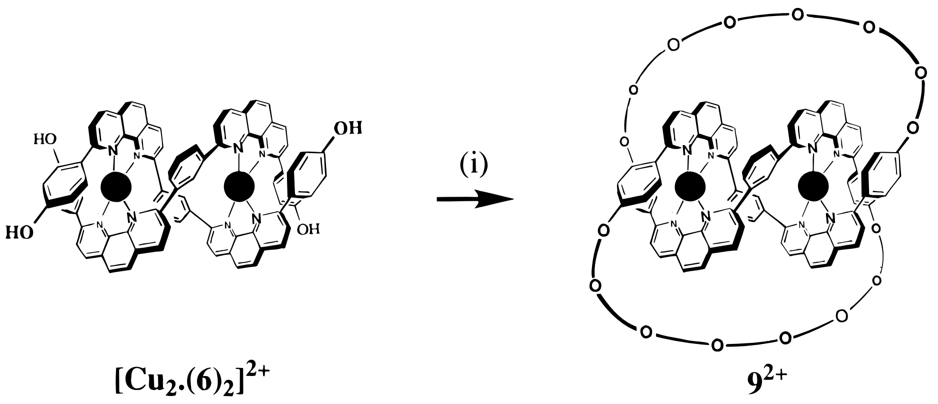


Figure 3. (a) The two helicoidal dicopper(I) precursor complexes: preknot $\mathbf{2}^{2+}$ and premacrocycle $\mathbf{3}^{2+}$. (b) Schematic representation of their enantiomers.



(i) = $ICH_2(CH_2OCH_2)_6CH_2I$, Cs_2CO_3 , DMF , 60°C

Figure 4. Synthesis of the reference prime knot $\mathbf{9}^{2+}$.

(I) as shown by ES-MS. Additional information about their precise structures was only gained after we achieved the independent synthesis of the corresponding prime trefoil knot $\mathbf{9}^{2+}$ depicted in Figure 4.

Careful comparison between the ^{1}H NMR and ^{13}C NMR spectra of the well-characterized knot $\mathbf{9}^{2+}$ and the mixture of precursor complexes ($\mathbf{2}^{2+}$, $\mathbf{3}^{2+}$) allowed us to identify the minor component $\mathbf{2}^{2+}$ as being the expected (E) type preknot of Figure 1. $\mathbf{9}^{2+}$ and $\mathbf{2}^{2+}$ had virtually superimposable spectra both in the aromatic region and for the signals corresponding to the poly(oxyethylene) fragments. This evidenced the strong similarity in the spatial arrangement of the organic backbone for $\mathbf{9}^{2+}$ and $\mathbf{2}^{2+}$. These preliminary conclusions were later fully confirmed when we determined the structures of the cyclization compounds derived from $\mathbf{2}^{2+}$ and $\mathbf{3}^{2+}$.

(3) Cyclodimerization Leading to the Composite Knots. Since the precursors $\mathbf{2}^{2+}$ and $\mathbf{3}^{2+}$ could not be isolated pure, the acetylenic oxidative coupling reaction (cyclodimerization step expected to afford the composite knots) was attempted on their crude mixture following the procedure described earlier.[17] A DMF solution containing ($\mathbf{2}^{2+}$, $\mathbf{3}^{2+}$) was stirred for 3 days at room temperature in the presence of large amounts of CuCl and $CuCl_2$. After workup and chromatographic separation (on silica with CH_2Cl_2 plus small amounts of CH_3OH as eluent), three varieties of complexes were isolated and characterized as the compounds ($\mathbf{10}^{4+}$, $\mathbf{11}^{4+}$), ($\mathbf{12}^{4+}$, $\mathbf{13}^{4+}$), and ($\mathbf{14}^{4+}$, $\mathbf{15}^{4+}$) in 2.5, 4.8, and 1.8% yield, respectively (Figure 5).

An ES-MS study readily showed that the complexes isolated and depicted in Figure 5, $\mathbf{10}^{4+}$ to $\mathbf{15}^{4+}$, were all *cyclic dimers*. They all displayed exactly the same mass spectra as the one expected for the composite knots: three peaks observed at 1873.94, 1200.85, and 864.47 corresponding to [dimer $(PF_6)_2]^{2+}$, [dimer$(PF_6)]^{3+}$, and [dimer]$^{4+}$, respectively. But since these tetranuclear species resulted from cyclodimerization reactions

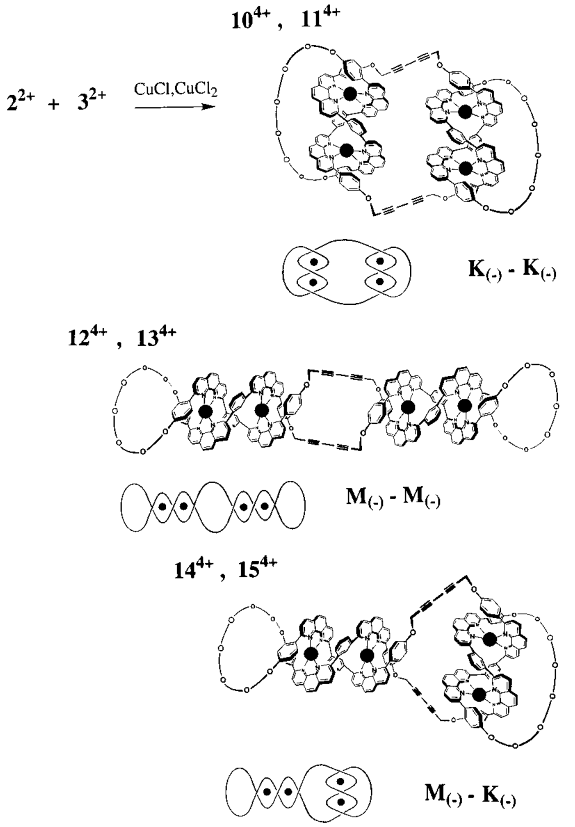


Figure 5. Cyclization reaction leading to the three families of dimers, K−K, M−M, and K−M. Note that $\mathbf{10}^{4+}$ (K$_{(-)}$−K$_{(-)}$) and $\mathbf{11}^{4+}$ (K$_{(-)}$−K$_{(+)}$) correspond to (F) and (G) in Figure 1, respectively.

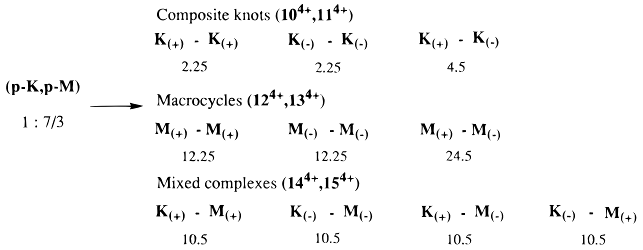


Figure 6. Expected theoretical yields of the various topological diastereoisomers when starting from a preknot (p-K) and premacrocycle (p-M) mixture in a 1:7/3 ratio.

occurring among two types of precursors (preknot $\mathbf{2}^{2+}$ and premacrocycle $\mathbf{3}^{2+}$), each of them being chiral, many isomers were equally expected. The various topological stereoisomers (enantiomers or diastereoisomers) that were assumed to be the outcome from cyclodimerization reactions between $\mathbf{2}^{2+}$ and $\mathbf{3}^{2+}$ are schematically represented in Figure 6. Presuming that both precursors display the same reactivity and knowing that they were present in the initial mixture in a 1/3−7/3 ratio, we were also able to forsee, according to statistical laws, the proportions in which each product will be formed.

Table 1

	$\mathbf{9}^{2+}$	($\mathbf{10}^{4+}$ + $\mathbf{11}^{4+}$) major	($\mathbf{10}^{4+}$ + $\mathbf{11}^{4+}$) minor	($\mathbf{12}^{4+}$ + $\mathbf{13}^{4+}$)^{a}
$H_{3/3'}$	*6.49*	6.61/*6.52*	6.55/*6.52*	6.45
$H_{4/4'}$	*7.86*	8.22/*7.87*	8.01/*7.86*	7.73
$H_{5/5'}$	*7.91*	8.23/*7.92*	*7.93*	7.78
$H_{6/6'}$	*7.99*	8.02/*7.99*	*7.99*	7.90/7.85
$H_{7/7'}$	*8.39*	8.35/*8.42*	8.44/*8.40*	8.32/8.23
$H_{8/8'}$	*7.66*	7.62/*7.70*	7.72/*7.74*	7.62/7.43
$H_{9/9'}$		4.56/4.44	4.63/4.51	4.41/3.82
H_a	*9.71*	*9.72*	*9.74*	9.55
$H_{b/b'}$	*6.95*	*6.96*	*6.96*	*6.82*
H_c	7.18	7.15	7.21	7.03
$H_{o/o'}$	*7.07*	*7.07*/7.19	*7.10*/7.16	7.09/6.88
$H_{m/m'}$	*5.71*	*5.70*/5.93	*5.72*/5.98	5.85/5.63
H_{α}	*3.29*	*3.29*	*3.29*	3.52
H_{η}	*3.91*	*3.90*	*3.90*	2.83

[a] Dimers $\mathbf{12}^{4+}$ and $\mathbf{13}^{4+}$ being formed in a 1/1 ratio and presenting strong similarities in their ^{1}H NMR spectra; the table gives only average values for the chemical shifts of their protons. Depending on which proton is considered, this average concerns either two identical protons belonging to both diastereoisomers $\mathbf{12}^{4+}$ and $\mathbf{13}^{4+}$ (H_c for example) or two nonidentical but undiscrimable protons located on the same diastereoisomer as for example H_3 and $H_{3'}$.

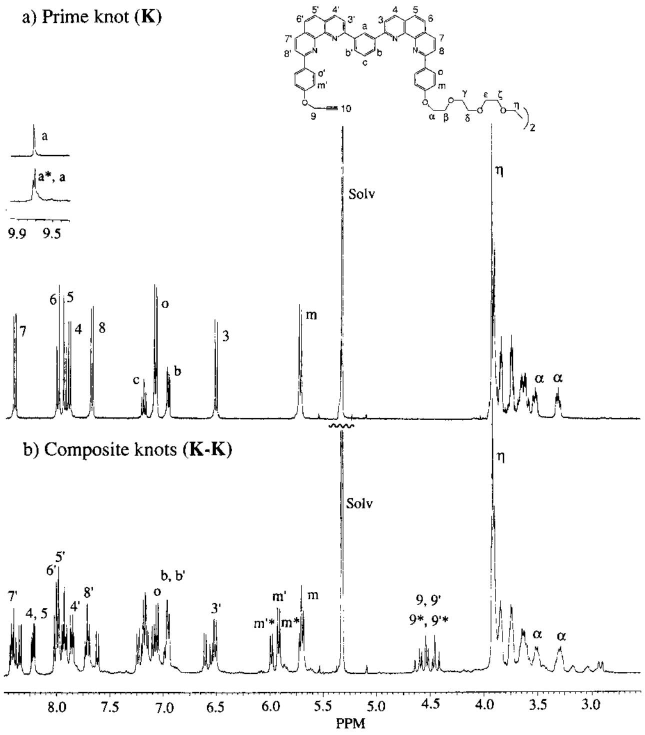


Figure 7. ^{1}H NMR spectra at 400 MHz in CD_2Cl_2 of the prime knot K ($\mathbf{9}^{2+}$) and the composite knots (K−K) (dimers $\mathbf{10}^{4+}$, $\mathbf{11}^{4+}$) with numbering scheme.

B. Characterization of the Composite Knots. Whereas the dimeric nature of the copper(I) complexes belonging to one of the three topologically different families given in Figure 6 (K−K, M−M, or K−M family) was easily established by mass spectroscopy, discrimination between them appeared much more difficult and could finally only be achieved after an extensive 1- and 2-D ^{1}H NMR study. The data obtained during these studies are collected in Table 1 (see Experimental Section) and clearly indicate close similarities between the reference prime trefoil knot $\mathbf{9}^{2+}$ and the complexes ($\mathbf{10}^{4+}$, $\mathbf{11}^{4+}$). Although we cannot specify which diastereoisomer of the latter family is involved, we see nevertheless that the ^{1}H NMR spectrum of one of them is totally superposable with that of $\mathbf{9}^{2+}$. This striking analogy observed in the aromatic region as well as in the 3−4 ppm region (where the various signals corresponding to the polyoxyethylenic chains appear) strongly suggested that the dimers ($\mathbf{10}^{4+}$, $\mathbf{11}^{4+}$) were the desired target composite knots (Figure 7). Our assumption was fully confirmed by the observation of a *strong interfragment NOE between the central protons of the flexible chains (H_{η}) and some of the protons located on the phenanthroline backbones ($H_{4'}$ and $H_{5'}$).* This effect, also observed for $\mathbf{9}^{2+}$ and all the previous knots studied so far[13] brought precious information about the spatial arrangement of the $OCH_2(CH_2OCH_2)_nCH_2O$ fragments relative to the phenanthrolines. Such spatial relative disposition was not

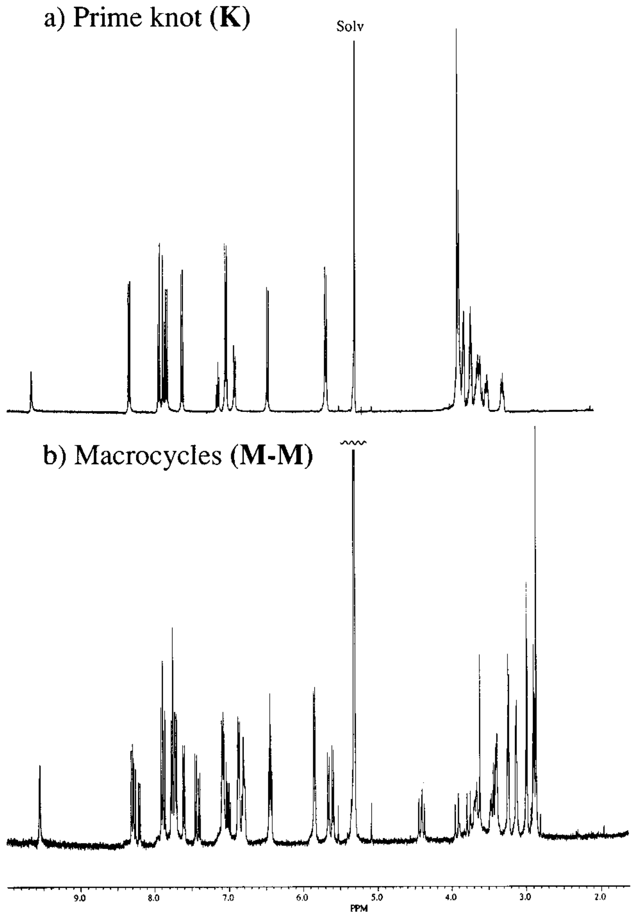


Figure 8. ^1H NMR spectra at 400 MHz in CD_2Cl_2 of the prime knot K ($\mathbf{9}^{2+}$) and the M−M dimer family (complexes $\mathbf{12}^{4+}$, $\mathbf{13}^{4+}$).

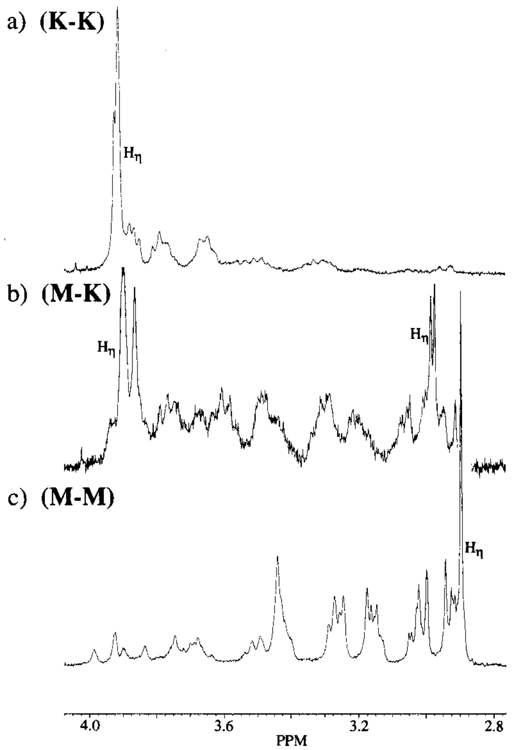


Figure 9. ^1H NMR spectra (3−4 ppm region) at 400 MHz in CD_2Cl_2 of the dimers, K−K, K−M, and M−M.

observed for the two other families of dimers, ($\mathbf{12}^{4+}$, $\mathbf{13}^{4+}$) and ($\mathbf{14}^{4+}$, $\mathbf{15}^{4+}$).

Contrasting strongly with ($\mathbf{10}^{4+}$, $\mathbf{11}^{4+}$), the family of the major dimers isolated ($\mathbf{12}^{4+}$, $\mathbf{13}^{4+}$) showed between 3 and 4 ppm a ^1H NMR pattern totally different from that observed for the prime knot $\mathbf{9}^{2+}$, its most striking feature being the chemical shift of the H_η protons located in the central part of the polyoxyethylenic chains; their signal at 2.83 ppm (upfield chemical shift of over 1 ppm when compared to the 3.9 value in $\mathbf{9}^{2+}$ or ($\mathbf{10}^{4+}$, $\mathbf{11}^{4+}$) indicated that they were located very close to aromatic nuclei. On the other hand, the aromatic region of the spectrum, although slightly different from that obtained for the prime or composite knots, brought clear evidence that the dimers ($\mathbf{12}^{4+}$, $\mathbf{13}^{4+}$) contained like ($\mathbf{10}^{4+}$, $\mathbf{11}^{4+}$) double helices in their central core (see Figure 8). Finally, additional observation of a strong interfragment NOE between H_η and H_m, H_o of the pendent phenyl nuclei but no longer with the phenanthroline's $H_{4'}$ and $H_{5'}$, suggested that the flexible chains now stayed far away from the phenanthroline-containing helical core, as would be the case in a dimeric macrocycle curled up onto four copper(I) centers (see Figure 5). Our tentative structure elucidation could later be confirmed by a demetalation experiment. Reaction of the dimers ($\mathbf{12}^{4+}$, $\mathbf{13}^{4+}$) with a large excess of KCN afforded a white, almost insoluble solid in quantitative yield. Its FAB mass spectrum was the one expected for a dimer (peaks observed at 3206.8 and 1603.5 for $[M{\cdot}3H]^+$ and $[M{\cdot}3H]^{2+}$, respectively) whereas its ^1H NMR spectrum, very similar to that of the precursor molecular string **1**, corresponded fully to that expected for a large flexible macrocycle.

The third family of dimers obtained in the Glaser coupling reaction performed on the mixture of preknot $\mathbf{2}^{2+}$ and premacrocycle $\mathbf{3}^{2+}$ could be identified by comparative ^1H NMR studies as being "mixed" complexes. The latter denomination accredits only their special topology: according to the NMR data, each topological diastereoisomer of the ($\mathbf{14}^{4+}$, $\mathbf{15}^{4+}$) family appeared as the summation of one preknot (p-K) and one premacrocycle (p-M). Each of these species being chiral (left- or right-handed), their association may lead to four topologically distinct compounds and hence we expected a rather complicated ^1H NMR spectrum.

The ^1H NMR spectrum of ($\mathbf{14}^{4+}$, $\mathbf{15}^{4+}$) did indeed present an intractable aromatic region from which no structural information could be drawn, but by contrast, the 3−4 ppm area brought clear evidence for the "mixed" structure proposed. As shown in Figure 9, the signals between 3 and 4 ppm (protons of the polyoxyethylenic chains) resulted from the overlap of the two patterns characterizing the composite knots K−K ($\mathbf{10}^{4+}$, $\mathbf{11}^{4+}$) and the dimers of type M−M ($\mathbf{12}^{4+}$, $\mathbf{13}^{4+}$), respectively. It is worthwhile to mention that these K−M type dimers present only three crossing points and therefore are, despite their complicated appearance, simple trefoil knots.

Identification of the three types of dimers K−K, M−M, and K−M being achieved, we were subsequently able to estimate the global outcome of the coupling reaction to which a precursors p-K and p-M mixture had been submitted. The most striking feature was certainly the fact that target composite knot K−K was obtained in a yield far superior to the one anticipated. Indeed, according to statistical distribution laws, we expected the dimers K−K/M−M/K−M in a 9/49/42 ratio, but in fact they were obtained in the ratio 28/54/18. This diastereoselection favoring strongly the composite knots K−K versus dimers M−M and K−M may be related to a more suitable spatial arrangement of the two terminal acetylenic functions in a relatively rigid preknot p-K when compared to that in premacrocycle p-M. Similar considerations may also help to explain an other surprising observation: within each family of dimers containing the K subunit (either K−K or K−M) the various possible topological diastereoisomers (see Figure 6) were again not formed according to the statistical distribution laws. The ^{1}H NMR spectrum of the composite knots given in Figure 7 illustrates nicely this latter statement: instead of the 1/1 ratio expected for the two enantiomers ($K_{(+)}-K_{(+)}$; $K_{(-)}-K_{(-)}$) and the meso diastereoisomer $K_{(+)}-K_{(-)}$, we observe a 1/2 ratio. In this case, enantioselectivity is clearly observed. Either homochiral or heterochiral composite knots are preferred, indicating that in the course of the cyclization reaction leading to the product, weak forces between the two constituent preknot fragments are significant and tend to favor interactions between preknots of identical or different chirality respectively.

In conclusion, the present work demonstrates the power of synthetic strategies based on the use of transition metals as templates. Some time ago, simple catenanes were made available on a real preparative scale,[24] and the level of complexity of the compounds prepared increased gradually with time since the first report. In parallel, the simplest nontrivial knot was obtained, first in very low yield and, recently, in a much more preparative fashion.[14] This improvement suggested that more complex knots and composite knots should become accessible, although the real making of such molecular systems would have appeared totally unrealistic only a decade ago. The synthesis of the composite knots **10**$^{4+}$ and **11**$^{4+}$ is still far from being really preparative, but it represents a good indication that molecular chemical topology may be extended in the future toward more and more complex systems, in a way reminiscent of the DNA-based approach developed by Seeman and co-workers.[11] In addition to the synthesis of the composite knots **10**$^{4+}$ and **11**$^{4+}$, an interesting but unexpected observation was made, related to the selectivity of dimer formation. Remarkably, when two preknots p-K (E of Figure 1 or **2**$^{2+}$ of Figure 3) react with one another to form a cyclic product (composite knot), some kind of enantioselection clearly takes place via intermolecular interactions between the two units to be coupled.

Experimental Section

General Procedures. All the chemicals were of the best commercially available grade and were used without further purification. Thin-layer chromatography (TLC) was performed on aluminum sheets coated with silica gel 60 F_{254} (Merck 5554), or on plastic sheets precoated with aluminium oxide N/UV_{254} (Macherey Nagel 802021). After elution, the plates were either examined under a UV lamp or exposed to I_2. Column chromatography was carried out on silica gel 60 (Merck 9385, 230−400 mesh). UV−visible spectra were recorded on a Kontron Instruments Uvikon 860 spectrophotometer. Fast atom bombardment mass spectrometry (FAB-MS) was performed using a krypton primary atom beam in conjunction with a 3-nitrobenzyl alcohol matrix on a ZAB-HF mass spectrometer. Electrospray mass spectrometry was performed by dissolving the compound or complex in CH_2Cl_2 and injecting the solution into a VG BioQ triple-quadrupole spectrometer (VG BioTech Ltd., Altrincham, UK), with a mass-to-charge (m/z) range of 4000, using a cone voltage (V_c) of 40 V, and a source temperature of $\sim$30 °C. The ^{1}H NMR spectra were recorded with a Bruker AC 300, WP200 SY, or WP400SY spectrometer.

Preparation of 5. A 14.5 mL sample of *t*-BuLi (1.2 M in pentane, 17.4 mmol) was added very slowly to a degassed solution of 1.00 g (4.2 mmol) of 1,3-dibromobenzene in 50 mL of dry THF, under argon, at −78 °C.[18] After this addition, the solution was warmed to 0 °C and then immediately cooled to −78 °C. The solution was titrated according to the literature[21] in order to see whether all the *t*-BuLi had reacted and was then added over 3 h to a degassed solution of 2.43 g (8.5 mmol) of **4**[22] in 100 mL of dry THF, under argon at room temperature. After the resulting dark red solution was stirred for a further 45 h under argon at room temperature, it was hydrolyzed with water and then evaporated to dryness. The crude product was dissolved in CH_2Cl_2 and washed with water. The organic layer was rearomatized with MnO_2 ($\sim$20 g), dried over $MgSO_4$, filtered, and adsorbed on aluminium oxide (activity grade II−III). Column chromatography on aluminium oxide eluted with $CHCl_3$/hexane (1/1), then with $CHCl_3$, and finally with $CHCl_3$ + 5% MeOH afforded pure **5** (3.45 g, 5.3 mmol, 62% yield): ^{1}H NMR ($CDCl_3$) δ 9.75 (s, 1H, H_a), 8.72 (d, 2H, H_b, $J = 7.8$ Hz), 8.55 (m, 8H, $H_{3,4,o}$), 8.30 (d, 2H, H_7, $J = 8$ Hz), 8.11 (d, 2H, H_8, $J = 8$ Hz), 7.82 (t, 1H, H_c, $J = 7.8$ Hz), 7.80 (s, 4H, $H_{6,5}$), 7.06 (d, 4H, H_m, $J = 8$ Hz); FAB-MS m/z found 647.2 $[MH]^+$, calcd 647.7.

Preparation of 6. 6 was obtained following the literature procedure:[22] 1.22 g (1.0 mmol) of **5** was added, under argon, to $\sim$60 mL of anhydrous pyridinium hydrochloride at 130 °C. After the solution was refluxed at 190−200 °C for 4 h, the mixture was cooled to 130 °C and hydrolyzed. The yellow crude acidic diphenol **6** was suspended in 80 mL of hot water and the suspension neutralized to pH $\sim$7.3. Filtration and drying afforded red **6** (1.02 g, 1.6 mmol, 86% yield): ^{1}H NMR (DMSO-d_{-6}) δ 9.87 (s, 2H, H_{OH}), 9.74 (s, 1H, H_a), 8.72 (d, 2H, H_b, $J = 7.8$ Hz), 8.66 (m, 4H, $H_{3,4}$), 8.50 (d, 2H, H_7, $J = 8.4$ Hz), 8.40 (d, 4H, H_o, $J = 8.4$ Hz), 8.27 (d, 2H, H_8, $J = 8.4$ Hz), 8.00 (s, 4H, $H_{6,5}$), 7.91 (t, 1H, H_c, $J = 7.8$ Hz), 6.88 (d, 4H, H_m, $J = 8.4$ Hz); FAB-MS m/z found 619.1 $[MH^+]$, calcd 619.6.

Preparation of 7. According to literature,[23] 1 g (1.6 mmol) of **6** and 0.66 g (3.84 mmol) of K_2CO_3 in 50 mL of DMF were stirred under argon at 50 °C for 1 h; a solution of 121 μL (1.6 mmol) of $BrCH_2C\equiv CH$ in 10 mL of DMF was then added dropwise. After a further 6 h stirring at 50 °C, the suspension was cooled, filtered, and evaporated to dryness. Column chromatography over aluminium oxide (eluent $CHCl_3$ + 4% MeOH) yielded pure **7** (0.49 g, 0.74 mmol, 46% yield): ^{1}H NMR (DMSO-d_{-6}) δ 9.81 (s, 1H, H_{OH}), 9.77 (s, 1H, H_a), 8.75−8.50 (m, 10H, $H_{b,b',o,o',3,3',4,4'}$), 8.37 (d, 2H, $H_{7,7'}$, $J = 9$ Hz), 8.28 (m, 2H, $H_{8,8'}$), 8.03 (s, 2H, $H_{6,5}$), 8.00 (s, 2H, $H_{6',5'}$), 7.90 (t, 1H, H_c, $J = 7.8$ Hz), 7.02 (d, 2H, H_m, $J = 8.4$ Hz), 6.82 (d, 2H, $H_{m'}$, $J = 8.4$ Hz), 4.85 (d, 2H, H_9, $J = 2$ Hz), 3.61 (t, 1H, H_{10}, $J = 2$ Hz); FAB-MS m/z found 657.1 $[MH^+]$, calcd 657.7.

Preparation of 1. A suspension of **7** (0.78 g, 1.19 mmol) and Cs_2CO_3 (3 g, 9.2 mmol) was stirred in 12 mL of freshly distilled DMF, under argon at 60 °C, for 1 h. Then a solution of **8**[20] (0.31 g, 0.47 mmol) in 30 mL of DMF was added dropwise over 8 h. The solution was stirred overnight, under argon at 60 °C, then cooled, filtered, and evaporated to dryness. Crude **1** was dissolved in $CHCl_3$, washed with water, and then adsorbed onto aluminium oxide. Column chromatography over aluminium oxide (eluent, $CHCl_3$/EtOEt = 1/1 and then $CHCl_3$) yielded pure **1** (0.612 g, 0.382 mmol, 82% yield): ^{1}H NMR ($CDCl_3$) δ 9.72 (s, 2H, H_a), 8.76 (m, 4H, $H_{b,b'}$), 8.40 (m, 16H, $H_{o,o',3,3',4,4'}$), 8.26 (d, 2H, H_7, $J = 8.4$ Hz), 8.24 (d, 2H, $H_{7'}$, $J = 8.4$ Hz), 8.07 (d, 2H, H_8, $J = 8.4$ Hz), 8.05 (d, 2H, $H_{8'}$, $J = 8.4$ Hz), 7.82 (t, 2H, H_c, $J = 8$ Hz), 7.78 (s, 8H, $H_{6',5',6,5}$), 7.12 (d, 4H, $H_{m'}$, $J = 8.8$ Hz), 7.04 (d, 4H, H_m, $J = 8.4$ Hz), 4.77 (d, 4H, H_9, $J = 2.2$ Hz), 4.19 (m, 4H, H_α), 3.89 (m, 4H, H_β), 3.65 (m, 20H, $H_{\gamma\rightarrow\eta}$), 2.59 (t, 2H, H_{10}, $J = 2.2$ Hz); ES-MS m/z found 1604.3 ($[MH]^+$) calcd 1604.7; found 802.5 ($[M{\cdot}2H]^{2+}$), calcd 802.9; found 535.3 ($[M{\cdot}3H]^{3+}$), calcd 535.6; found 401.7 ($[M{\cdot}4H]^{4+}$), calcd 401.9.

Preparation of 2^{2+} and 3^{2+}. Complexes **2**$^{2+}$ and **3**$^{2+}$ were obtained according to the literature[22] by mixing 120 mg (0.075 mmol) of **1** and 55.8 mg (0.15 mmol) of $[Cu(CH_3CN)_4]PF_6$ in CH_3CN, under argon. The solution was stirred for 1 h, and after the solvent was evaporated to dryness **2**$^{2+}$ and **3**$^{2+}$ were obtained in quantitative yield as a mixture. The two complexes exhibit the same color and R_f. Therefore, they could not be isolated and fully characterized: ^{1}H NMR (CD_2Cl_2) δ 9.68 (s, 2H, H_a), 8.42−8.35 (m, 4H, $H_{7,7'}$), 8.00−7.78 (m, 12H, $H_{6',5',6,5,44'}$), 7.66 (m, 4H, $H_{8,8'}$), 7.16−7.06 (m, 8H, $H_{o,o'}$), 7.01 (t, 2H, H_c, $J = 8$ Hz), 6.94−6.87 (m, 4H, $H_{b,b'}$), 6.58−6.47 (m, 4H, $H_{3,3'}$), 5.91−5.66 (m, 8H, $H_{m,m'}$) 4.24−4.21 (m, 4H, H_9), 3.90−2.83 (m, 28H, OCH_2CH_2O), 2.65 (t, 2H, H_{10}, $J = 2.2$ Hz). ES-MS m/z found 1875.8 ($[M(PF_6)]^+$), calcd 1875.9; found 864.9 ($[M]^{2+}$), calcd 865.4.

Preparation of 9^{2+}. A 388 mg (0.628 mmol) sample of **6** was reacted according to the literature[14,22] in CH_3CN with 234 mg (0.628

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(21) Gilman, H.; Cartledge, F. K. J. *J. Organomet. Chem.* **1964**, *2*, 447.

(22) Dietrich-Buchecker, C. O.; Nierengarten, J. F.; Sauvage, J.-P.; Armaroli, N.; Balzani, V.; De Cola, L. *J. Am. Chem. Soc.* **1993**, *115*, 11237.

(23) Dietrich-Buchecker, C. O.; Hemmert, C.; Khemiss, A. K.; Sauvage, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 8002.

(24) Dietrich-Buchecker, C. O.; Sauvage, J. P.; Kintzinger, J. P. *Tetrahedron Lett.* **1983**, *24*, 5095. Dietrich-Buchecker, C. O.; Sauvage, J.-P.; Kern, J.-M. *J. Am. Chem. Soc.* **1984**, *106*, 3043.

mmol) of $[Cu(CH_3CN)_4]PF_6$ to obtain the tetraphenolic double helix. The 520 mg (0.314 mmol) of the tetraphenolic double helix and 360 mg (0.659 mmol) of **8** in the presence of 1.1 g (3.4 mmol) of Cs_2CO_3 were reacted according to the literature.[14,22] Column chromatography on silica gel (eluent, CH_2Cl_2 + 4% MeOH) and then on aluminium oxide (eluent, CH_2Cl_2 + 2.5% MeOH) yielded $\mathbf{9}^{2+}$ (160 mg, 0.071 mmol, 22% yield): ^1H NMR, see Table 1; ES-MS *m*/*z* found 2090.0 ($[M(PF_6)]^+$), calcd 2090.1; found 972.5 ($[M]^{2+}$), calcd 972.6.

Preparation of the Dimers $\mathbf{10}^{4+}$ to $\mathbf{15}^{4+}$. Under highly anhydrous conditions, 450 mg (0.223 mmol) of the crude mixture ($\mathbf{2}^{2+}$ + $\mathbf{3}^{2+}$), 3.02 g (30.5 mmol) of anhydrous CuCl, and 0.72 g (5.3 mmol) of anhydrous $CuCl_2$ were suspended in 32 mL of dry DMF in a simple one-necked, round-bottomed flask. The latter was stoppered with a drying tube filled with silica gel so that the mixture was protected against moisture but in contact with air. The dark brown-red suspension was magnetically stirred at room temperature over 3 days, after which the DMF was evaporated to dryness. The almost black solid residue was taken up in 200 mL of CH_2Cl_2 and 200 mL of 5% HCl−water solution. After decantation, the acidic aqueous layer was extracted five times with 50 mL portions of CH_2Cl_2. The combined organic layers were washed twice with 100 mL portions of 5% HCl solution and once with pure water. This wet CH_2Cl_2 phase was then treated (overnight, magnetic stirring) with a large excess of KPF_6 dissolved in a minimum of water. By means of this exchange reaction the dimers were obtained exclusively as their PF_6^- salts. The resulting organic layer, washed with water, was dried and evaporated to dryness to yield ∼102 mg of a crude dark red mixture of dimers $\mathbf{10}^{4+}$ to $\mathbf{15}^{4+}$. Column chromatography on silica gel (eluent, CH_2Cl_2 + 3% MeOH) afforded 23 mg of ($\mathbf{10}^{4+}$ + $\mathbf{11}^{4+}$) (2.5% yield), 40 mg of ($\mathbf{12}^{4+}$ + $\mathbf{13}^{4+}$) (4.8% yield) and 14 mg of ($\mathbf{14}^{4+}$ + $\mathbf{15}^{4+}$) (1.6% yield): ^1H NMR, see Table 1; ES-MS *m*/*z* found 1873.9 ($[M(PF_6)_2]^{2+}$), calcd 1873.9; found 1200.8 ($[M(PF_6)]^{3+}$), calcd 1200.9; found 864.5 ($[M]^{4+}$), calcd 864.5.

Demetalation of ($\mathbf{12}^{4+}$, $\mathbf{13}^{4+}$). Pure ($\mathbf{12}^{4+}$, $\mathbf{13}^{4+}$) (0.040 g, 0.01 mmol) in CH_2Cl_2 (20 mL) was treated with a large excess of KCN (0.440 g, 6.8 mmol) at room temperature. This demetalation reaction, monitored by TLC and the disappearance of the characteristic dark red color of the magnetically stirred solution, was only complete after 4 days, during which the KCN had been added in successive batches (∼110 mg each). After decantation of the colorless CH_2Cl_2 layer, we observed the formation of a white precipitate between both phases. It was filtered on paper, washed with water, and dried affording the pure macrocycle **16** as a colorless solid (0.030 g, quantitative yield): ^1H NMR (DMSO-d_{-6}) δ 9.68 (s, 4H, H_a), 8.50 (d, 8H, $H_{b,b'}$, $J = 8$ Hz), 8.48−8.44 (m, 8H, $H_{3,3'}$), 8.40−8.35 (m, 8H, $H_{4,4'}$), 8.33−8.26 (m, 24H, $H_{7,7',o,o'}$), 8.05 (d, 4H, $H_{8'}$, $J = 8.4$ Hz), 8.03 (d, 4H, H_8, $J = 8.4$ Hz), 7.82 (s, 8H, $H_{5',6'}$), 7.80 (s, 8H, $H_{5,6}$), 7.66 (t, 4H, H_c, $J = 8$ Hz), 6.80 (d, 8H, $H_{m'}$, $J = 8.9$ Hz), 6.73 (d, 8H, H_m, $J = 8.9$ Hz), 4.85 (s, 8H, H_9), 3.92 (m, 8H, H_α), 3.63 (m, 8H, H_β), 3.50−3.43 (m, 40H, $H_{\gamma\rightarrow\eta}$); FAB-MS *m*/*z* found 3206.8 ($[M{\cdot}3H]^+$), calcd 3206.6; found 1603.5 ($[M{\cdot}3H]^{2+}$), calcd 1603.3.

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