quenched with a solution of citric acid. The mixture was diluted with DCM (100 mL) and washed with sodium bicarbonate (sat.), water, and brine (25 mL each). The organic layer was dried (Na_2SO_4), evaporated, and the residue was dissolved in DCM/MeOH (98/2) and filtered through a plug of silica gel. Evaporation gave the crude precursor of **2** (773 mg). To this crude product (746 mg) in dry THF (40 mL) was added methanesulfonic acid (300 µL). After stirring the mixture at RT for 72 h under nitrogen, pyridine (400 µL), DIPEA (1.5 mL), and acetic anhydride were added at 0 °C. After 2 h the solution was diluted with DCM (100 mL), washed with sodium bisulfate (1 M), water, sodium bicarbonate (sat.), water, and brine (25 mL each). The organic layer was dried (Na_2SO_4), filtered, evaporated, and chromatographed (silica gel, DCM/MeOH (98/2)) to afford **2** (360 mg, 40 % based on **1**).

3: To **2** (60 mg, 0.051 mmol) in DCM (1 mL), TFA (0.5 mL) was added dropwise and stirred for 1 h at 0 °C. The reaction mixture was diluted with DCM (50 mL) and washed three times with sodium bicarbonate (sat.) then water and brine (10 mL each). The organic layer was dried (Na_2SO_4), evaporated, and redissolved in DCM (0.5 mL). Boc-(2*S*,3*R*,4*R*,6*E*)-3-hydoxy-4-methyl-2-(methylamino)-6-octenoic acid (Boc-MeBmt) [21] (18.7 mg, 0.062 mmol), bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP) [22] (27 mg, 0.060 mmol) and DIPEA (27 µL) were added at 0 °C under nitrogen. After 2 h at 0 °C the reaction was allowed to warm to RT, diluted with DCM (50 mL), washed with sodium bisulfate (1 M), water, sodium bicarbonate (sat.), water, and brine (20 mL each). The organic layer was dried (Na_2SO_4), filtered, evaporated and chromatographed (flash silica gel, EtOAc/acetone (9/1)) to give **3** (56 mg, 81 %).

4: To **3** (27 mg, 0.022 mmol) in DCM (1 mL), TFA (0.5 mL) was added dropwise and stirred for 1 h at 0 °C, diluted with DCM (50 mL) and washed three times with with sodium bicarbonate (sat.), water and brine (10 mL each). The organic layer was dried (Na_2SO_4), filtered and evaporated. To the residue in DCM (30 µL), Fmoc-N-MeIle (12 mg, 0.032 mmol), PyBroP (14 mg, 0.032 mmol) and DIPEA (15 µL) were added and the mixture was stirred for 6 h at 0 °C and 30 min at RT. Fmoc-N-MeIle (5 mg, 0.013 mmol), PyBroP (5 mg, 0.011 mmol) were added again at 0 °C and allowed to warm to RT overnight. The mixture was diluted with DCM (50 mL), washed with sodium bisulfate (1 M), water, sodium bicarbonate (sat.), water, brine (20 mL each). The organic layer was dried (Na_2SO_4), filtered, evaporated, and chromatographed (silica gel, EtOAc/acetone 9:1) to afford **4** (19 mg, 60 %).

5: To **4** (4.6 mg, 0.0028 mmol) in THF/water (10:1, 200 µL), DBU (3 µL) and lithium bromide (2 mg) were added. After stirring overnight at RT, DBU (4 µL) and lithium bromide (3 mg) were added again. After 5 h, the reaction was quenched with acetic acid (20 µL) and purified by reverse-phase HPLC (Beckman ODS ultrasphere 5 µ 10 mm × 25 cm, 0.1 % TFA/MeCN 70/30 → 10/90 in 30 min, 70 °C, 3 runs) to yield the peptide precursor of **5** (2.1 mg, 60 %). A solution of this peptide precursor (1.2 mg, 970 nmol), AOP [17] (4 mg, 0.009 mmol) and 2,6-lutidine (4 µL) in DCM (1.2 mL) was stirred for 48 h at RT. The reaction mixture was quenched with acetic acid (30 µL), the DCM evaporated, and the residue dissolved in acetonitrile and purified by reverse-phase HPLC (Beckman ODS ultrasphere 5 µ 10 mm × 25 cm, 0.1 % TFA/MeCN 70/30 → 10/90 in 30 min. 70 °C) to afford the pure cyclic peptide **5** (0.65 mg, 55 %).

Received: June 9, 1995 [Z8080IE]
German version: *Angew. Chem.* **1995**, *107*, 2313–2317

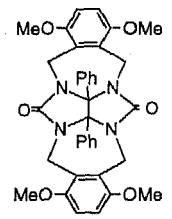
Keywords: cyclophilin · cyclosporin · immunophilins · protein dimerization

[1] D. J. Austin, G. R. Crabtree, S. L. Schreiber, *Chem. & Biol.* **1994**, *1*, 131.
[2] M. A. Lemmon, J. Schlessinger, *Trends Biochem. Sci.* **1994**, *19*, 459.
[3] A. C. Chan, D. M. Desai, A. Weiss, *Annu. Rev. Immunol.* **1994**, *12*, 555.
[4] W. H. Landschulz, P. F. Johnson, S. L. McKnight, *Science* **1988**, *240*, 1759.
[5] D. M. Spencer, T. J. Wandless, S. L. Schreiber, G. R. Crabtree, *Science* **1993**, *262*, 1019.
[6] M. N. Pruschy, D. M. Spencer, T. M. Kapoor, H. Miyaki, G. R. Crabtree, S. S. L. Schreiber, *Chem. & Biol.* **1994**, *1*, 163.
[7] H. Ke, D. Mayrose, P. J. Belshaw, D. G. Alberg, S. L. Schreiber, Z. Y. Chang, F. A. Etzkorn, S. Ho, C. T. Walsh, *Structure (London)* **1994**, *2*, 33.
[8] G. Pflugl, J. Kallen, T. Schirmer, J. N. Jansonius, M. G. Zurini, M. D. Walkinshaw, *Nature* **1993**, *361*, 91.
[9] V. F. Quesniaux, M. H. Schreier, R. M. Wenger, P. C. Hiestand, M. W. Harding, M. H. V. Van Regenmortel, *Eur. J. Immunol.* **1987**, *17*, 1359.
[10] T. Clackson, J. A. Wells, *Science* **1995**, *267*, 383.
[11] J. S. Richardson, D. C. Richardson in *Prediction of protein structure and the principles of protein conformation, Vol. XIII*; (Ed. G. D. Fasman), Plenum, New York, **1989**.
[12] G. Sarkar, S. S. Sommer, *BioTechniques* **1990**, *8*, 404.
[13] P. J. Belshaw, S. L. Schreiber, *Chem. & Biol.*, submitted.
[14] R. Oliyai, V. J. Stella, *Pharm. Res.* **1992**, *9*, 617.
[15] A. Ruegger, M. Kuhn, H. Lichti, H. R. Loosli, R. Huguenin, C. Quiquerez, W. A. Von, *Helv. Chim. Acta.* **1976**, *59*, 1075.
[16] R. E. Ireland, W. J. Thompson, *Tetrahedron Lett.* **1979**, 4705.
[17] L. A. Carpino, F. A. El, *J. Org. Chem.* **1994**, *59*, 695.
[18] R. E. Handschumacher, M. W. Harding, J. Rice, R. J. Drugge, D. W. Speicher, *Science* **1984**, *226*, 544.
[19] H. Husi, M. Zurini, *Anal. Biochem.* **1994**, *222*, 251.
[20] L. D. Zydowsky, F. A. Etzkorn, H. Y. Chang, S. B. Ferguson, L. A. Stolz, S. I. Ho, C. T. Walsh, *Protein Sci.* **1992**, *1*, 1092.
[21] W. D. Lubell, T. F. Jamison, H. Rapoport, *J. Org. Chem.* **1990**, *55*, 3511.
[22] J. Coste, E. Frerot, P. Jouin, *J. Org. Chem.* **1994**, *59*, 2437.
[23] A. Nicholls, K. A. Sharp, B. Honig, *Prot. Struct. Funct. Genet.* **1991**, *11*, 283.

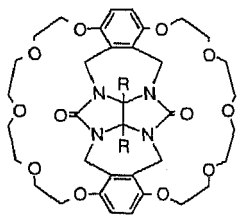
Strong Binding of Paraquat and Polymeric Paraquat Derivatives by Basket-Shaped Hosts**

Albertus P. H. J. Schenning, Bas de Bruin, Alan E. Rowan,* Huub Kooijman, Anthony L. Spek, and Roeland J. M. Nolte

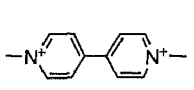
Clip-shaped host molecules of type **1** can bind uncharged aromatic guest molecules, for example resorcinol, by π–π stacking and hydrogen bonding interactions.[1] Basket-shaped derivates of **1** containing crown ether moieties (compounds of type **2**) are, in addition, able to bind alkali metal ions and protonated amines.[2] We report here on the binding affinities of these host molecules towards charged aromatic compounds, such as paraquat **3** and the polymeric paraquat derivatives **4** and



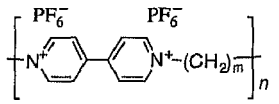
1



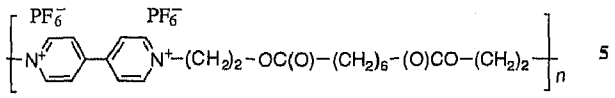
2 a, R = C_6H_5
b, R = $CH_3C_6H_4$



3



4 a, *m* = 5
b, *m* = 8



5

5. There is currently a great deal of interest in paraquat-binding, which has resulted in the design and construction of new molecular structures, as exemplified by the elegant work by Stoddart et al. on catenands and rotaxanes.[3] We describe here that com-

[*] Dr. A. E. Rowan, Dipl.-Chem. A. P. H. J. Schenning, Dipl.-Chem. B. de Bruin, Prof. Dr. R. J. M. Nolte
Department of Organic Chemistry, NSR Center
University of Nijmegen
Toernooiveld, NL-6525 ED Nijmegen (The Netherlands)
Telefax: Int. code +(80) 553450
Dr. H. Kooijman, Dr. A. L. Spek
Bijvoet Center for Biomolecular Research, Crystal and Structural Chemistry
Utrecht University (The Netherlands)

[**] This work was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO).

pound **2** is an exceptionally good host for paraquat. This opens the possibility of clipping host molecules of type **2** to polymeric chains containing paraquat units. The X-ray structure and properties of the complex between **2** and paraquat are also presented.

Compounds **1** and **2** were synthesized as described previously.[1, 2] For the synthesis of **2b**, 4,4'-dimethylbenzil was used as the starting material. Compounds **3** and **4** were prepared by using literature procedures.[3, 4] Compound **5** was prepared by the condensation of *N*,*N*'-bis(2-hydroxyethyl)-4,4'-bipyridinium hexafluorophosphate in acetonitrile with one equivalent of adipoyl chloride with triethylamine as the base,[5] and purified by precipitation from ethyl acetate.

Addition of **3**-Cl_2 to a solution of host **2b** in for example methanol/chloroform led to an immediate color change from colorless to yellow-orange, indicative of the formation of a charge-transfer complex.[3] ^{1}H NMR spectroscopic studies revealed that in this complex the paraquat guest is located in the cleft of the cavity.[6] Fast atom bombardment mass spectrometry (FAB MS) showed a peak at *m/z* 1094 (matrix: nitrobenzyl alcohol), which corresponds to the mass of the host–guest complex. Crystals of the complex between **2b** and **3**-$(PF_6)_2$ suitable for X-ray analysis were grown from a mixture of **2b** and tetrabutylammonium hexafluorophosphate dissolved in chloroform, which was layered with **3**-Cl_2 dissolved in methanol. The X-ray structure of complex is shown in Figure 1 (top).[7] It reveals a

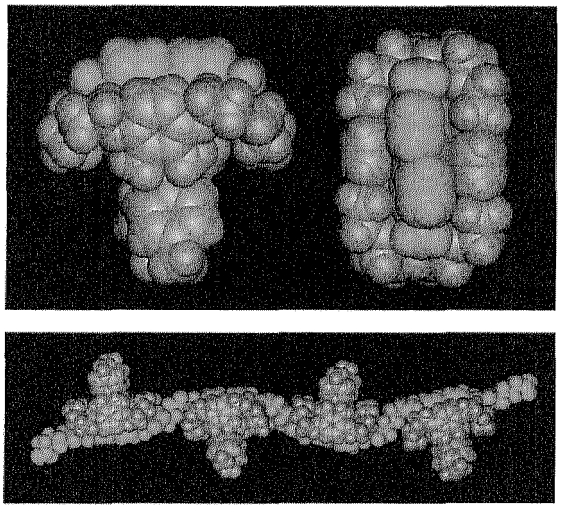


Fig. 1. Top: Crystal structure of the complex between **2b** and **3**-$(PF_6)_2$. Left top view, right side view [14]. Bottom: Computer-generated model of the complex between **2b** and **5**.

perfect complementarity between host and guest. The paraquat guest sits symmetrically within the walls of the basket; the methyl substituents are partially encapsulated by the crown ether rings. The crystal structure is different from that of the complex of paraquat with "bis(paraphenylene)-[34]crown-10" (the same macrocycle as compound **2a**, but without the diphenylglucoluril unit), as published by Stoddart et al.[3] In the case of the latter the bipyridinium guest is flat, whereas in the crystal structure described herein the two bipyridinium units are twisted by an angle of 22.5(3)°. This is a consequence of being less sterically constrained by the aromatic side walls of the basket. In Stoddart's compound the bipyridinium is tilted at an angle of about 28° with respect to the O–O axis of the paraphenylene unit; in our case the bipyridinium guest in the basket is not tilted. The binding constant of the bis(paraphenylene)-[34]crown-10 macrocycle with **3**-$(PF_6)_2$ in acetone is 730 M^{-1}. The binding properties of **1** and **2** were evaluated by recording the intensity of the charge-transfer absorption band at approximately 425 nm at different host–guest ratios. The results for different solvents are presented in Table 1. The basket-shaped host molecules **2** bind paraquat approximately 25–75 times stronger than the bis(paraphenylene)-[34]crown-10 macrocycle.[3] This result can be explained from the fact that compounds **2** are more preorganized for binding than Stoddart's compound.[8] Only a very small K_a of 80 M^{-1} was found for the binding of **3** in the cavity of clip molecule **1**. This clearly demonstrates the importance of the crown ether moieties in **2** for the complexation of paraquat.

Table 1. Binding constants [a] of the complexes between hosts **1** and **2** and guests **3**, **4**, and **5**.

Host	Guest	K_a [M^{-1}]
1	**3**-Cl_2	80 [b]
2a	**3**-$(PF_6)_2$	57000 [c]
2a	**3**-$(PF_6)_2$	20000 [d]
2b	**3**-Cl_2	22000 [b]
2a	**4a** [f]	1800 [c, e]
2a	**4b** [g]	4500 [c, e]
2a	**5** [h]	19000 [c, e]

[a] Association constants were calculated using the Benesi–Hildebrand equation [13]. Good correlations ($R > 0.995$) were obtained for all titration curves assuming a 1:1 host–guest complexation. Estimated error in K_a is 10%. For the K_a measured in acetone, the error is 50% due to the poor solubility of the host molecule in this solvent. [b] Methanol-chloroform (1:1, v/v). [c] Acetonitrile. [d] Acetone. [e] Per polymer repeat unit. [f] Intrinsic viscosity of polymer $[\eta] = 0.006$ dL g^{-1} (acetonitrile, 25 °C). [g] Intrinsic viscosity of polymer $[\eta] = 0.293$ dL g^{-1} (acetonitrile, 25 °C). [h] Average degree of polymerization = 4 (NMR, endgroup analysis).

The electrochemical behavior of the complex between **3**-$(PF_6)_2$ and compound **2a** was studied in acetonitrile. In this solvent the guest showed two reversible one-electron transfers: $E_{1/2}(2+/1+) = -0.423$ V, $E_{1/2}(1+/0) = -0.840$ V (vs. SCE, for both transitions $\Delta E_p = 60$ mV). Upon the addition of one equivalent of **2a** the first redox transfer shifted 100 mV to more negative potential, whereas the second electron transfer potential remained unaffected. These data indicate that **2a** binds and stabilizes the doubly charged paraquat species, which results in a more negative redox potential for the first redox transfer. It is well known that in this type of host–guest system the guest reduced by one electron dissociates form the host, and this explains the unaltered second redox potential.[3]

Polymeric paraquat derivatives have previously been investigated as redox-active films and more recently as optical data storage materials and show a wide variety of electrochromic and thermochromic behavior.[4, 9, 10] The polymeric paraquat derivative with tosylate counterions has been shown to possess liquid crystalline properties.[11, 12] We felt that host–guest complexation might be an interesting way to modify and control the physical properties of this interesting class of polymers. The results of binding studies carried out in acetonitrile, showed that **2a** can be clipped to polymeric paraquat derivatives **4a**, **4b**, and **5** with association constants of 1800 M^{-1}, 4500 M^{-1}, and 19000 M^{-1}, respectively (per polymer repeat unit, see Table 1, Fig. 1). The binding constants of **4a** and **4b** are lower than those observed for paraquat itself. Molecular modeling studies have revealed that in the case of **4a** and **4b**, complexation of a basket to a paraquat unit in the polymer is sterically hindered by baskets complexed to adjacent paraquat units. The overall lower binding constants reflect this steric hindrance, which is less for

  0570-0833/95/3419-2133 $ 10.00+.25/0

the polymer with a longer spacer (**4b**) than for the one with the smaller spacer (**4a**). Viscosity measurements showed that the specific viscosity of the polymers solubilized in acetonitrile increases upon the addition of 0.03 equivalents of the host molecule **2a** per repeat unit: for example, **4a**: $\eta_{sp} = 0.006$, **4a** + **2a** $\eta_{sp} = 0.008$; **4b**: $\eta_{sp} = 0.068$, **4b** + **2a** $\eta_{sp} = 0.070$. These results indicate that the average molecular mass of the polymers increases on complexation with **2a**. The redox potentials of the polymers were also influenced by the hosts. Polymer **4a** displayed the following redox transitions in acetonitrile: $E_{1/2}(2+/1+) = -0.387$ V, $E_{1/2}(1+/0) = -0.840$ V (vs. SCE, for both transitions $\Delta E_p = 60$ mV). Upon the addition of one equivalent of **2a** per repeat unit the first redox transfer shifted 20 mV to more negative potential, whereas the second redox transfer remained unchanged. Addition of three equivalents of **2a** resulted in a 35 mV shift in the negative direction. These shift values are smaller than the 100 mV shift measured for paraquat (**3**) which may be the result of the lower binding affinity of **2a** for the polymeric paraquat derivatives. These preliminary results indicate that the electrochemical behavior of polymeric paraquat derivatives can easily be tuned by the addition of basket molecules. This may be of interest for future application of these polymers as optical data storage systems or as molecular switches, etc.

In conclusion, we have shown that host molecules of the type **2** strongly bind paraquat **3** and that it is possible to clip these molecules to polymeric paraquat derivatives. Further studies are underway.

Received: March 14, 1995 [Z 7792 IE]
German version: *Angew. Chem.* **1995**, *107*, 2288–2289

Keywords: crown ethers · paraquat · supramolecular chemistry

[1] R. P. Sijbesma, A. P. M. Kentgens, E. T. G. Lutz, J. H. van der Maas, R. J. M. Nolte, *J. Am. Chem. Soc.* **1993**, *115*, 8999.
[2] J. W. H. Smeets, R. P. Sijbesma, L. van Dalen, A. L. Spek, W. J. J. Smeets, R. J. M. Nolte, *J. Org. Chem.* **1989**, *54*, 3710.
[3] a) B. L. Allwood, N. Spencer, H. Shahriari-Zavareh, J. F. Stoddart, D. J. Williams, *J. Chem. Soc. Chem. Commun.* **1987**, 1064; b) P. L. Anelli, P. R. Ashton, R. Ballardini, V. Balzani, M. Delgado, M. T. Gandolfi, T. T. Goodnow, A. E. Kaifer, D. Philp, M. Pietraszkiewicz, L. Prodi, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, C. Vicent, D. J. Williams, *J. Am. Chem. Soc.* **1992**, *114*, 193.
[4] T. Ohsaka, M. Nakanishi, O. Hatozaki, N. Oyama, *Electrochim. Acta* **1990**, *35*, 63.
[5] P. R. Ashton, D. Philip, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, D. J. Williams, *J. Chem. Soc. Chem. Commun.* **1991**, 1680.
[6] The following ^{1}H NMR signals of **2a** are shifted by complexation with 3-$(PF_6)_2$ (1:1): (200 MHz, $CD_3CN/CDCl_3$ (7/3, v/v), 25 °C): $\Delta\delta = -0.81$ (s, 4H, Ar-H), +0.07 (AB quartet, 4H, CH_2-N), −0.87 (m, 8H, CH_2O-Ar); likewise for 3-$(PF_6)_2$ by complexation with **2a**: $\Delta\delta = -1.08$ (d, 4H, Ar-H), +0.12 (d, 4H, Ar-H), +0.22 (s, 6H, CH_3).
[7] Crystal data for $[(\mathbf{2b})\cdot(\mathbf{3})\cdot 2PF_6\cdot 2CHCl_3]$: $C_{64}H_{74}N_6O_{12}P_2F_{12}Cl_6$, $M_r = 1622.0$, monoclinic, space group $C2/c$, $a = 32.968(5)$, $b = 13.6135(14)$, $c = 17.875(2)$ Å, $\beta = 118.375(11)°$, $V = 7058.6(17)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.5263(4)$ g cm^{-3}, $Mo_{K\alpha}$ radiation (graphite monochromator), $\mu = 3.9$ cm^{-1}, 7352 intensity data collected at 150 K, 6778 unique, Lp correction, no absorption correction. The structure was solved by direct methods (SHELXS-86) and refined on F^2 (SHELXL-93), no observance criterion applied during refinement. Final $wR2 = 0.226$, $R1 = 0.099$ (for 3162 $I > 2\sigma(I)$), $S = 1.00$. Residual electron density was in the range −0.34, 0.50 (near PF_6). Further details of the crystal structure investigation may be obtained from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB2 1EZ (UK), on quoting the full journal citation.
[8] E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore, D. J. Cram, *J. Am. Chem. Soc.* **1977**, *99*, 2564.
[9] T. Nagumura, Y. Isoda, *J. Chem. Soc. Chem. Commun.* **1991**, 72.
[10] L. P. Yu, E. T. Samulski in *Oriented Fluids and Liquid Crystals, Vol. 4* (Eds.: A. C. Griffin, J. F. Johnson), Plenum, New York, **1984**, p. 697.
[11] P. K. Bhowmik, W. Xu, H. Han, *J. Polym. Sci. Part A: Polym. Chem.* **1994**, *32*, 3205.
[12] P. K. Bhowmik, H. Han, *J. Polym. Sci. Part A: Polym. Chem.* **1995**, *33*, 1745.
[13] J. A. Hildebrand, H. A. Benesi, *J. Am. Chem. Soc.* **1949**, *71*, 2703.

Formation of a "*meso*-Helicate" by Self-Assembly of Three Bis(catecholate) Ligands and Two Titanium(IV) Ions

Markus Albrecht* and Sirpa Kotila

Double- or triple-helical oligonuclear coordination compounds that are formed spontaneously by self-assembly of two or three oligodentate ligands and several metal ions are called helicates. Due to their helicity, such molecules are chiral.[1] On the other hand, *meso*-helicates are analogous metal complexes with two differently configurated helical units and are thus achiral. In a topological sense, the *meso*-helicates are helices that inverse their helical twist.[2]

An octahedral complex formed by one metal center and three bidentate ligands is the most simple helical unit. It can have two configurations (Δ or Λ).[3] Triple bridging between the ligands of two such octahedrons results in the formation of three different coordination compounds: the enantiomeric Δ,Δ- and Λ,Λ-helicates, and the diasteromeric Δ,Λ-form—the most simple triple-stranded *meso*-helicate (Fig. 1).

The coordination chemistry of linear oligodentate nitrogen donor ligands with soft metal ions has recently become the focus of a great deal of attention. To our knowledge, investigations towards the metal-directed self-assembly of helicates have resulted only in the characterization of double-[1, 4] and triple-helical[5] and double-stranded non-helical metal complexes, which do not possess units with helical chirality.[6] In this context, the triple-stranded *meso*-helicate is a missing structural motif.

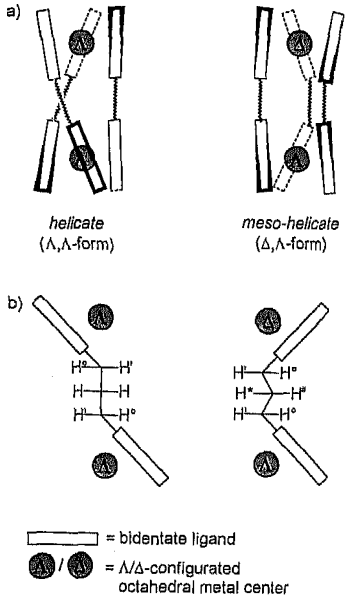


Fig. 1. Schematic representation of a) a helicate (here: Λ,Λ-form) and the corresponding *meso*-helicate (Δ,Λ-form) and b) a binuclear C_3-bridged helicate and *meso*-helicate (only one of the ligand strands is shown).

This stimulated our interest in self-assembly processes based on oxygen donor ligands in combination with hard metal ions.[7, 8] The use of early transition metals should provide access to new supramolecular aggregates, whose properties should differ from those of the "traditional" compounds.

Catechol ligands seem to be ideal bidentate chelating units for this purpose.[8] Initially we chose the $(CH_2)_3$ group as a spacer

[*] Dr. M. Albrecht
Institut für Organische Chemie der Universität
Richard-Willstätter-Allee, D-76131 Karlsruhe (Germany)
Telefax: Int. code + (721)698529
Dr. S. Kotila
Organisch-Chemisches Institut der Universität Münster (Germany)

[**] This work was supported by the Fonds der Chemischen Industrie (Liebig Stipendium), the Deutsche Forschungsgemeinschaft, and the Academy of Finnland. Dr. H. Röttele is thanked for the NMR measurements, Mrs. B. Wibbeling's and Dr. R. Fröhlich's help with the X-ray structure analysis is gratefully acknowledged.