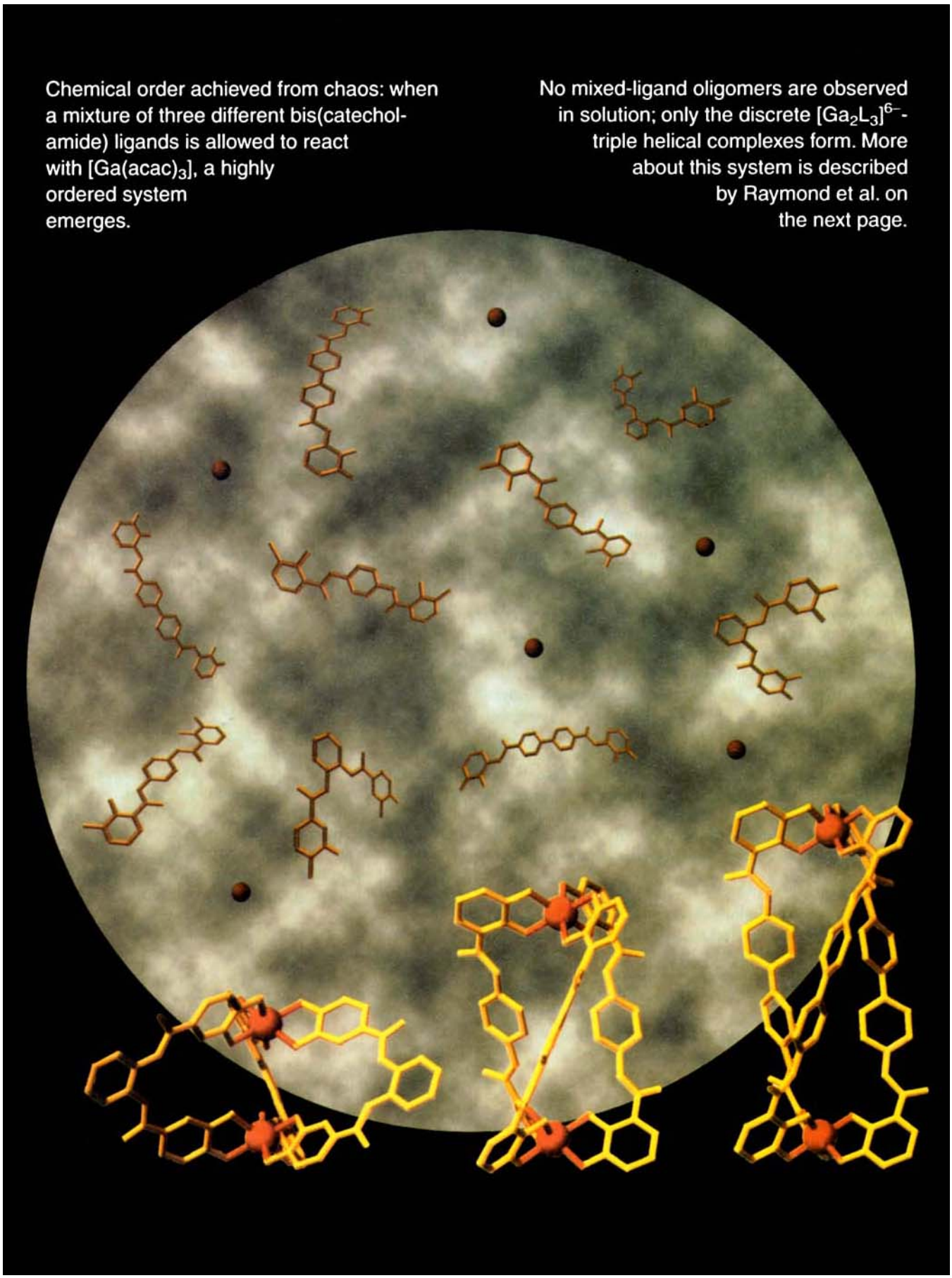
Chemical order achieved from chaos: when a mixture of three different bis(catecholamide) ligands is allowed to react with $[Ga(acac)_3]$, a highly ordered system emerges.

No mixed-ligand oligomers are observed in solution; only the discrete $[Ga_2L_3]^{6-}$-triple helical complexes form. More about this system is described by Raymond et al. on the next page.



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Supramolecular Self-Recognition and Self-Assembly in Gallium(III) Catecholamide Triple Helices**

Dana L. Caulder and Kenneth N. Raymond*

Supramolecular chemistry has been described as a type of molecular information science:[1] a supramolecular assembly is manufactured from the information stored in preprogrammed molecular components. In nature there are numerous examples of highly symmetric supramolecular clusters, including the 24 subunit protein ferritin (pure rotation group *O*) and the 60 subunit coat of the human rhinovirus (pure rotation group *I*).[2, 3] In an analogous process, a few metal–ligand interactions can be used in place of the many, but weaker, interactions that drive the formation of natural molecular clusters. Recently the synthesis of some highly symmetric supramolecular architectures have been reported,[4–7] and we have described a rational design of such structures based on the incommensurate coordination numbers of interacting sites of the cluster.[4, 8]

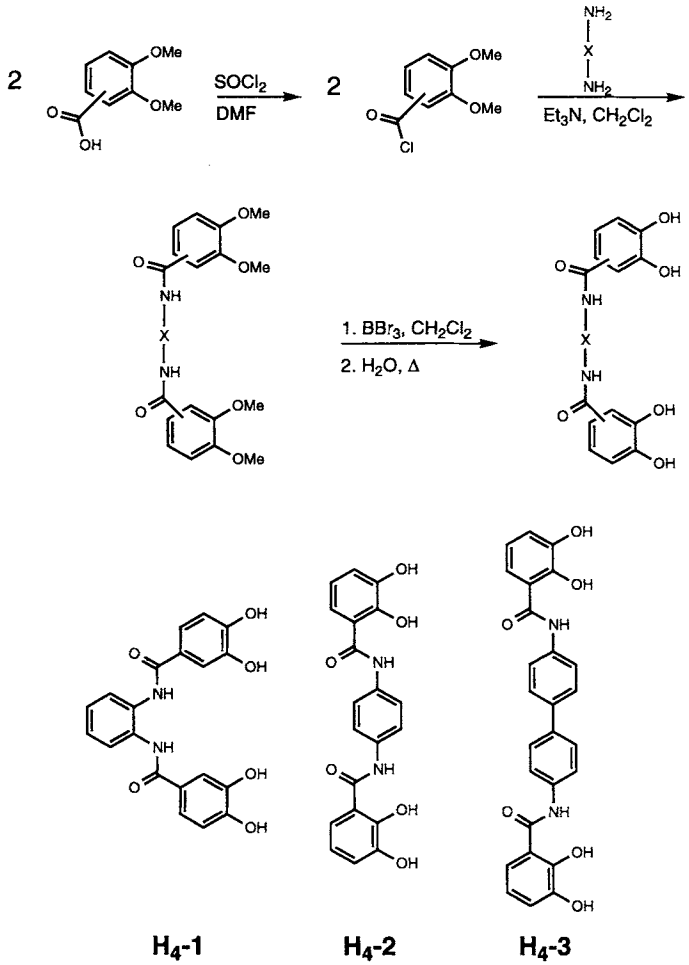
The triple helix formed by two metal centers is one of the simplest assemblies of this type. There are numerous examples of synthetic complexes with helical motifs incorporating bipyridine and benzimidazol ligands.[1, 9–11] More recently there have been examples of helical complexes with oxygen donor ligands, including catechol.[12–14] The exclusive formation of a predesigned cluster requires ligand rigidity, kinetically labile metal–ligand interactions, and thermodynamic stability. These features drive the formation of the thermodynamically favored cluster over the large number of other intermediate polymers. The complexes of catecholamides with Ga^{III} satisfy these requirements.[15, 16]

In a rational design of these self-assembling supramolecular clusters, a series of three bis(catecholamide) ligands (H_4-**1**–H_4-**3**) has been synthesized according to Scheme 1. Molecular mechanics calculations show that for all ligands the chiral helicate is lower in energy than the *meso*-$[M_2L_3]$ cluster.[17, 18] The synthesis of ligand H_4-**2** and the X-ray crystal structures of the gallium complexes of two derivatized versions of this ligand have been reported previously and confirm the helix structure.[12]

It was intended that the information stored in these rigid bis(catecholamide) ligand systems be used to overcome the intrinsic disorder of mixtures in order to produce a highly ordered system of complexes in solution. As will be shown, this has been achieved.

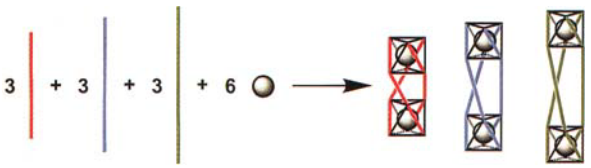
The three ligands H_4-**1**–H_4-**3** were designed to increase the metal–metal distance systematically in the dinuclear helicates, the goal being to probe the effect that size has on the ability of the helicates to form by self-assembly. So far a size limit has not been reached. When three equivalents of any ligand (H_4-**1**–H_4-**3**) are allowed to react with two equivalents of $[M(acac)_3]$ (M = Fe^{III}, Al^{III}, Ga^{III}; acac = acetylacetonate) and KOH in methanol at room temperature, the $K_6[M_2L_3]$ triple helical complexes can be isolated in high yield (70–80%) [Eq. (a)].

$$3\,LH_4 + 2\,[Ga(acac)_3] \xrightarrow[CH_3OH]{KOH} K_6[Ga_2L_3] \qquad \text{(a)}$$



Scheme 1. Synthesis of H_4-**1**–H_4-**3**.

When the complexes are prepared in the presence of excess ligand, there is no disruption of the formation of the $[M_2L_3]$ clusters. The ^{1}H NMR spectrum in all cases shows two sets of peaks, one for the complex and one for the excess ligand. This cooperativity ultimately facilitates the synthesis of controlled mixtures of complexes. Remarkably, when mixtures of any two or all three of the ligands (H_4-**1**–H_4-**3**) are allowed to react with $[Ga(acac)_3]$ under the conditions described above, only complexes containing one type of ligand form (Scheme 2). No



Scheme 2. Schematic representation of self-recognition of ligands in gallium catecholamide triple helices. Rods represent ligands of varying lengths and spheres represent Ga^{III} ions. Only the discrete complexes containing one type of ligand form in solution. No mixed or oligomeric species are observed.

oligomeric mixed-ligand species are observed in solution with ^{1}H NMR spectroscopy or with electrospray mass spectrometry (ES-MS). The ^{1}H NMR spectrum of the resulting solution shows a 1:1:1 mixture of the $K_6[Ga_2(\mathbf{1})_3]$, $K_6[Ga_2(\mathbf{2})_3]$, and $K_6[Ga_2(\mathbf{3})_3]$ helical complexes (Figure 1). This can be confirmed by comparing the resulting spectrum to a simulated spectrum

[*] Prof. K. N. Raymond, D. L. Caulder
Department of Chemistry
University of California
Berkeley, CA 94720-1460 (USA)
Fax: Int. code +(510)486-5283
e-mail: raymond@socrates.berkeley.edu

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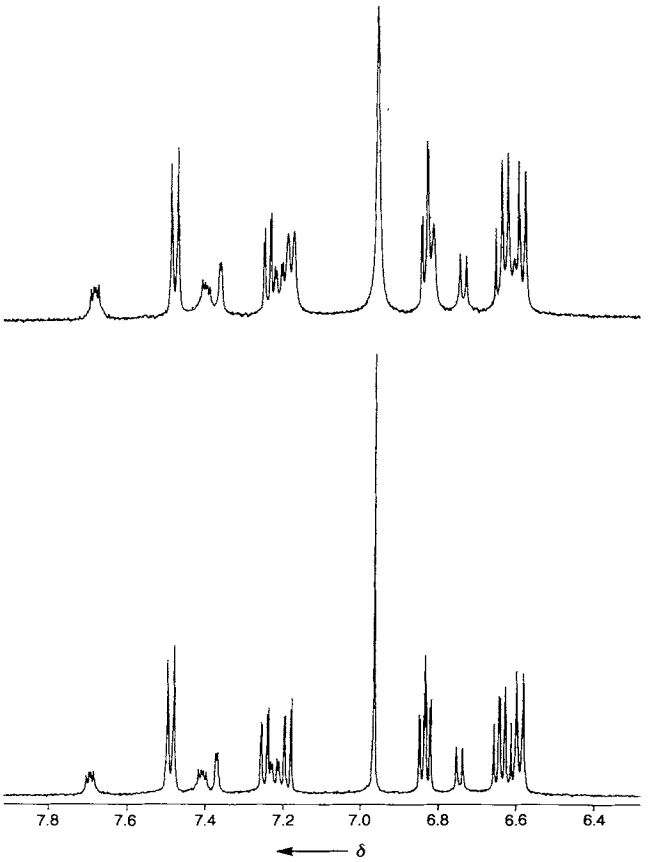

Figure 1. Bottom: ^{1}H NMR spectrum (5% K_2HPO_4, D_2O, pD = 9.2, 300 MHz) of a 3:3:3:2 mixture of **1**, **2**, **3** and [Ga(acac)$_3$] after workup. Top: simulation spectrum obtained by adding the spectra of the individually isolated gallium complexes of **1**, **2**, and **3**. No oligomeric species are observed in solution.

obtained by adding the spectra of the individual complexes. Positive-ion ES-MS (100% CH_3OH) also supports this conclusion, as no peaks from oligomeric mixed ligand species are found; only the $[Ga_2L_3]^{6-}$ complexes are observed.[19]

The driving force for the observed self-recognition is largely a concentration effect. In a closed coordination polymer (that is, all metal sites are coordinated by three catecholamide functionalities) for a simple system with one metal and one ligand, equilibrium (b) can be written. The equilibrium constant for this

$$n[M_2L_3] = [M_2L_3]_n \qquad (b)$$

equation should be approximately 1. Only if the polymer is significantly insoluble will the reaction be driven further to the right, but these species are highly charged and very soluble. Thus if $n = 4$ and the original concentration of the cluster is 2×10^{-3} M, then the polymer concentration will be approximately 10^{-11} M. This entropic driving force is also present with more complicated mixtures of ligands: the formation of mixed-ligand oligimers remains disfavored.

These ligand designs are unique, because the rigidity and different distances between the coordinating functionalities makes it geometrically impossible to form a mixed ligand $[M_2L_2L'_1]^{6-}$ complex. This steric factor makes closed polymers unattainable. Inevitably, there will be metal sites not coordinated by a catecholamide. For each mole of gallium ions coordinated by only two catecholamide functionalities, over 10 kcal of free energy is lost.[15, 16] Thus, fragments with uncoordinated ends are disfavored and removed in the equilibration of species.

In this work, a series of rigid bis(bidentate) catecholamide ligands has been designed and synthesized to form triple helicates with trivalent metal ions. As a consequence of the predesigned rigid geometry between the ligands' coordinating sites and the positive cooperativity displayed in the formation of the triple helicate systems, highly ordered systems are produced from a complex mixture of closely similar ligands upon addition of metal. Reaction of a mixture of the three bis(catecholamide) ligands (H_4-**1**–H_4-**3**) with [Ga(acac)$_3$] in methanol and KOH at room temperature yields only the individual complexes $K_6[Ga_2(\mathbf{1})_3]$, $K_6[Ga_2(\mathbf{2})_3]$, and $K_6[Ga_2(\mathbf{3})_3]$, according to both ^{1}H NMR and electrospray mass spectrometry. While similar self-recognition has been observed with mixtures of bipyridine-type ligands that differ in the number of metal coordination sites,[20] this demonstrates for the first time that molecular resolution can be achieved based solely on the distance between two metal coordination sites, cleanly separating as many as three ligand components.

Experimental Section

A solution of the appropriate diamine (3.0 mmol) and Et_3N (12 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a stirred solution of the dimethoxybenzoyl chloride [21] (6.2 mmol) in CH_2Cl_2 (100 mL) at 0°C. The reaction mixture was stirred at room temperature for 2 h and then washed with distilled water, 2 N NaOH, and 2 N HCl. The CH_2Cl_2 layer was separated off, dried over $MgSO_4$, and filtered. Upon evaporation of the solvent, the methyl-protected ligands were all isolated in 85–95% yields.

BBr_3 (38 mmol) was added by syringe to a stirred solution of the methyl-protected ligand (3.1 mmol) in CH_2Cl_2 (100 mL) at −78°C. The reaction mixture was stirred at room temperature for 48 h. The volatiles were removed under vacuum, and the remaining orange-yellow solid was stirred in distilled water at 100°C. After 4 h the resulting white precipitate was collected by filtration, washed with absolute ethanol and diethyl ether, and dried under vacuum at 70°C for 12 h to yield the ligands (all in 80–95% yield). All ligands were characterized by ^{1}H NMR spectroscopy, mass spectrometry, and elemental analysis (C, H, N).

Under nitrogen, the ligand H_4L (0.39 mmol) was stirred in methanol (30 mL). A solution of KOH (0.497 N, 0.79 mmol) in methanol was added by pipet, and the reaction mixture was stirred until the ligand dissolved completely. [Ga(acac)$_3$] (0.26 mmol) was then added, and the reaction mixture was stirred at room temperature for 4 h. The volatiles were removed under vacuum, and the residue washed with acetone (2 × 10 mL). The resulting off-white residue was characterized as the $K_6[Ga_2L_3]$ complex. The complexes darken upon exposure to air.

$K_6[Ga_2(\mathbf{1})_3]$: ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 9.14 (s, 6H, NH), 7.76 (m, 6H), 7.26 (s, 6H), 7.10 (m, 6H), 6.99 (d, J = 7.6 Hz, 6H), 6.27 (d, J = 8.0 Hz, 6H); ^{1}H NMR (5% K_2HPO_4 in D_2O, 500 MHz): δ = 7.69 (dd, J = 3.6, 5.9 Hz, 6H), 7.40 (dd, J = 3.5, 5.9 Hz, 6H), 7.37 (d, J = 2.2 Hz, 6H), 7.21 (dd, J = 2.3, 8.1 Hz, 6H), 6.74 (d, J = 8.1, 6H). Positive-ion ES-MS: m/z: 1542[MK$^+$], 1526 [MNa$^+$], 1504 [MH$^+$] (1503 calcd. for $M = K_6Ga_2C_{60}H_{36}N_6O_{18}$).

$K_6[Ga_2(\mathbf{2})_3]$: ^{1}H NMR (5% K_2HPO_4 in D_2O, 500 MHz): δ = 7.18 (d, J = 7.8 Hz, 6H), 6.96 (s, 12H), 6.82 (d, J = 7.2 Hz, 6H), 6.62 (t, J = 7.8 Hz. 6H). Additional data as previously reported in Ref. [12].

$K_6[Ga_2(\mathbf{3})_3]$: ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 9.62 (s, 6H), 7.48 (d, J = 8.0 Hz, 12H), 6.83 (dd, J = 1.6, 8.0 Hz, 6H), 6.31 (dd, J = 1.6, 7.2 Hz, 6H), 6.15 (t, J = 7.2 Hz, 6H), 6.15 (d, J = 8.0 Hz, 12H); ^{1}H NMR (5% K_2HPO_4 in D_2O, 500 MHz) δ = 7.48 (d, J = 8.5 Hz, 12H), 7.25 (dd, J = 1.6, 8.2 Hz, 6H), 6.84 (dd, J = 1.6, 7.5 Hz, 6H), 6.64 (t, J = 7.9 Hz, 6H), 6.59 (d, J = 8.6, 12H); positive-ion ES-MS: m/z: 1770 [MK$^+$], 1753[MNa$^+$], 1732[MH$^+$] (1731 calcd. for $M = K_6Ga_2C_{78}H_{48}N_6O_{18}$).

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A Bridged Porphyrinato(thiolato)iron(III) Complex as a Model of the Active Center of the Cytochrome P-450 Isozyme

Heinrich Volz* and Martin Holzbecher

Dedicated to Professor Leopold Horner on the occasion of his 85th birthday

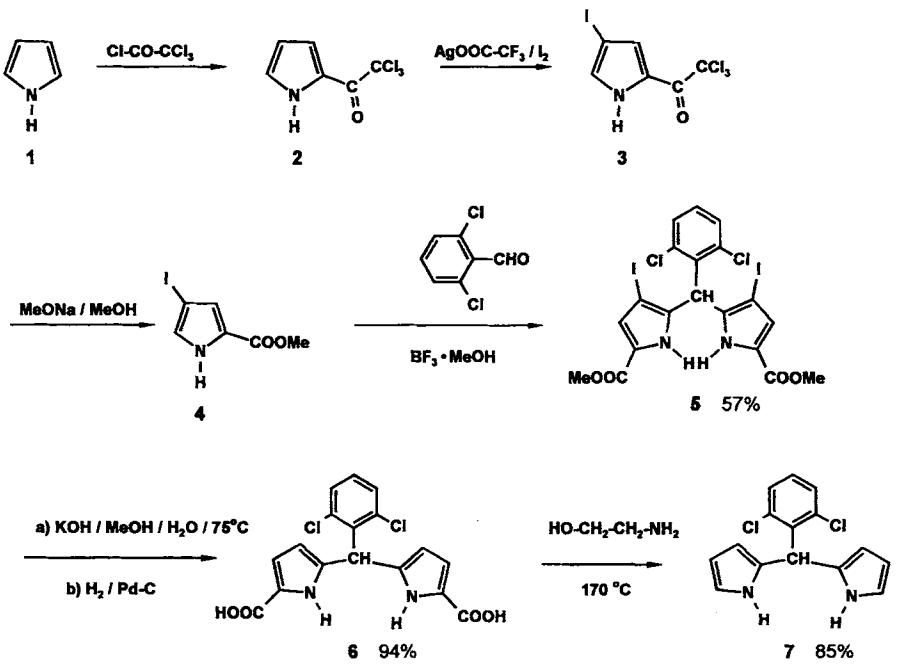
The ubiquitous cytochrome P-450 isozymes are heme–thiolate enzymes, which function as oxygen-activating components in monooxygenase systems. They play a vital role both in the construction and destruction of cellular substances, catalyze the oxidative metabolism of lipophilic xenobiotics,[1] activate vitamins, and convert a range of chemical compounds into carcinogens in the course of chemical cancerogenesis.[2] Under anaerobic conditions O donors such as ROOH, RCO_3H, IO_4^-, ClO_3^-, and PhIO can be used in place of oxygen.[3]

According to crystal structure investigations of the isozyme cytochrome P-450_{CAM}[4] the heme group is embedded in a hydrophobic environment between the helices L and I. The heme group provides the largest hydrophobic surface for interaction with the substrate. The fifth ligand L_5 is the thiolate group of cysteine 357, which is situated in a hydrophobic pocket constructed from the amino acids Phe 350–Leu 358–Gln 360. The Fe–S bond is thus shielded to a large extent from the environment. Removal of the thiolate ligand leads to loss of monooxygenase activity.[5] Chloroperoxidase[6] and NO synthase[7] are also heme–thiolate enzymes. The chemoselectivity of these enzymes is also controlled by the heme–thiolate group.

Due to the very high molecular weight of the cytochrome P-450 isozyme (at least 45 kDa), an exact description of the mechanism of the oxidation of substrates and the nature of the iron-containing intermediates is difficult. One possible method that might cast some light on this problem is the study of chemically produced model compounds containing iron porphyrins, which resemble the natural product. To ensure that the thiolate models cannot lead to S oxidation or allow the production of μ-oxo or μ-peroxo complexes, not only the Fe–S bond but also the opposite side of the porphyrin molecule must be effectively shielded by hydrophobic groups. None of the thiolate model compounds yet described fulfills both these criteria.[8] Except for the model described by Hirobe and co-workers, these compounds were therefore not used for oxidation with O donors.[9]

We report here the synthesis of the bridged porphyrinato(thiolato)iron(III) complex **16** as a model of the active center of the cytochrome P-450 isozyme. Complex **16** was prepared from pyrrole **1** and 1,6-dibromohexane **8** in an 18-step convergent synthesis.

Pyrrole **1** was converted by known methods,[10] via 2-trichloroacetylpyrrole (**2**) and 2-chloroacetyl-4-iodopyrrole (**3**), into 2-methoxycarbonyl-4-iodopyrrole (**4**) (Scheme 1). The iodo substituent serves as protection against electrophilic attack at the 4-position in the subsequent reaction. Compound **4** is then treated with 2,6-dichlorobenzaldehyde in the presence of $BF_3 \cdot MeOH$ (20% BF_3 in MeOH) to give the dipyrromethane **5** in 57% yield. Alkaline hydrolysis of the ester followed by hydrogenolytic cleavage of the C–I bond produced the dicarboxylic acid **6** in 94% yield. This was then decarboxylated



Scheme 1. Synthesis of 5-(2,6-dichlorophenyl)dipyrromethane (7).

[*] Prof. Dr. H. Volz, Dr. M. Holzbecher
Institut für Organische Chemie der Universität
Richard-Willstätter-Allee, D-76128 Karlsruhe (Germany)
Fax: Int. code +(721)69-8529