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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

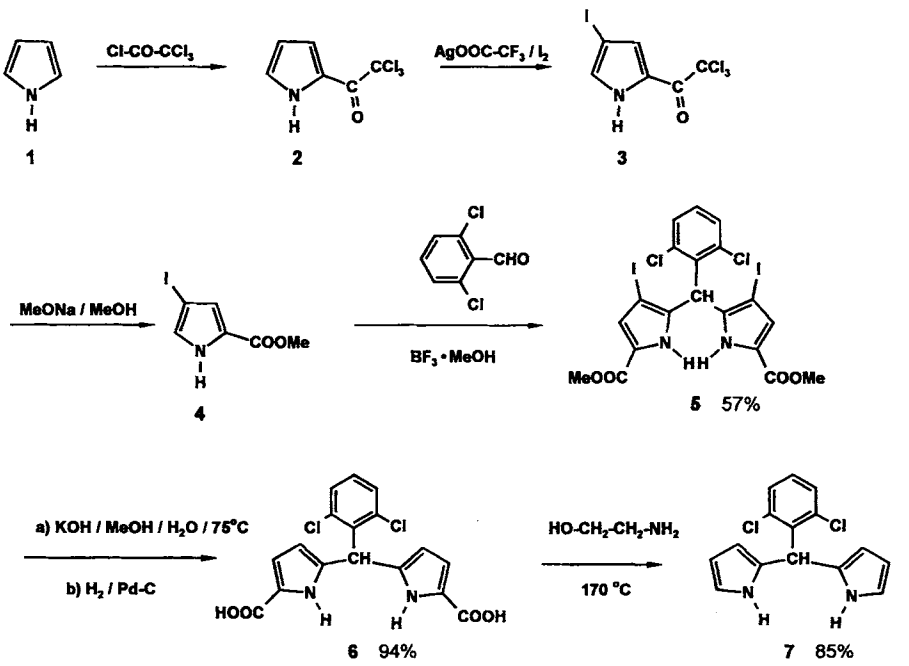
The ubiquitous cytochrome P-450 isozymes are heme–thiolate enzymes, which function as oxygen-activating components in monooxygenase systems. They play a vital role both in the construction and destruction of cellular substances, catalyze the oxidative metabolism of lipophilic xenobiotics,[1] activate 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

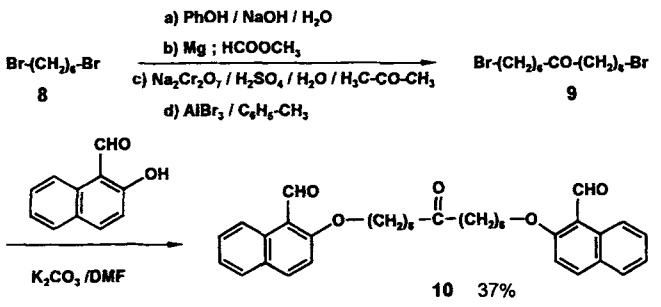


Scheme 1. Synthesis of 5-(2,6-dichlorophenyl)dipyrromethane (7).

[*] 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

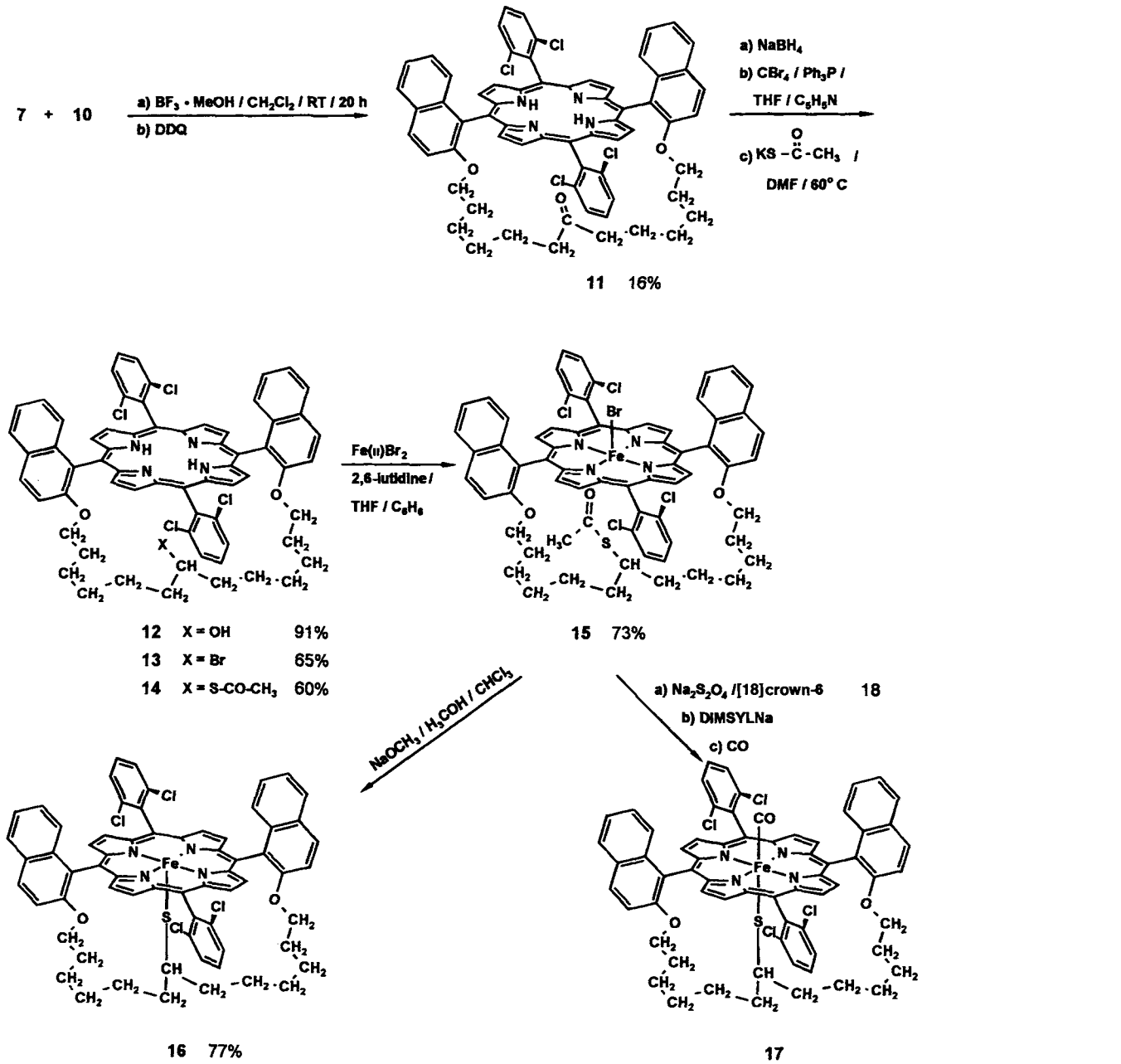
to 5-(2,6-dichlorophenyl)dipyrromethane (**7**) by heating in ethanolamine[11] (170 °C, 1.5 h).

1,6-Dibromohexane (**8**) was converted into 1,13-dibromotridecan-7-one (**9**) in four steps (Scheme 2), in analogy to the method described for 1,4-dibromobutane.[12] This was then treated with 2-hydroxy-1-naphthalenecarbaldehyde to give the dialdehyde **10**.



Scheme 2. Synthesis of the dialdehyde **10**.

The coupling reaction of **7** and **10** catalyzed by BF_3–methanol and the subsequent oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) yielded the porphyrinophane **11** in 16% yield (Scheme 3). Reduction of the carbonyl group in **11** with $NaBH_4$ led to **12**, which was converted into the bromide **13** by reaction with CBr_4/Ph_3P/pyridine/THF.[13] This reacted with potassium thioacetate to give the thioester **14**.[8b] Metalation of **14** to yield the iron complex **15** was achieved with $FeBr_2$/lutidine,[14] and finally reaction with $NaOCH_3$ in $MeOH/CHCl_3$ produced the bridged porphyrinato(thiolato)iron(III) complex (**16**) in 77% yield. This crystallized together with a molecule of methanol, which is coordinated to the iron atom (Soret band at 415 nm). The methanol could be removed



Scheme 3. The [2+2] synthesis of the porphyrinophane **11** from the components **7** and **10**, and the subsequent reaction steps from **11** to the *thiolate complex* **16**, *and the preparation of the CO-porphyrinato(thiolato)iron(II) complex* **17**.

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Table 1. Selected physical and spectroscopic data for **7** and **10**–**16**

7: Isolation by column chromatography (in the dark, cooled to −78 °C, silica gel, CH_2Cl_2); m.p. 104 °C; ^{1}H NMR ($CDCl_3$): δ = 8.26 (br. s, 2H), 7.32 (d, 2H), 7.12 (t, 1H), 6.70 (m, 2H), 6.46 (s, 1H), 6.17 (m, 2H), 6.05 (m, 2H); HRMS ($C_{15}H_{12}Cl_2N_2$): calcd 290.03775, found 290.0370.

10: M.p. 90 °C; ^{1}H NMR ($CDCl_3$): δ = 10.93 (s, 2H), 9.28 (d, 2H), 8.03 (d, 2H), 7.78 (d, 2H), 7.62 (dt, 2H), 7.40 (m, 2H), 7.28 (d, 2H), 4.19 (t, 4H), 2.43 (t, 4H), 1.88 (quint., 4H), 1.60 (m, 8H), 1.41 (m, 4H); HRMS ($C_{35}H_{38}O_5$): calcd 538.2719, found 538.2734.

11: Purification by column chromatography: a) Al_2O_3, basic, activation grade I, CH_2Cl_2/Et_2O 95/5; b) silica gel, CH_2Cl_2; ^{1}H NMR ($CDCl_3$): δ = 8.60 (d, 4H), 8.55 (d, 4H) 8.30 (d, 2H), 8.03 (d, 2H), 7.70 (m, 8H), 7.27 (d, 2H), 6.88 (t, 2H), 6.50 (d, 2H), 4.18 (t, 4H), 1.16 (quint., 4H), 0.46 (m, 4H), −0.16 (m, 4H), −0.30 (m, 4H), −1.04 (t, 4H), −2.23 (s, 2H); UV/Vis (CH_2Cl_2): λ_{max} ($\varepsilon \times 10^{-3}$) = 420.8 (308), 513.8 (22.3), 545.2 (3.9), 589.4 (6.9), 645.2 nm (1.3); HRMS ($C_{65}H_{52}Cl_4N_4O_3$): calcd 1076.27935, found 1076.265.

12: Purification by column chromatography on silica gel, CH_2Cl_2; ^{1}H NMR ($CDCl_3$): δ = 8.47 (m, 8H), 8.21 (d, 2H), 7.95 (d, 2H), 7.6 (m, 8H), 7.22 (t, 2H), 6.86 (t, 2H), 6.63 (d, 2H), 4.04 (m, 4H), 0.97 (m, 5H), 0.42 (m, 4H), 0.15 (m, 4H), −0.28 (m, 4H), −0.55 (m, 4H), −2.41 (s, 2H); UV/Vis (CH_2Cl_2): λ_{max} ($\varepsilon \times 10^{-3}$) = 420.8 (294), 514.2 (21.3), 545.6 (3.8), 589.4 (6.7), 645.2 nm (1.3); HRMS ($C_{65}H_{54}Cl_4N_4O_3$): calcd 1078.2950, found 1078.311.

13: Purification by column chromatography: silica gel, CH_2Cl_2/*n*-hexane 7/3; ^{1}H NMR ($CDCl_3$): δ = 8.7 (m, 8H), 8.29 (d, 2H), 8.02 (d, 2H), 7.72 (m, 8H), 7.31 (t, 2H), 6.95 (dt, 2H), 6.71 (d, 2H), 4.12 (m, 4H), 2.30 (m, 1H), 1.05 (m, 4H), 0.51 (m, 4H), 0.22 (m, 4H), −0.05 (m, 6H), −0.31 (m, 2H), −2.28 (s, 2H); UV/Vis (CH_2Cl_2): λ_{max} ($\varepsilon \times 10^{-3}$) = 421.2 (221), 514.2 (15.8), 545.8 (2.8), 589.6 (4.9), 645.4 nm (1).

14: Purification by column chromatography: silica gel, a) CH_2Cl_2/*n*-pentane 6/4, b) CH_2Cl_2; ^{1}H NMR ($CDCl_3$): δ = 8.57 (m, 8H), 8.31 (d, 2H), 8.05 (d, 2H), 7.7 (m, 8H), 7.31 (t, 2H), 6.98 (dt, 2H), 6.80 (d, 2H), 4.06 (m, 4H), 2.01 (s, 3H), 0.98 (m, 4H), 0.40 (m, 4H), 0.21 (m, 5H), −0.02 (m, 8H), −2.81 (s, 2H); UV/Vis (CH_2Cl_2): λ_{max} ($\varepsilon \times 10^{-3}$) = 421.4 (239), 514.4 (18.1), 546.6 (3.8), 590 (5.9), 646.4 nm (1.3); IR (KBr): $\tilde{\nu}$ = 1685 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$): δ = 195.94 (C=O); HRMS ($C_{67}H_{56}Cl_4N_4O_3S$): calcd 1136.2827, found 1136.274.

15: Purification by thin-layer chromatography: Al_2O_3, basic, CH_2Cl_2; ^{1}H NMR ($CDCl_3$): δ = 80.5 (br., 8H, pyrrole-H); UV/Vis (CH_2Cl_2): λ_{max} ($\varepsilon \times 10^{-3}$) = 418 (80.3), 579 (8.5), 628 nm (2.6); IR (KBr): $\tilde{\nu}$ = 1684 cm^{-1} (C=O); magnetic susceptibility X_{mol}/magnetic moment μ_{eff} ($CDCl_3$, Ref.[19]): X_{mol} = 1.83×10^{-7} m^3 mol^{-1}; μ_{eff} = 5.85 μ_B; elemental analysis for $C_{67}H_{54}BrCl_4FeN_4O_3S$ (1272.81): calcd N 4.40, S 2.52; found N 4.17, S 2.05.

16: ^{1}H NMR ($CDCl_3$): δ = 83 (br. s, 4H, pyrrole-H), 69 (br. s, 4H, pyrrole-H); UV/Vis (CH_2Cl_2): λ_{max} ($\varepsilon \times 10^{-3}$) = 415 (82.9), 506 (11.02), 580 (4.85), 641 nm (3.07); IR (KBr): $\tilde{\nu}$ = 3057, 2955, 2924, 2853, 1621, 1592, 1556, 1530, 1509,1463, 1428, 1377,1328, 1272, 1190, 1147, 1115, 1069, 1040, 1019, 997, 981, 884, 835, 802, 791, 777, 746, 715, 697, 668, 643 cm^{-1}; EPR (pure): $g_\perp$ = 5.37 (strong signal), g = 4.18 (weak signal), g = 1.98 (weak signal); magnetic susceptibility X_{mol}/magnetic moment μ_{eff} ($CDCl_3$, Ref.[19]): X_{mol} = 1.18×10^{-7} m^{3}mol^{-1}; μ_{eff} = 4.7 μ_B; HRMS ($C_{65}H_{51}{}^{35}Cl_3{}^{37}ClFeN_4O_2S$): calcd 1149.179, found 1149.171; elemental analysis for $C_{65}H_{51}Cl_4FeN_4O_2S \cdot H_3COH$ (1181.91): calcd Fe 4.70, N 4.74, O 4.06, S 2.71; found Fe 5.17, N 4.63, O 4.44, S 3.07.

17: UV/Vis (DMSO): λ_{max} ($\varepsilon \times 10^{-3}$) = 376 (41.6), 463 (97.1), 517 (10), 555 (10.8), 609 cm^{-1} (7.6).

by drying under extreme conditions, which moved the Soret band to 399 nm (blue shift). Addition of methanol restored the original spectrum. Reduction of **15** with the $Na_2S_2O_4$-[18]crown-6 complex **18**[15] in DMSO, cleavage of the thioester with the DMSO monoanion DIMSYL-Na, and introduction of CO into the solution yielded the CO complex **17**, which displays a split Soret band (376 nm, 463 nm; hyperporphyrin). The cause of the blue- and red-shifted Soret bands in carboxycytochrome P-450 and CO-porphyrinato(thiolato)iron(II) model compounds is a charge transfer transition from an occupied p orbital on the thiolate sulfur atom (lone electron pair) to the porphyrin $e_g(\pi^*)$ orbital and the strong interaction of this transition with the transitions $a_{1u}(\pi)$,$a_{2u}(\pi) \rightarrow e_g(\pi^*)$ of the porphyrin.[16] Charge transfer transitions are quite strongly solvent dependent;[17] this is probably the reason for the slight red shift of the long wavelength Soret bands of the CO–porphyrinato(thiolato) model compounds in DMSO upon the addition of base[8a, 8e] relative to carboxycytochrome P-450.

As can be seen from molecular modeling studies[18] of **16**, the chloro substituents and the phane chain shield the thiolate group effectively from attack by oxidants (O donors). On the other side of the molecule the chloro and naphthyl substituents hinder the formation of μ-oxo and μ-peroxo complexes (Figure 1).

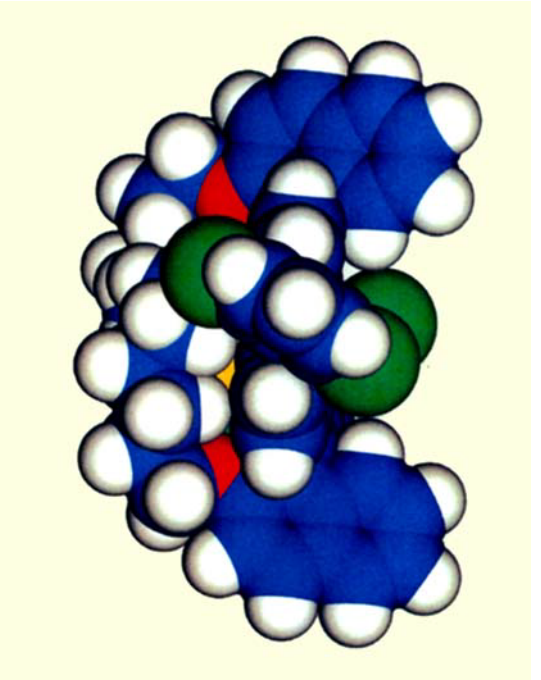
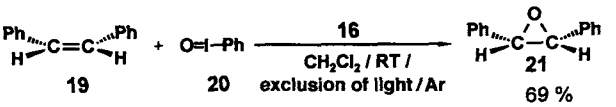


Fig. 1. Space-filling model of the porphyrinato(thiolato)iron(III) complex **16**.

Measurement of the magnetic susceptibility of **16** yields a magnetic moment μ_{eff} of 4.7 μ_B. This value is significantly smaller than the value of 5.9 μ_B expected for a high spin porphyrinatoiron(III) complex (S = 5/2) and substantially larger than that of a low spin porphyrinatoiron(III) complex (S = 1/2), where a value of 1.73 μ_B is expected. The ^{1}H NMR spectrum of **16** displays two broad signals, each of intensity 4H, at δ = 83 and 69, which we ascribe to the porphyrin protons. The porphyrin protons are not equivalent due to the unsymmetrical disposition of the phane chain and the orientation of the thiolate ligand.



Scheme 4. Epoxidation of *cis*-stilbene to *cis*-stilbene oxide by iodosylbenzene catalyzed by **16**.

The reaction of *cis*-stilbene (**19**) with iodosylbenzene (**20**) as O donor and **16** as catalyst (room temperature, dichloromethane, exclusion of light) led to the formation of *cis*-stilbene oxide (**21**) as the single reaction product in 69% yield. This is in agreement with the conclusions drawn from molecular modeling studies and demonstrates how effectively the thiolate ligand is shielded from direct attack by the O donor iodosylbenzene.

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Experimental Section

16: To a solution of **15** (92 mg, 0.072 mmol) in chloroform/methanol 1/2 (80 mL) was added 1 M $NaOCH_3/CH_3OH$ (2 mL, 2 mmol). This was held at reflux for 4 h under argon in the dark. After removal of the solvent and drying, the residue was purified by preparative thin layer chromatography (neutral Al_2O_3, CH_2Cl_2, exclusion of light; R_f of **16** is about 1). After drying at 40 °C/10^{-2} Torr, 64 mg of **16** was obtained (0.056 mmol, 77%).

17: All reactions were carried out in a glove box under argon. Iron complex **15** (0.56 mg, 4×10^{-7} mol) and crown complex **18** (16 mg, 21.2×10^{-6} mol) were dissolved in DMSO (4 mL) and allowed to react for 30 min. After the addition of a DIMSYLNa solution (31.44 mg NaH) and a further 30 min reaction, the volume of the solution was increased to 20 mL, and CO was bubbled through the solution.

Epoxidation of *cis*-stilbene (under argon with light exclusion): *cis*-stilbene (450 mg, 2.5 mmol), **16** (28.8 mg, 0.025 mmol), and iodosylbenzene (55 mg, 0.25 mmol) were stirred in CH_2Cl_2 (6 mL) for 5 h at room temperature. After removal of the solvent (30 °C, 300 mbar), the residue was taken up in 200 mL *n*-pentane, and the catalyst removed by filtration (25–30% **16** was recovered unchanged); the solvent was then removed (30 °C, 300 mbar). Quantitative analysis of the reaction products was carried out by ^1H NMR spectroscopy with 4-chlorotoluene as internal standard.

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Self-Assembly of Supramolecular Polyoxometalates: The Compact, Water-Soluble Heteropolytungstate Anion $[As^{III}_{12}Ce^{III}_{16}(H_2O)_{36}W_{148}O_{524}]^{76-}$ **

Knut Wassermann, Michael H. Dickman, and Michael T. Pope*

Dedicated to the memory of GTP (1959–1996)

The hundreds of known examples of polyoxoanions of vanadium, molybdenum, and tungsten comprise a class of inorganic complexes of unrivaled versatility and structural variation, and have applications in many fields of science.[1] Very commonly these species have structures incorporating 6, 12, or 18 metal atoms and one or more other "heteroatoms" in positive oxidation states. The Keggin tungstophosphate $[PW_{12}O_{40}]^{3-}$ is a familiar example.

There are indications that much larger polyoxometalate anions might be synthesized. The structures of complexes such as $[Mo_{36}O_{112}(H_2O)_{18}]^{8-}$[2] and $[H_7P_8W_{48}O_{148}]^{33-}$[3] incorporate smaller known polyoxoanion units ($[Mo_7O_{24}]^{6-}$ and $[H_2P_2W_{12}O_{48}]^{12-}$ respectively), and more recently a class of mixed-valent, nitrosyl-containing polymolybdates with 57 molybdenum atoms per anion has been identified and characterized.[4] Following a general polymerization–reduction–polymerization protocol that has proved to be appropriate for the latter species, Müller et al. have succeeded in synthesizing a spectacular cyclic ("big wheel") anion with 154 molybdenum atoms.[5]

We now report that polyoxometalates with 148 tungsten atoms per anion can be easily and efficiently synthesized by straightforward "self assembly" processes in aqueous solution. The title anion **1** has been isolated as an ammonium salt in a yield of roughly 35%. The new compounds are by far the largest and heaviest discrete polyoxotungstates known. Other somewhat smaller compounds with 29 and 40 tungsten atoms have also been characterized and will be reported elsewhere.[6]

The structure of **1** is illustrated in bond, polyhedral, and space-filling representations in Figures 1–3. The anion has virtual D_{2d} symmetry and incorporates twelve B-α $[As^{III}W_9O_{33}]^{9-}$ and four $[W_5O_{18}]^{6-}$ groups. The AsW_9 units are augmented by additional tungsten and cerium atoms and are linked into a *folded* cyclic structure by pairs of edge-shared WO_6 octahedra.

The anion **1** may therefore be formulated as shown below.

$[Ce_{16}(H_2O)_{36}(B\text{-}\alpha\text{-}AsW_9O_{33})_{12}(WO_2)_4(W_2O_6)_8(W_5CeO_{18})_4]^{76-}$ **1**

Details of the structural motifs are shown in Figure 4. As revealed by the space-filling representation (Figure 3) the folded structure is very compact with no large central cavity as found for Mo_{154} and other polyoxoanions of comparable size, such as $[H_7P_8W_{48}O_{148}]^{33-}$. The structure analysis suggests that the central core of **1** contains four ammonium cations and/or water molecules. In the crystal, the disc-shaped anions (diameter ap-

[*] Prof. M. T. Pope, Dr. K. Wassermann, Dr. M. H. Dickman
Department of Chemistry
Box 571227, Georgetown University, Washington, DC 20057-1227 (USA)
Fax: Int. code +(202)687-6209
e-mail: pope@guvax.georgetown.edu

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