The rate of disappearance of A can also be expressed as in eq 14a

$$-d[A]/dt = k_0 \quad (14a)$$

From eq 10a and 14a

$$k_0 = R_1 - k_2[B] \quad (15a)$$

Inserting [B] into eq 13a

$$k_0 = R_1 - k_2\left(\frac{R_1}{k_2 + k_3[RX]}\right) \quad (16a)$$

$$k_0 = \frac{R_1 k_3[RX]}{k_2 + k_3[RX]} \quad (17a)$$

Inverting, we obtain

$$k_0^{-1} = \left(\frac{k_2}{R_1 k_3}\right)[RX]^{-1} + \left(\frac{1}{R_1}\right) \quad (6)$$

Registry No. 1a, 100927-74-0; **1b**, 100927-75-1; **1c**, 100927-76-2; **2a**, 100927-77-3; **2b**, 100927-78-4; **2c**, 100927-79-5; $Re_2(CO)_8(\mu$-*cis*-dppet), 100927-80-8; $Re_2(CO)_8(\mu$-dppe), 100927-81-9; $Re_2(CO)_8(\mu$-dpph), 100927-82-0; $(\mu$-H)$Re_2(CO)_8(\mu$-CH=CHC$_4$H$_9$), 88294-19-3; $Re_2(CO)_{10}$, 14285-68-8; ·(OC)$_4$Re(μ-dmpe)Re(CO)$_4$·, 100927-83-1; ·(OC)$_4$Re(μ-dppe)Re(CO)$_4$·, 100927-84-2; ·(OC)$_4$Re(μ-*cis*-dppet)Re(CO)$_4$·, 100927-85-3; ·(OC)$_4$Re(μ-dpppe)Re(OC)$_4$·, 100927-86-4; ·(OC)$_4$Re(μ-dpph)Re(CO))$_4$·, 100927-87-5; THF, 109-99-9; CCl_4, 56-23-5; CH_2Br_2, 74-95-3; ·Re(CO)$_4$(PPh$_2$Et), 100927-88-6; decaline, 14727-56-1; tetralin, 119-64-2; mesitylene, 108-67-8; toluene, 108-88-3; benzyl alcohol, 100-51-6; benzene, 71-43-2; acetonitrile, 75-05-8.

Complexation of Arenes by Macrocyclic Hosts in Aqueous and Organic Solutions[1]

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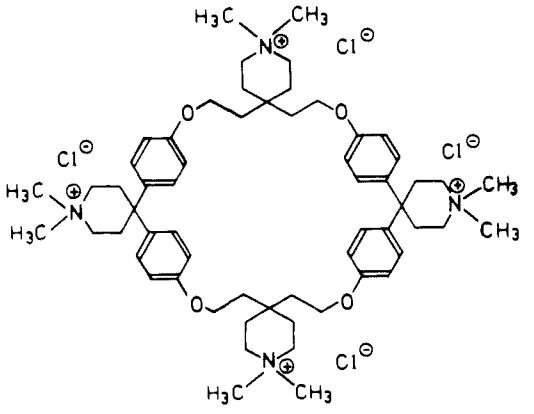
Abstract: As spherical hosts for neutral arenes, the macrobicyclic compounds **2** and **3** were synthesized. 1-Acetyl-4,4-bis[4-succinimidyloxycarbonylmethoxy-3,5-dimethylphenyl]piperidine (**8**) and 1-ethyl-4,4-bis[4-(2-aminoethoxy)-3,5-dimethylphenyl]piperidine (**10**) were cyclized to the tetraoxadiaza[7.1.7.1]paracyclophane **4**. Cyclization component **8** was obtained by starting from 1-acetyl-4,4-bis(4-hydroxy-3,5-dimethylphenyl)piperidine and following the reaction sequence **6** → **7** → **8**. Compound **10** was obtained with use of the reaction sequence **8** → **9** → **10**. Reduction of **4** afforded 1′,1″-diethyl-9,13,17,19,29,33,37,39-octamethyldispiro[1,7,21,27-tetraoxa-4,24-diaza[7.1.7.1]paracyclophane-14,4′:34,4″-bispiperidine] (**5**). **5** was cyclized with 1-benzyloxycarbonyl-4,4-bis[chloroformylmethoxy-3,5-dimethylphenyl]piperidine (**12**), obtained by the reaction sequence **6** → **11** → **12**, to yield the macrobicyclic compound **13**. The advantages of amide macrocyclizations with *N*-hydroxysuccinimide esters as activated carboxylic acid derivatives are discussed. **13** was transformed into the target host **2** by following the sequence **13** → **14** → **2**. Host **3** was obtained by using the sequence **14** → **15** → **3** or by reduction of host **2**. Host **3**, 1′,1″,1‴-triethyl-6,12,22,28,37,43,48,51,52,55,56,59-dodecamethyltrispiro[4,14,20,30,35,45-hexaoxa-1,17-diazaoctacyclo[15.15.15.2^{5,8}.2^{10,13}.2^{21,24}.2^{26,29}.2^{36,39}.2^{41,44}]nonapentaconta-5,7,10,12,21,23,26,28,36,38,41,43,48,50,52,54,56,58-octadecaene-9,4′:25,4″:40,4‴-trispiperidine], has D_{3h} symmetry. In host **3**, three diphenylmethane units bearing *N*-ethylpiperidine rings are attached each by two –O–CH$_2$–CH$_2$– chains to two cryptand–nitrogen atoms, through which the D_{3h} symmetry axis passes. In host **2**, one of the three diphenylmethane units is attached to the two nitrogens by two O–CH$_2$–C(O) bridges. The complexation between hosts **2** and **3** and neutral arenes in weakly acidic aqueous solution is studied. Association constants of the complexes were determined from solid–liquid and liquid–liquid extractions. The geometry of complexes in aqueous solution was elucidated by ^{1}H NMR spectroscopy. The considerable difference in binding, which was observed with the two very similar hosts **2** and **3**, is discussed. The first extensive study of the binding between neutral arenes and artificial macrocyclic hosts in various organic solvents of different polarity is presented. The complexation between arenes and hosts **2**, **3**, and **16** in organic solvents was monitored by electronic absorption and emission spectroscopy and ^{1}H NMR spectroscopy. Host **3** is a better binder for arenes in organic solvents than hosts **2** and **16**. Complexation between **3** and perylene, pyrene, or fluoranthene was even observed in benzene. The geometry of the complex of a specific host and a guest was found to be very similar in all solvents. The association constants of the complexes in organic solvents are discussed in terms of the contribution of attractive van der Waals interactions between host and guest in the complex and in terms of contributions of solvation–desolvation processes.

Artificial host–guest complexation in aqueous solution is closely related to complexation in biological systems and has attracted considerable interest during the past years.[4] In order to investigate the interaction between apolar hosts and guests in aqueous solution, we have designed and synthesized water-soluble macromonocyclic hosts such as **1**.[5–10] These compounds possess cavities of very pronounced hydrophobic character as binding sites for apolar guests in aqueous solution. Extensive studies of binding by cyclodextrins[11] and by synthetic macrocycles in our[5–10] and in other laboratories[12–21] have definitely established that apolar hosts and

(1) This paper is dedicated to Prof. H. A. Staab on the occasion of his 60th birthday.
(2) University of California, Los Angeles.
(3) Max-Planck-Institut für medizinische Forschung, Heidelberg.
(4) For a recent review on host–guest complexation in aqueous solution, see: Diederich, F. *Nachr. Chem., Tech. Lab.* **1984**, *32*, 787–795.
(5) Diederich, F.; Dick, K. *Tetrahedron Lett.* **1982**, *23*, 3167–3171.
(6) Diederich, F.; Dick, K. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 715–717; *Angew. Chem. Suppl.* **1983**, 957–972.
(7) Diederich, F.; Dick, K. *J. Am. Chem. Soc.* **1984**, *106*, 8024–8036.
(8) Diederich, F.; Griebel, D. *J. Am. Chem. Soc.* **1984**, *106*, 8037–8046.
(9) Diederich, F.; Dick, K.; Griebel, D. *Chem. Ber.* **1985**, *118*, 3588–3619.
(10) Diederich, F.; Dick, K. *Chem. Ber.* **1985**, *118*, 3817–3829.
(11) Bender, M. L.; Komiyama, M. "Cyclodextrin Chemistry": Springer: Berlin, 1978.
(12) Murakami, Y. *Top. Curr. Chem.* **1983**, *115*, 107–159.
(13) Tabushi, I.; Yamamura, K. *Top. Curr. Chem.* **1983**, *113*, 145–182.
(14) Odashima, K.; Koga, K. In "Cyclophanes"; Keehn, P. M.; Rosenfeld, St. M., Eds.; Academic Press: New York, 1983; Vol. 2, pp 629–678.
(15) (a) Jarvi, E. T.; Whitlock, H. W. *J. Am. Chem. Soc.* **1982**, *104*, 7196–7204. (b) Miller, S. P.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 1492–1494.
(16) Winkler, J.; Coutouli-Argyropoulou, E.; Leppkes, R.; Breslow, R. *J. Am. Chem. Soc.* **1983**, *105*, 7198–7199.

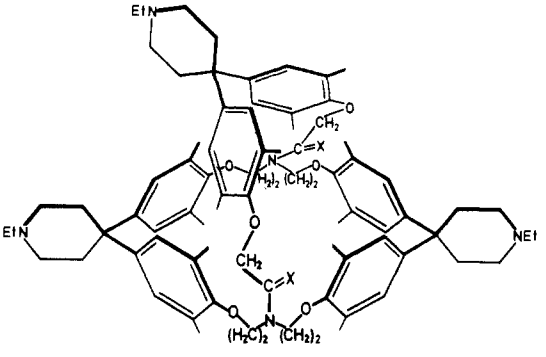
0002-7863/86/1508-2273$01.50/0

guests can form stoichiometric complexes in aqueous solution. It is now of importance to optimize synthetic hosts for specific apolar guests and to learn about the maximum free energy ΔG that can be gained from their complexation. From such studies, more insight into the nature of the driving force of complexation between apolar binding partners in aqueous solution can be expected. Attractive van der Waals interactions as well as hydrophobic interactions, which are based on solvation-desolvation processes,[22] are thought to be the major driving forces of complexation.[7,9,23]



1

At the time we started the present work,[24] the macromonocycle **1** was the best artificial host for polycyclic arenes like perylene (K_a = 1.6 × 10^7 L·mol^{-1} for the 1:1 complex in water, T = 293 K), fluoranthene (K_a = 1.2 × 10^6 L·mol^{-1}), and pyrene (K_a = 1.1 × 10^6 L·mol^{-1}).[7] A more efficient encapsulation and a stronger complexation of these large arenes could be expected from suitably sized, more spherical hosts. We therefore decided to introduce a third diphenylmethane unit into the new host systems **2** and **3**.

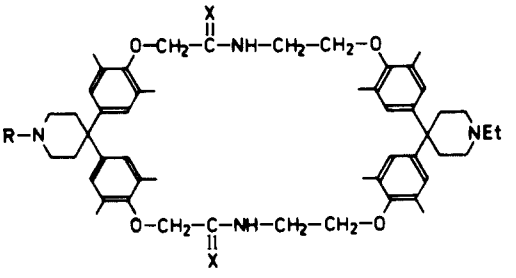


2: X = O
3: X = 2H

In this paper, the synthesis of the macrobicyclic compounds **2** and **3** will be described. The complexation between these hosts and arenes in weakly acidic aqueous solution will be reported. The first extensive study of the complexation between synthetic hosts and arenes in organic solvents of different polarity will be presented. To date, only a few examples of the complexation between neutral binding partners in organic solvents have been reported. The binding of cyclodextrins and small molecules like toluene, anisole, and ferrocene in Me_2SO and DMF[25] and in alcohols[26] has been described. Other studies in organic solvents deal with the binding of CS_2 and methylacetylene[27] as well as of CH_2Cl_2[28] by artificial hosts and with the binding of nitrophenols and indoles to modified cyclodextrins.[29,30]

Synthesis of the Macrobicycles 2 and 3

Compounds **2** and **3** possess three diphenylmethane units that are attached via bridges to two cryptand nitrogen atoms. Their preparation follows the general scheme established by Lehn[31] for the synthesis of cryptands. The macromonocyclic compound **4** is a key intermediate on the way to **2** and **3**. Its reduction was expected to yield the tetraamine component **5** needed for the amide cyclization to give the macrobicyclic framework of **2** and **3**.

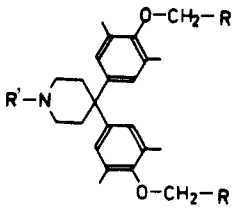


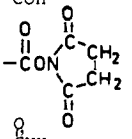
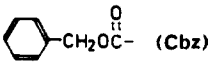
4: R = Ac, X = O
5: R = Et, X = 2H

The synthesis of the activated carboxylic acid derivative and of the amine component needed for the amide cyclization to give **4** started from 1-acetyl-4,4-bis(4-hydroxy-3,5-dimethylphenyl)-piperidine.[9] Reaction of this compound with ethyl α-bromoacetate in tetrahydrofuran in the presence of potassium hydroxide yielded the diester **6** (67%). Hydrolysis of **6** with potassium carbonate in aqueous ethanol gave the dicarboxylic acid **7** in 98% yield. Compound **7** could not be transformed into the corresponding diacid dichloride, a potential cyclization component. In the presence of an excess of sulfinyl chloride or of oxalyl chloride, a quantitative cleavage of the *N*-acetyl group of **7** occurred. Even with stoichiometric amounts of these reagents in inert solvents like benzene or toluene, a clean conversion to the N-acetylated diacid dichloride was not possible. The cleavage of the *N*-acetyl group was evident from the ^{1}H NMR spectra of the reaction mixtures. *N*-Hydroxysuccinimide esters have been successfully used as activated carboxylic acid derivatives in peptide synthesis.[32] When **7** was treated with *N*-hydroxysuccinimide in dioxane in the presence of dicyclohexylcarbodiimide, an 84% yield of the bis-(*N*-hydroxysuccinimide ester) **8** was obtained. Introduction of gaseous ammonia into the reaction mixture to give **8** led to the formation of the triamide **9** in 84% yield. Reduction of **9** with borane–tetrahydrofuran afforded **10** in 96% yield.

Cyclization of **8** with **10** under high dilution in dichloromethane at 0 °C gave **4** in 42% yield. Some advantages of amide cyclizations with *N*-hydroxysuccinimide esters over macrocyclizations with acid chlorides should be mentioned. There is no additional base needed to trap liberated acid. *N*-hydroxysuccinimide esters react selectively with amines and they are rather stable toward

(17) (a) Vögtle, F.; Müller, W. M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 712–714. (b) Franke, J.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 219–221.
(18) Mock, W. L.; Shih, N.-Y. *J. Org. Chem.* **1983**, *48*, 3618–3619.
(19) Takeuchi, K. J.; Busch, D. H. *J. Am. Chem. Soc.* **1983**, *105*, 6812–6816.
(20) Dahnens, M.; Lacombe, L.; Lehn, J.-M.; Vigneron, J. P. *J. Chem. Soc., Chem. Commun.* **1984**, 1097–1099.
(21) Shinkai, S.; Mori, S.; Tsubaki, T.; Sone, T.; Manabe, O. *Tetrahedron Lett.* **1984**, *25*, 5315–5318.
(22) Ben-Naim, A. "Hydrophobic Interactions", 2nd ed.; Plenum: New York, 1983.
(23) (a) VanEtten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242–3253. (b) Tabushi, I.; Kiyosuke, Y.; Sugimoto, T.; Yamamura, K. *J. Am. Chem. Soc.* **1978**, *100*, 916–919.
(24) A part of this work has appeared as a preliminary communication: Diederich, F.; Dick, K. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 810–812.
(25) Siegel, B.; Breslow, R. *J. Am. Chem. Soc.* **1975**, *97*, 6869–6870.
(26) Harada, A.; Takahashi, S. *Chem. Lett.* **1984**, 2089–2090.
(27) Cram, D. J.; Stewart, D. D.; Goldberg, I.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2574–2575.
(28) Conceill, J.; Lacombe, L.; Collet, A. *C. R. Acad. Sci. Sec. II* **1984**, *298*, 39–42.
(29) Nakai, Y.; Yamamoto, K.; Terada, K.; Horibe, H. *Chem. Pharm. Bull.* **1982**, *30*, 1796–1802.
(30) Menger, F. M.; Dulany, M. A. *Tetrahedron Lett.* **1985**, *26*, 267–270.
(31) Dietrich, B.; Lehn, J.-M.; Sauvage, J. P.; Blanzat, J. *Tetrahedron* **1973**, *29*, 1629–1645.
(32) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1964**, *86*, 1839–1842.



	R	R'
6	$-\overset{O}{\overset{\|}{C}}OCH_2CH_3$	Ac
7	$-\overset{O}{\overset{\|}{C}}OH$	Ac
8		Ac
9	$-\overset{O}{\overset{\|}{C}}NH_2$	Ac
10	$-CH_2NH_2$	Et
11	$-\overset{O}{\overset{\|}{C}}OH$	 (Cbz)
12	$-\overset{O}{\overset{\|}{C}}Cl$	Cbz

alcohols and water. As a consequence, there is no need for carefully dried solvents and for inert gas atmosphere during the cyclization. With their high stability and their relatively high melting points, the *N*-hydroxysuccinimide esters can be easily purified by recrystallization and fully characterized.[33]

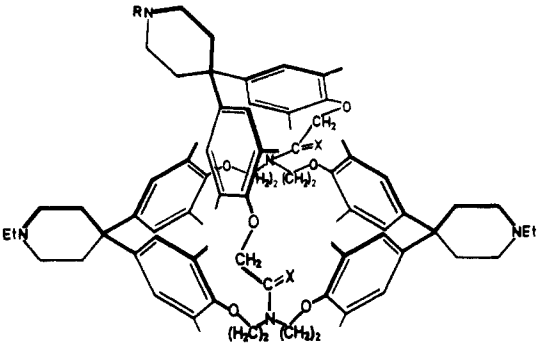
The triamide **4** was reduced with borane–tetrahydrofuran to **5** in 96% yield. In an attempt to cyclize **5** with **8**, we found that the bis(*N*-hydroxysuccinimide ester) did not react with the secondary amino groups of **5**. We are currently investigating if this selectivity for primary amino groups is general in the reactions of *N*-hydroxysuccinimide esters.[34]

We prepared the diacid dichloride **12** for the cyclization to the macrobicyclic system. Compound **6** was hydrolyzed with 2 N NaOH and the crude product was allowed to react with benzyl chloroformate to give the dicarboxylic acid **11** (92%). Reaction of **11** with sulfinyl chloride in benzene gave compound **12**, which was then cyclized, without further purification, with **5** to yield the macrobicycle **13** (38%). The cyclization proceeded under high dilution at 0 °C in toluene. No additional base was needed to trap the liberated HCl since **13** possesses two tertiary amine groups. The spectroscopic data (^{1}H NMR, FAB-MS[35]) of **13** are consistent with the proposed macrobicyclic structure.

Catalytic cleavage of the amine-protecting group of **13** with H_2/Pd (10% on charcoal) furnished **14** in 98% yield. Reductive alkylation of **14** with sodium borohydride in acetic acid[36] afforded the target compound **2** in 55% yield. Acetylation of **14** with acetic anhydride gave **15** (85%) which could be reduced with borane–tetrahydrofuran to the second target compound **3** (79%). Alternatively, **3** could be prepared by reduction of **2** with borane–tetrahydrofuran (83%). The mass spectra (EI and FAB) and ^{1}H NMR spectra of **2** and **3** support their assigned structures.

Complexation of Arenes by the Macrobicyclic Hosts 2 and 3 in Aqueous Solution

Compounds **2** and **3** are readily soluble in aqueous solution at pH <5. Stoichiometric host–guest complexation in aqueous solution has to be studied below the critical micelle concentration (CMC) of host and guest in order to avoid the interference of aggregation effects. The aggregation behavior of **2** and **3** in aqueous solution was investigated by ^{1}H NMR spectroscopy as described previously for **1** and other hosts.[7,9] Hosts such as **1–3** are dissolved in aqueous solution in their molecular-dispersed form, if the chemical shifts of their protons are independent of concentration. Above the CMC, their chemical shifts become strongly dependent on concentration. The ^{1}H NMR spectra [360 MHz, 303 K, 0.5 M solution of KD_2PO_4 in D_2O, pD = 4.3,[37] sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate (TSP) as external standard in D_2O] showed concentration-independent shifts at [**2**] $< 10^{-3}$ mol·L^{-1} and [**3**] $<5 \times 10^{-3}$ mol·L^{-1}. All complexation experiments in aqueous solution were consequently carried out at pH <5 and [host] $< 10^{-3}$ mol·L^{-1}. Examinations of CPK molecular models indicated that both **2** and **3** offer a binding cavity with a suitably sized entrance for one arene as large as pyrene and even perylene. The cavities of **2** and **3**, according to the models, are highly preorganized prior to complexation.[38] We observed, however, a considerable difference in the complexation behavior of the two host molecules under the above-mentioned conditions.



13: R = Cbz, X = O
14: R = H, X = O
15: R = Ac, X = O

In weakly acidic aqueous solution, the macrobicycle **2** possesses a binding cavity of pronounced apolar character since the protonated amine nitrogen atoms are directed outwards. Our complexation studies showed that **2** is a very good host for appropriately sized neutral arenes. With [**2**] = 5.0×10^{-4} mol·L^{-1} in a 0.5 M aqueous solution of KH_2PO_4, a $\approx 2.3 \times 10^{-4}$ M aqueous solution of pyrene was obtained by solid–liquid extraction.[7] By using the maximum solubility of the guest (G) in such a solution in the absence of **2** ([G_{H_2O}max] = 2.0×10^{-7} mol·L^{-1}), the association constant K_a of the 1:1 complex could be calculated as $K_a = 4.1 \times 10^6$ L·mol^{-1} (293–295 K).[7] From liquid–liquid extractions, the association constant was determined as $K_a = 3.1 \times 10^6$ L·mol^{-1}. In liquid–liquid extraction experiments, a 10^{-2} M solution of pyrene in *n*-hexane was extracted with a 0.5 M aqueous solution of KH_2PO_4 containing [**2**] = 2.0×10^{-4} mol·L^{-1}. A concentration of pyrene of 2.5×10^{-5} mol·L^{-1} was obtained in the aqueous phase. In a distribution experiment in the absence of host under the same conditions, a concentration of pyrene of only 4.5×10^{-8} mol·L^{-1} was obtained in the aqueous phase.

By using the experimental conditions described above for the studies with pyrene, a 4.3×10^{-4} M aqueous solution of naphthalene was obtained by solid–liquid extraction. With [G_{H_2O}max] = 1.3×10^{-4} mol·L^{-1}, the association constant of the **2**·naphthalene complex was calculated as $K_a = 1.2 \times 10^4$ L·mol^{-1}. A liquid–liquid extraction experiment using the experimental conditions described above gave $K_a = 1.6 \times 10^4$ L·mol^{-1}. In this experiment, a 8.3×10^{-6} M concentration of naphthalene was obtained in the aqueous phase after extraction. In the absence of host, a distribution experiment afforded a 2.0×10^{-6} M aqueous solution of naphthalene. We found that the complexation between **2** and arenes

(33) In our laboratories, *N*-hydroxysuccinimide esters have now been successfully used as activated carboxylic acid derivatives in many other amide cyclizations: Lutter, D.; Schürmann, G.; Diederich, F., unpublished results.
(34) For a recent review on the various methods of preparation of macrocyclic amides, see: Rossa, L.; Vögtle, F. *Top. Curr. Chem.* **1983**, *113*, 1–86.
(35) We thank Prof. H. Schwartz, Berlin, and Dr. L. Grotjahn, Braunschweig, for recording the FAB mass spectra of the present work.
(36) Gribble, G. W.; Jasinski, J. M.; Pellicone, J. T.; Panetta, J. A. *Synthesis* **1978**, 766–768.
(37) For the determination of the pD value, see: Glasoe, P. K.; Long, F. A. *J. Phys. Chem.* **1960**, *64*, 188–190.

is virtually independent of the nature of the inorganic ions present in the solution up to ionic strengths of 0.5 mol·L^{-1}. For the complexes of pyrene and naphthalene, we obtained within experimental error the same K_a values in 0.5 M aqueous solution of KH_2PO_4, in 0.1 M aqueous hydrochloric acid, or in 0.1 M aqueous sulfuric acid.

The ^{1}H NMR spectrum (360 MHz, 0.5 M solution of KD_2PO_4 in D_2O, pD = 4.3, TSP ext.) demonstrates the strong complexation between **2** and pyrene. At 303 K, the exchange between host and guest is slow on the NMR time scale. In the spectrum of the solution with [**2**] = 5.0×10^{-4} mol·L^{-1} and [pyrene] = 2.3×10^{-4} mol·L^{-1}, signals of the free and complexed host are present in an intensity ratio of ≈2.7:2.3 along with the signals of the completely complexed pyrene. At 353 K, the exchange between host and guest is fast on the 360 MHz time scale. The averaged signals of the host, however, are still very broad. **2** and pyrene form a highly structured complex. Pyrene is located in the plane of **2** passing through the three spiro carbon atoms. This orientation, expected from examinations of CPK molecular models, is supported by the changes upon complexation of the chemical shifts of the protons of both binding partners. The signals of the protons of pyrene in the solution of complex are strongly shifted upfield [$\Delta\delta$ = +2.04 (1-H), +1.03 (2-H),[39] +1.99 (4-H).[40,41] The resonances of the protons of **2**, which lie about perpendicular to the plane of pyrene (O–CH_2–CH_2–N–C(O)–CH_2–O), are shifted upfield and the signals of the protons for **2** in this plane (e.g., aryl-*H*) are shifted downfield.

Complexed naphthalene is also exclusively located in the plane of **2** passing through the three spiro carbon atoms. At 303 K with [**2**] = 5.0×10^{-4} mol·L^{-1} and [naphthalene] = 4.3×10^{-4} mol·L^{-1}, averaged signals of both components are observed as a result of fast exchange between host and guest. The resonances of the protons of complexed naphthalene are shifted considerably upfield [$\Delta\delta$ = +1.69 (1-H) and +1.30 (2-H)].[41] The signals of **2** in the solution of the **2**·naphthalene complex show the same up- and downfield pattern as described above for the solution of the **2**·pyrene complex.

A complete assignment of the signals of free or complexed **2** in acidic aqueous solution was not possible. Several dynamic processes are frozen at T = 273–353 K on the 360 MHz time scale. The rotations around the two amide bonds and the ring inversions of the three protonated spiro piperidinium rings with equatorially positioned *N*-ethyl groups are slow. Hence, the ^{1}H NMR spectra are very complex. In the solution of free **2**, as many as ten highly resolved signals of various intensity are observed for the protons of the methyl groups of the diphenylmethane units (T = 273–353 K). Also, a multitude of signals is observed for the aromatic protons. From the solution of complex, it is difficult to determine exact $\Delta\delta$ values of specific protons of **2**. However, the up- and downfield shifts upon complexation of the different groups of resonances (e.g., aryl-*H*, O–CH_2–CH_2–N–C(O)–CH_2–O) can be clearly seen in the spectra.

The ring inversion of the three spiro piperidinium rings of free and complexed host **3** in acidic aqueous solution is expectedly also slow on the 360 MHz NMR time scale. In the spectrum of pure host **3** in a 0.5 M solution of KD_2PO_4 in D_2O (T = 303 K), the different resonances of H_{ax} and of H_{eq} of the three piperidinium rings are not overlapped by other signals and can be clearly observed. The signals of the various axial and equatorial protons appear at δ 2.33 ("t", $J \approx 12$ Hz; 3′,3″,3‴-H_{ax}), 2.60 ("d", $J \approx 12$ Hz; 3′,3″,3‴-H_{eq}), 3.03 ("t", $J \approx 12$ Hz; 2′,2″,2‴-H_{ax}), and 3.57 ("d", $J \approx 12$ Hz; 2′,2″,2‴-H_{eq}).

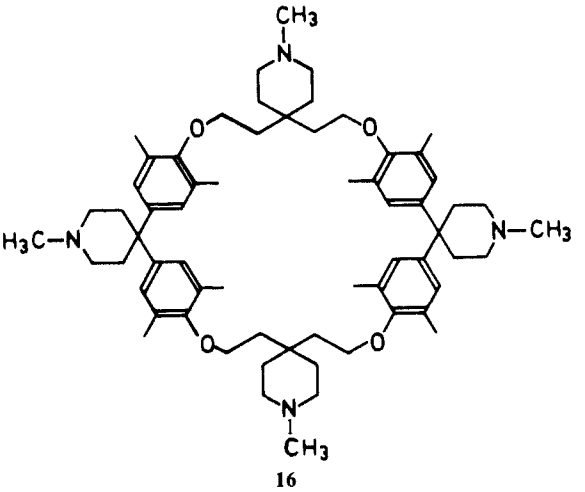
The complexation between **3** and neutral arenes in acidic aqueous solution is considerably weaker. With a 0.5 M aqueous solution of KH_2PO_4 ([**3**] = 5.0×10^{-4} mol·L^{-1}), only a ≈ 2.3×10^{-6} M solution of pyrene was obtained by solid–liquid extraction. With a 0.1 M aqueous hydrochloric acid ([**3**] = 5.0×10^{-4} mol·L^{-1}), the extraction by complexation was even weaker. Only a ≈5.4×10^{-7} M concentration of pyrene in the aqueous phase was obtained. Similarly, in the liquid–liquid extraction experiments, the extraction of pyrene was considerably less effective with host **3** than with host **2**. The same difference between **2** and **3** was also observed in the extractions with naphthalene as guest.

That the weak complexation of arenes by **3** in acidic aqueous solution is not due to geometric factors is supported by the strong complexation observed between nonprotonated **3** and pyrene or other suitably sized arenes in alcohols (see below). The very different complexing behavior of **2** and **3** toward arenes in acidic aqueous solution underscores the *significance of the outward directing ionic groups* responsible for promoting solubility in water. In acidic aqueous solution, **2** has a binding cavity of pronounced apolar character and hence is a very good host for neutral arenes of complementary size. The two protonated amine nitrogen atoms in the cavity of **3** in acid solution, on the other hand, considerably reduce the hydrophobic character of this cavity. As a consequence, **3** is a weaker host for arenes in this medium.

The complexation of pyrene in aqueous solution by the spherical, macrobicyclic host **2** (K_a = 4.1×10^6 L·mol^{-1}) is not so much stronger than the complexation by the macromonocyclic host **1** (K_a = 1.1×10^6 L·mol^{-1}).[7] The complexation of naphthalene by both hosts is even very similar ($K_a \approx 1.2 \times 10^4$ L·mol^{-1}).[7] This finding was rather unexpected. It indicates that **2** is already a very good host in aqueous solution, which envelops and encapsulates efficiently arenes of complementary size.

Complexation of Arenes in Organic Solutions

During our binding studies with hosts **1**–**3** in aqueous solution, we also monitored qualitatively by ^{1}H NMR their binding behavior in organic solvents. With **1** and pyrene, weak complexation was observed in methanol-d_4 and we could not detect any complexation in Me_2SO-d_6.[8] We also observed only weak complexation between non-protonated host **2** and pyrene in methanol-d_4. We observed, however, a surprisingly strong complexation between non-protonated host **3** and pyrene in this solvent.[24] These first results initiated the present study of the complexation between the neutral hosts **2**, **3**, **16**,[10] and arenes of different size in organic solvents. The solubility properties of the three hosts allowed a study of their complexation behavior in a large range of solvents of different polarity.



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(38) For the importance of the concept of the preorganization of a binding site prior to complexation, see: Cram, D. J. *Science* **1983**, *219*, 1177–1183.

(39) The triplet of 2-H is only visible at 353 K when the exchange between host and guest is rapid; the quoted upfield shift was measured at this temperature.

(40) The change of the chemical shift upon complexation is defined as $\Delta\delta$ (ppm) = δ of pure host or pure guest in solution − δ of host or guest in the solution of complex. The plus signal then refers to a shift to higher magnetic field. In solutions of complexes, where the exchange between free and complexed host and/or between free and complexed guest is fast on the NMR time scale, the signals of both components appear at the average of the chemical shifts of free and complexed host and/or free and complexed guest. The average is weighed by the fractional population of the host and/or guest in the free and in the complexed form.

(41) For the calculation of the complexation shifts ($\Delta\delta$) of the protons of the guest, the spectra of pure pyrene in methanol-d_4 [δ = 8.20 (1-H), 8.02 (2-H), and 8.10 (4-H), TSP ext. in methanol-d_4][8] and of pure naphthalene in D_2O [δ = 7.99 (1-H) and 7.60 (2-H), TSP ext. in D_2O][9] have been used.

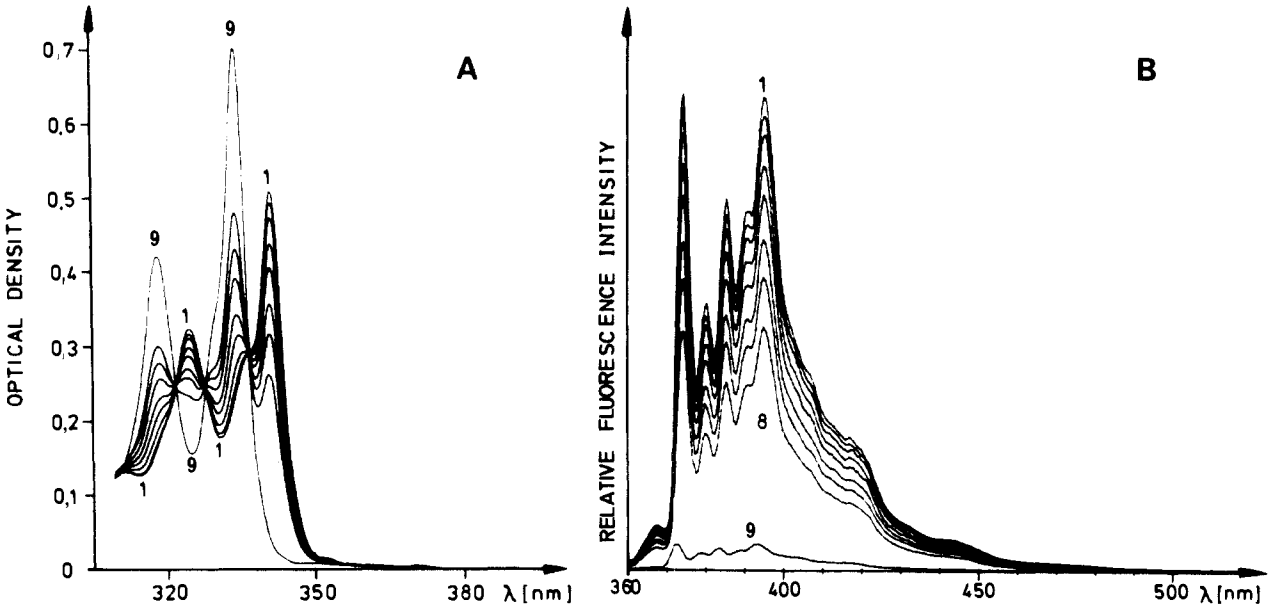

Figure 1. Electronic absorption (A) and emission (B) titrations to determine the association constant of the **3**·pyrene complex in ethanol (T = 303 K). The absorption titration was evaluated at λ = 341 nm, d = 5 cm; the emission titration was evaluated at λ_{exc} = 341 nm and λ_{em} = 395 nm. In both titrations, $[G_0]$ is 2.99 × 10^{-6} mol·L^{-1}, and $[H_0]$ is the following from spectrum 1 to spectrum 9: 3.00, 2.41, 1.80, 1.20, 0.90, 0.60, 0.45, 0.30, and 0 × 10^{-4} mol·L^{-1}.

A. Determination of Association Constants K_a from Optical Titrations. When host **3** was added to solutions of perylene, pyrene, and fluoranthene in methanol, changes in the optical spectra of these guests became visible. Host **3** does not absorb light above λ = 310 nm. Upon addition of **3**, the p-bands of these guests, which appear above 310 nm,[42] showed significant bathochromic shifts. The p-bands of pyrene appear in pure methanol at λ_{max} = 334, 318, and 304 nm. They are shifted in the presence of **3** to λ_{max} = 341, 325, and 311 nm. These bathochromic shifts are accompanied by a considerable reduction of the molar extinction coefficients of the bands. The p-bands of pure perylene in methanol appear at λ_{max} = 433, 428 (sh), 406, 384, and 366 (sh) nm. They are shifted in the presence of **3** to λ_{max} = 440, 434, 412, 390, and 371 nm. The maxima of the p-bands of fluoranthene move in the presence of **3** from λ_{max} = 357, 341, and 322 nm to λ_{max} = 363, 347, and 324 nm. Interestingly, the shape and position of the α-bands of pyrene are not changed to the same extent in the presence of **3**. Almost no hypochromicity and red shifts of only 1 nm at maximum are observed for these weak bands, which, in a solution of pure pyrene in methanol, appear at λ_{max} = 372, 363, 357, and 351 nm.

Bathochromic shifts were also observed in the fluorescence spectra of the guests in methanol upon addition of **3**. Host **3** did not show fluorescence emission under the experimental conditions used. Comparable changes in the electronic absorption and emission spectra of the guests upon addition of hosts, **3**, **2**, or **16** were observed in all organic solvents in which significant complexation occurred. We took advantage of these spectral changes in the presence of the hosts and determined from optical titrations the association constants of the complexes formed with perylene, pyrene, and fluoranthene in organic solvents. The K_a values determined from optical titrations under Benesi–Hildebrand conditions ($[H_0] \gg [G_0]$)[43,44] are given in Table I. Experimental data of the titrations are included in Tables I and III. Electronic absorption data were evaluated by using eq 1 and fluorescence data were evaluated by using eq 2.[7] The association constants of the complexes of **3** with durene and naphthalene in methanol (Table I) were obtained from competitive inhibition of the binding

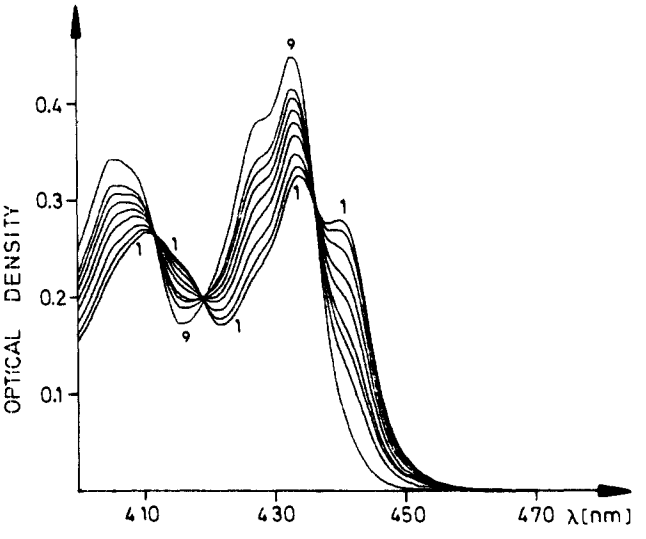

Figure 2. Electronic absorption titration to determine the association constant of the **2**·perylene complex in methanol (T = 303 K). The titration was evaluated at λ = 440 nm, d = 5 cm. $[G_0]$ is 2.18 × 10^{-5} mol·L^{-1}, and $[H_0]$ is the following from spectrum 1 to spectrum 9: 4.19, 3.35, 2.52, 1.68, 1.26, 0.84, 0.63, 0.42, and 0 × 10^{-3} mol·L^{-1}.

of perylene and evaluation of the fluorescence of perylene by a Benesi–Hildebrand type treatment ($[I_0] \gg [H_0] \gg [G_0]$; eq 3).[7]

$$\frac{[G_0]d}{\Delta Abs} = \frac{1}{K_a \cdot \Delta\epsilon}\frac{1}{[H_0]} + \frac{1}{\Delta\epsilon} \quad (1)$$

$$\frac{1}{\Delta F} = \frac{1}{K_a \Delta F_{max}}\frac{1}{[H_0]} + \frac{1}{\Delta F_{max}} \quad (2)$$

$$\frac{1}{\Delta F} = \frac{1}{\Delta F_{max}} + \frac{1}{\Delta F_{max}[H_0]K_G}(1 + K_I[I_0]) \quad (3)$$

In eq 1 and 2, $[H_0]$ and $[G_0]$ are the total concentrations of host and guest. d(cm) is the length of the UV cell, ΔAbs and ΔF are the increase in the absorbance and fluorescence intensity of the guest upon addition of host. $\Delta\epsilon$ and ΔF_{max} are the increase in molar absorptivity and in fluorescence intensity if all guest is complexed. The values of K_a and ΔF_{max} or $\Delta\epsilon$ were obtained with

(42) Clar, E. "Polycyclic Aromatic Hydrocarbons"; Academic Press: London, 1964; Vol. 1 and 2.
(43) Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703–2707.
(44) Bergeron, R. J.; Roberts, W. P. *Anal. Biochem.* **1978**, *90*, 844–848.

Table I. Association Constants K_a ($L \cdot mol^{-1}$) of 1:1 Complexes formed between Hosts **2**, **3**, or **16** and Arenes in Organic Solutions (T = 303 K)[a]

complex	solvent	K_a ($L \cdot mol^{-1}$)	$-\Delta G$ ($kcal \cdot mol^{-1}$)	method
	A. Complexes of Host **3**			
3·perylene	MeOH	1.1×10^5	7.0	A
	EtOH	6.3×10^4	6.6	A
	acetone	2.2×10^3	4.6	A
	acetone-d_6	1.5×10^3	4.4	E
	Me_2SO-d_6	8.0×10^2	4.0	E
	DMF-d_7	3.6×10^2	3.5	E
	THF-d_8	1.5×10^2	3.0	E
	$CDCl_3$	42	2.2	E
	benzene-d_6	27	2.0	E
3·pyrene	MeOH	4.4×10^4	6.4	A
		3.4×10^4	6.3	B
	MeOH-d_4	3.3×10^4	6.3	D
	EtOH	2.5×10^4	6.1	A
		2.4×10^4	6.1	B
	EtOH-d_6	2.6×10^4	6.1	D
	acetone	1.2×10^3	4.3	A
		8.4×10^2	4.1	B
	acetone-d_6	8.9×10^2	4.1	E
	Me_2SO-d_6	6.9×10^2	3.9	E
	DMF-d_7	1.6×10^2	3.0	E
	THF-d_8	84	2.7	E
	$CDCl_3$	43	2.3	E
	benzene-d_6	12	1.5	E
	CS_2	9	1.3	E
3·fluoranthene	MeOH	7.2×10^4	6.7	A
	acetone-d_6[b]	1.1×10^3	4.2	E
	THF-d_8[b,c]	$\approx 1.2 \times 10^2$	≈ 2.9	E
3·naphthalene	MeOH	1.2×10^2	2.9	C
	acetone-d_6	<10	<1.4	E
	Me_2SO-d_6	<10	<1.4	E
	THF-d_8	<3	<0.6	E
	DMF-d_7	no complexation observed		
	$CDCl_3$			
	benzene-d_6			
3·durene	MeOH	27	2.0	C
	no complexation observed in nonalcoholic solvents			

complex	solvent	K_a ($L \cdot mol^{-1}$)	$-\Delta G$ ($kcal \cdot mol^{-1}$)	method
	B. Complexes of Host **2**			
2·perylene	MeOH	5.6×10^2	3.8	B
	Me_2SO-d_6	38	2.2	E
	DMF-d_7	11	1.4	E
	$CDCl_3$	<3	<0.6	E
2·pyrene	MeOH	65	2.5	B
	MeOH-d_4	55	2.4	E
	DMSO-d_6	27	2.0	E
	DMF-d_7	<10	<1.4	E
	THF-d_8	<2	<0.4	E
	benzene-d_6	no complexation observed		
2·naphthalene	MeOH-d_4	25	1.9	E
	C. Complexes of Host **16**			
16·perylene	MeOH	8.4×10^2	4.0	B
16·pyrene[b]	MeOH-d_4	$\approx 1.2 \times 10^2$	≈ 2.9	E
	Me_2SO-d_6	≈ 16	≈ 1.7	E
	$CDCl_3$	no complexation observed		
16·fluoranthene[b]	MeOH-d_4	1.1×10^2	2.8	E
	$CDCl_3$	<2	<0.4	E
16·naphthalene	MeOH-d_4	≈ 14	≈ 1.6	E

[a] The methods applied are (A) Benesi–Hildebrand treatment of data from fluorescence titrations, (B) Benesi–Hildebrand treatment of data from electronic absorption titrations, (C) competitive inhibition of the binding of perylene and evaluation of the fluorescence of perylene by a Benesi–Hildebrand type treatment, (D) direct evaluation of the ^1H NMR titration curve at half-saturation binding of the guest, and (E) determination of the degree of complexation in a single ^1H NMR experiment, using the complexation shifts $\Delta\delta$, $\Delta\delta_{sat}$ and the concentrations $[H_0]$, $[G_0]$ of Table II. See Table III (Experimental Section) for the concentrations $[H_0]$, $[G_0]$, and $[I_0]$ used in the titrations. Electronic absorption titrations are evaluated at λ = 440 nm (perylene) and λ = 341 nm (pyrene). Fluorescence titrations are evaluated at λ_{exc} = 441 nm, λ_{em} = 472 nm (perylene), λ_{exc} = 341 nm, λ_{em} = 395 nm (pyrene), and λ_{exc} = 365 nm, λ_{em} = 464 nm (fluoranthene). [b] Larger margin of error of the K_a values, see ref 52. [c] Overlapping signals reduce the accuracy of the determination of the complexation shifts $\Delta\delta$ in the ^1H NMR spectra.

good agreement by graphic evaluation of the data or by a least-square-fit treatment with constant absolute error. In eq 3, K_G is the association constant of the complex of the guest (perylene) whose binding is inhibited. $[I_0]$ is the total concentration of the inhibitor and K_I is the association constant of the complex of host and inhibitor. K_I is obtained from the intersect of the straight line in the Benesi–Hildebrand type plot with the abscissa.[7]

The association constant K_a of the 1:1 complex formed between **3** and pyrene in ethanol was determined from both electronic absorption and emission data. The two titrations are shown in Figure 1. The K_a values from both titrations are in excellent agreement (Table I). In the absorption spectra, several isosbestic points indicate the exclusive formation of a 1:1 complex. Isosbestic points have been obtained in all absorption titrations: Figure 2 shows the titration to determine the association constant of the 1:1 complex of **2** and perylene in methanol (Table I).

A strong increase in fluorescence intensity was observed upon addition of **3** to the solution of pyrene in methanol (Figure 1). This considerable increase, which allows an accurate evaluation of K_a, results to a large extent from selective excitation. At the excitation wavelength λ_{exc} = 341 nm, the molar extinction coefficient of free pyrene is only $\approx$2100 (see Figure 1). At this wavelength, complexed pyrene has an absorption maximum with a molar extinction coefficient of $\approx$36 000. Irradiation at this wavelength therefore results mainly in the excitation of complexed pyrene. In all fluorescence titrations, the excitation wavelength was chosen to predominantly excite the complexed guest. A strong increase in emission intensity was always observed upon addition of host. Besides being the result of selective excitation, the increase in fluorescence intensity might also be partially due to the protection of the encapsulated excited guest against quenching by oxygen in the nondegassed solutions.[45]

All binding constants in organic solvents were found to be strongly dependent on temperature. Both optical and ^1H NMR studies showed that the complexation is weaker at higher than at lower temperatures. The association constant of the 1:1 complex of **3** and perylene in ethanol was determined between 283 and 323 K. Evaluation of the van't Hoff plot with use of K_a values from fluorescence titrations of 1.9×10^5 $L \cdot mol^{-1}$ (283 K), 1.08×10^5 $L \cdot mol^{-1}$ (293 K), 6.35×10^4 $L \cdot mol^{-1}$ (303 K), 3.42×10^4 $L \cdot mol^{-1}$ (313 K), and 1.91×10^4 $L \cdot mol^{-1}$ (323 K) gave $\Delta H = -10.7$ $kcal \cdot mol^{-1}$ and $\Delta S_{303} = -13.4$ $cal \cdot mol^{-1} \cdot K^{-1}$.

Strong 1:1 complexation between pyrene and host **3** was also demonstrated by the complete absence of excimer fluorescence in equimolar solutions of **3** and pyrene in the concentration range of 10^{-5}–10^{-2} $mol \cdot L^{-1}$. We took advantage of the strong binding between **3** and pyrene in methanol to inhibit the formation of an

(45) DeKorte, A.; Langlois, R.; Cantor, C. R. *Biopolymers* **1980**, *19*, 1281–1288.

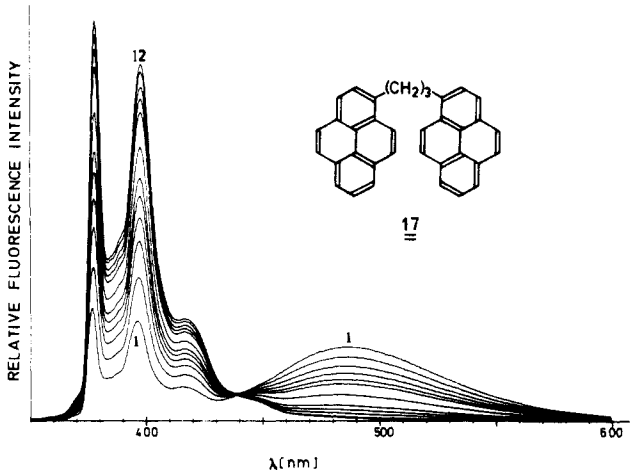

Figure 3. Electronic emission spectra in methanol of 1,3-bis(1-pyrenyl)propane (**17**) in the absence (spectrum 1) and in the presence of host **3** (spectra 2-12). $[G_0]$ is 2.4×10^{-6} mol·L^{-1}; T = 292.5 K; λ_{exc} = 341 nm. From spectrum 2 to spectrum 12, the concentration of **3** is the following: 1.47, 2.94, 4.41, 5.88, 7.35, 12.0, 24.0, 36.0, 60.0, 206.0, and 515.0×10^{-6} mol·L^{-1}.

intramolecular excimer by 1,3-bis(1-pyrenyl)propane (**17**).[46] After excitation, compound **17** forms an intramolecular excimer in very dilute solution in methanol ($[\mathbf{17}] = 2.4 \times 10^{-6}$ mol·L^{-1}, λ_{exc} = 340 nm, T = 292.5 K). The excimer fluorescence at these conditions is shown in spectrum 1 of Figure 3.[46] Upon addition of **3**, the excimer emission decreases and the monomer emission increases. With $[\mathbf{3}] \approx 10^{-5}$ mol·L^{-1}, the excimer emission has completely disappeared and only the monomeric fluorescence of pyrene is visible.

After encapsulation of one pyrene moiety of **17** in the cavity of host **3**, the geometric proximity and orientation of the two pyrene moieties, required for the formation of an intramolecular excimer, can no longer be established.[47] We still have to investigate if, beyond the 1:1 complex, a 2:1 host-guest complex can form between **3** and **17**. In such a complex, each pyrene moiety of **17** would be enclosed in a cavity of a host.

B. Geometry of Complexes in Organic Solvents and Association Constants K_a from ^{1}H NMR Data. In previous work,[8-10] ^{1}H NMR spectroscopy provided valuable information on the geometry of the complexes in solution. In the present study, the structural information from ^{1}H NMR data allowed the estimation of association constants of weaker complexes in many organic solvents, which were difficult to obtain by other methods.

Small binding constants have to be determined in higher concentration ranges.[48] Under these conditions, fluorescence titrations could not be applied. The K_a values from fluorescence studies in higher concentration ranges were no longer in agreement with the values obtained from electronic absorption or NMR titrations and seemed to be too high. Electronic absorption and ^{1}H NMR titrations under Benesi-Hildebrand conditions were also only of limited use for the evaluation of small K_a values. The solubility of the hosts and also of guests like perylene, pyrene, and fluoranthene in many solvents did not allow titrations with $[H_0] \gg [G_0]$ or $[G_0] \gg [H_0]$ in higher concentration ranges (c of the major component $\gg 5 \times 10^{-3}$ mol·L^{-1}). The use of ^{1}H NMR titrations under Benesi-Hildebrand conditions was further restricted by the fact that the weak signals of the minor component disappeared over large parts of the titration below the very strong peaks of the major component. If saturation binding is reached, the special Benesi-Hildebrand conditions have no longer to be applied and the association constants can be directly obtained from the evaluation of titration curves.[7] With the restricted solubility of hosts and guests at higher concentrations, however, saturation binding was only obtained in alcohols, where strong complexation occurs. We determined directly from titration curves the K_a values of the **3**·pyrene complexes in ethanol and methanol. These K_a values are in good agreement with the numbers obtained from optical titrations (Table I).

For the estimation of weak association constants, we finally took advantage of the observation made during the evaluation of ^{1}H NMR data, that the highly favored geometry of the complex of a host and a specific arene is very similar in all solvents. In all solutions of complexes in organic solvents, the complexation-decomplexation at 303 K is fast on the 360 MHz NMR time scale.[49] As mentioned above, saturation binding was obtained in the complexation between **3** and pyrene in alcohols. With $[\mathbf{3}] = 2.0 \times 10^{-2}$ mol·L^{-1} and $[\text{pyrene}] = 2.0 \times 10^{-3}$ mol·L^{-1} in methanol-d_4, all guest is complexed and the complexation shifts are $\Delta\lambda_{sat}$ = +1.79 (1-H), +1.21 (2-H), +1.98 (4-H). The complexation shifts of the protons of **3** in methanol-d_4 at saturation binding of the host ($[\text{pyrene}] = 2.0 \times 10^{-2}$ mol·L^{-1} and $[\mathbf{3}] = 2.0 \times 10^{-3}$ mol·L^{-1}) are $\Delta\delta_{sat}$ = −0.04 (N-CH_2-CH_3), +0.08 (aryl-CH_3), −0.04 (N-CH_2-CH_3), −0.43 [N-CH_2-CH_2-C(Ar)$_2$], −0.16 [N-CH_2-CH_2-C(Ar)$_2$], +0.85 (N-CH_2-CH_2-O), +2.14 (N-CH_2-CH_2-O), −0.60 (aryl-H) ppm.

In ethanol-d_6, all protons of **3** and of pyrene show within ±0.02 ppm the same complexation shifts at saturation binding ($\Delta\delta_{sat}$) as in methanol-d_4. This represents strong evidence for the formation of the same complex in both solvents. Pyrene is located within the plane passing through the three spiro carbon atoms of **3**. The protons 1-H and 3-H of pyrene are more oriented toward the shielding region of the aromatic rings of **3** than 2-H. The ^{1}H NMR data suggest that the same geometry of complex is also highly favored in nonalcoholic solvents. A very similar degree of complexation of pyrene in a given solvent is calculated from the observed complexation shift $\Delta\delta$ of each proton of pyrene and from the saturation shift $\Delta\delta_{sat}$ of the proton in methanol-d_4. Similarly, from the observed complexation shift $\Delta\delta$ of each proton of **3** and from the saturation shift $\Delta\delta_{sat}$ of the proton in methanol-d_4 (e.g., see Table V), almost the same degree of complexation of the host in the solution of complex can be calculated. With $[H_0] = [G_0]$, the calculated degrees of complexation of host and guest were found to be nearly identical. With $[H_0] \neq [G_0]$, different degrees of complexation were calculated for host and guest. These findings can only be expected if **3**·pyrene complexes with very similar geometry and very similar saturation shifts $\Delta\delta_{sat}$ form in methanol and in the other solvents, where complexation was monitored. We therefore can use the saturation shifts $\Delta\delta_{sat}$ observed in methanol-d_4 to determine the degree of complexation in other solvents where saturation binding cannot be reached. With $[H_0]$, $[G_0]$, and the degree of complexation being known, the association constants can be easily determined. The K_a values obtained independently from the degree of complexation of the host and of the guest were generally in good agreement. As an example, from the observed complexation shifts of the protons of pyrene in $CDCl_3$ ($[H_0] = 5.04 \times 10^{-3}$ mol·L^{-1}, $[G_0] = 5.23 \times 10^{-3}$ mol·L^{-1}), the degree of complexation of the guest is calculated as 15.08% (from 1-H), 14.65% (from 2-H), and 16.53% (from 4-H). K_a is calculated as 43 L·mol^{-1} from these values.

(46) Zachariasse, K.; Kühnle, W. *Z. Phys. Chem. NF* **1976**, *101*, 267-276.
(47) For a comparable study in cyclodextrin chemistry, see: Emert, J.; Kodali, D.; Catena, R. *J. Chem. Soc., Chem. Commun.* **1981**, 758-759.
(48) For discussions of the determination of equilibrium constants of weak complexes, see: (a) Person, W. B. *J. Am. Chem. Soc.* **1965**, *87*, 167-170. (b) Deranleau, D. A. *J. Am. Chem. Soc.* **1969**, *91*, 4044-4049. (c) LaBudde, R. A.; Tamres, M. *J. Phys. Chem.* **1970**, *74*, 4009-4014.

(49) Broadening of selected signals of host and guest, however, can be observed in many solutions which contain both free and complexed host and/or guest. The broadening indicates the beginning of the slowing of the exchange between host and guest on the NMR time scale. The observed broadening is expectedly largest for the signals of protons that show the most important complexation shifts $\Delta\delta$. In a solution of the **3**·pyrene complex in methanol-d_4 below 250 K, the exchange between host and guest is slow on the 360-MHz NMR time scale. With $[\mathbf{3}] = 6.0 \times 10^{-3}$ mol·L^{-1} and $[\text{pyrene}] = 3.0 \times 10^{-3}$ mol·L^{-1}, the signals of free and complexed host in the intensity ratio of 1:1 appear beside the signals of complexed pyrene. At the coalescence of the singlets of the aromatic protons of free and complexed host at 253 K ($\Delta\nu$ = 231.9 Hz), the first-order rate constant for the decomplexation process can be calculated as $k_{253K} = 515$ s^{-1}. The free enthalpy of activation of this process (ΔG_{253K}) is calculated as 11.6 kcal·mol^{-1}.

Table II. Complexation Shifts $+\Delta\delta$ (ppm) of the Protons of the Guests in Solutions of Complexes formed by Hosts **2**, **3**, and **16** in Deuterated Solvents (360 MHz, T = 303 K)[a]

A. Complexes of Host **3**

3·perylene	MeOH	acetone	Me_2SO	DMF	THF	$CDCl_3$	benzene
$10^3[H_0]$, mol·L^{-1}	4.99	4.97	5.00	4.97	5.02	5.11	5.04
$10^3[G_0]$, mol·L^{-1}	4.91	5.03	5.19	5.04	4.83	5.04	4.91
1-H	1.23 ($\Delta\delta_{sat}$)	0.88	0.75	0.59	0.43	0.19	0.14
2-H	0.66 ($\Delta\delta_{sat}$)	0.44	b	0.33	0.23	0.11	0.06
3-H	2.53 ($\Delta\delta_{sat}$)	1.77	1.50	1.18	0.83	0.37	0.31

3·pyrene	MeOH	EtOH	acetone	Me_2SO	DMF	THF	$CDCl_3$	benzene	CS_2
$10^3[H_0]$, mol·L^{-1}	20.0	20.0	5.03	5.00	5.04	4.99	5.04	4.99	4.96
$10^3[G_0]$, mol·L^{-1}	2.0	2.0	5.19	4.98	5.20	5.00	5.23	5.00	5.17
1-H	1.79 ($\Delta\delta_{sat}$)	1.77	1.09	b	0.65	0.43	0.27	0.10	0.07
2-H	1.21 ($\Delta\delta_{sat}$)	1.20	0.76	0.73	0.39	0.29	0.20	0.07	0.05
4-H	1.98 ($\Delta\delta_{sat}$)	1.97	1.22	≈1.14	0.69	0.48	0.29	0.11	0.08

3·fluoranthene[c]	MeOH	EtOH	acetone	THF
$10^3[H_0]$, mol·L^{-1}	20.0	5.03	4.98	5.05
$10^3[G_0]$, mol·L^{-1}	2.0	4.99	5.02	5.08
1-H	1.96 ($\Delta\delta_{sat}$)	1.94	1.29	0.58
2-H	0.78 ($\Delta\delta_{sat}$)	0.87	0.54	0.24
3-H	2.05 ($\Delta\delta_{sat}$)	2.00	1.22	≈0.6
7-H	2.08 ($\Delta\delta_{sat}$)	1.98	1.40	≈0.65
8-H	0.34 ($\Delta\delta_{sat}$)	0.41	b	≈0.10

3·naphthalene	MeOH	Me_2SO	acetone	THF	**3**·durene	MeOH
$10^3[H_0]$, mol·L^{-1}	4.99	4.99	5.04	4.97		5.00
$10^3[G_0]$, mol·L^{-1}	5.38	4.99	5.00	4.98		5.00
1-H	0.62 (2.12 = $\Delta\delta_{sat}$(calcd))[d]	0.07	0.06	0.03	H_{arom}	0.07
2-H	0.51 (1.75 = $\Delta\delta_{sat}$(calcd))[d]	0.06	0.05	0.02	CH_3	0.04

B. Complexes of Host **2**

2·perylene	MeOH	Me_2SO	DMF	$CDCl_3$
$10^3[H_0]$, mol·L^{-1}	4.99	5.09	5.00	5.01
$10^3[G_0]$, mol·L^{-1}	4.91	5.07	5.02	5.03
1-H	0.79 (1.43 = $\Delta\delta_{sat}$(calcd))[d]	≈0.20	0.07	0.02
2-H	0.39 (0.71 = $\Delta\delta_{sat}$(calcd))[d]	b	0.04	0.01
3-H	1.38 (2.50 = $\Delta\delta_{sat}$(calcd))[d]	0.36	0.13	0.03

2·pyrene	0.5 M KD_2PO_4	MeOH	Me_2SO	DMF	THF	**2**·naphthalene	0.5 M KD_2PO_4	MeOH
$10^3[H_0]$, mol·L^{-1}	0.50	4.98	4.89	5.05	5.00		0.50	5.01
$10^3[G_0]$, mol·L^{-1}	0.23	4.99	4.85	5.23	4.94		0.43	5.68
1-H	2.04 ($\Delta\delta_{sat}$)	0.37	0.20	0.05	0.03		1.69 ($\Delta\delta_{sat}$)	0.32
2-H	1.03 ($\Delta\delta_{sat}$)	0.19	0.11	0.03	0.02		1.30 ($\Delta\delta_{sat}$)	0.25
4-H	1.99 ($\Delta\delta_{sat}$)	0.38	0.22	0.05	0.03			

C. Complexes of Host **16**

16·perylene	MeOH[e]	Me_2SO	DMF	$CDCl_3$	**16**·pyrene[f]	MeOH	Me_2SO
$10^3[H_0]$, mol·L^{-1}	6.46	6.46	4.98	6.49		5.00	6.42
$10^3[G_0]$, mol·L^{-1}	5.02	5.03	5.30	5.11		5.00	5.36
1-H	0.72	0.14	0.06	0.03	1-H	0.31	0.08
2-H	0.33	0.06	0.03	0.02	2-H	0.17	0.06
3-H	0.73	0.16	0.08	0.04	4-H	0.31	0.08

16·fluoranthene[f]	MeOH	$CDCl_3$	**16**·naphthalene[f]	MeOH
$10^3[H_0]$, mol·L^{-1}	5.09	6.41		5.00
$10^3[G_0]$, mol·L^{-1}	5.14	4.99		5.00
1-H	0.37	0.03		0.07
2-H	0.15	0.01		0.05
3-H	0.36	0.03		
7-H	0.29	0.02		
8-H	0.04	0.01		

[a] The spectra of pure host **3** and of the pure guests in the various solvents are given in the Experimental Section (Table IV). The reference standard for the spectra in MeOH-d_4, EtOH-d_6, D_2O, and Me_2SO-d_6 is TSP ext. in these solvents; for the spectra in benzene-d_6, DMF-d_7, THF-d_8, and $CDCl_3$:TMS ext. in these solvents; for the spectra in CS_2:TMS ext. in benzene-d_6 (for deuterium lock). The binding constants K_a of Table I are calculated from the concentrations $[H_0]$ and $[G_0]$ and the complexation shifts $\Delta\delta$ and $\Delta\delta_{sat}$ given in this table. [b] Overlapping signals reduce the accuracy of the determination of $\Delta\delta$. [c] Considerable complexation was also evidenced in the spectra of **3**·fluoranthene in Me_2SO-d_6 and DMF-d_7. The complexation shifts in these solvents, however, could not be evaluated due to the overlapping of all signals of the guest to give an unresolved multiplet. [d] These complexation shifts at saturation binding ($\Delta\delta_{sat}$) are calculated from the observed complexation shift and from the association constant K_a determined by other methods (see Table I). [e] Remaining undissolved perylene was present in this solution. [f] For the estimation of K_a values (Table I), the complexation shifts at saturation binding ($\Delta\delta_{sat}$) of the protons of the guest in the complexes of **1** in D_2O are considered. **1**·pyrene: $\Delta\delta_{sat}$ = 1.02 (1-H), 0.44 (2-H), 1.25 (4-H). **1**·fluoranthene: $\Delta\delta_{sat}$ = 1.37 (1-H), 0.49 (2-H), 1.35 (3-H), 0.99 (7-H), 0.09 (8-H). **1**·naphthalene: $\Delta\delta_{sat}$ = 1.16 (1-H), 0.75 (2-H).[8]

The degree of complexation of **3** is determined as 16.82% (from N–CH_2–CH_2–O) and 16.66% (from aryl-H), and a K_a value of 46 L·mol^{-1} is calculated. Tables II and V give the observed complexation shifts $\Delta\delta$ of the protons of pyrene and of **3** in solutions of the **3**·pyrene complex together with the values of $[H_0]$ and $[G_0]$. Table I shows the association constants K_a that were calculated from the data of Table II.

The complexes between **3** and perylene, fluoranthene, naphthalene, or durene also have very similar geometry in all solvents used. All guests are located in the plane of **3**, which passes through the three spiro carbon atoms. We used the method described above to determine the association constants of the **3**·perylene and **3**·

fluoranthene complexes in different organic solvents. The observed complexation shifts $\Delta\delta$ of the protons of the guests, the saturation shifts $\Delta\delta_{sat}$ in methanol-d_4, and the concentrations $[H_0]$ and $[G_0]$ are shown in Table II.

We also estimated the association constants of the **2**·pyrene and **2**·naphthalene complexes in organic solvents by this method. We used the complexation shifts at saturation binding ($\Delta\delta_{sat}$) of both guests in weakly acidic aqueous solution (see above) to evaluate the degree of complexation of the guest in the solutions of complexes. In the cavity of **2** as in the cavity of **3**, all aromatic guests are located in the plane passing through the three spiro carbon atoms.

As expected, hosts **1** and **16** form complexes of similar geometry. In the cavities of **1** and **16**,[8] all arenes are located in the plane passing through the two spiro carbon atoms of the diphenylmethane units perpendicular to the mean molecular plane of the host. We could not observe the saturation binding of arenes by host **16** in organic solvents. We therefore considered the saturation shifts $\Delta\delta_{sat}$ of pyrene, fluoranthene, and naphthalene, complexed to **1** in aqueous solution, for the estimation of the degree of complexation in the solutions of the complexes of **16** and these guests in organic solvents (Table II). The estimated K_a values of the complexes of host **16** are shown in Table I. For the **1**·pyrene complex, we had previously estimated $K_a \approx 75$ L·mol^{-1} in methanol-d_4.[8] We calculated for the **16**·pyrene complex in methanol-d_4 a K_a value of $\approx 1.2 \times 10^2$ L·mol^{-1}.

In some binding studies, complexation shifts at saturation binding ($\Delta\delta_{sat}$) could not be determined. The binding between host and guest was either too weak in all solvents or the solubility of one of the binding partners was too low to record spectra in higher concentration ranges.[50] In these cases, we calculated the saturation shifts $\Delta\delta_{sat}$ of the protons of the guest from the complexation shift $\Delta\delta$ in a solvent, in which the association constant K_a of the complex was known from another method. Complexation shifts at saturation binding ($\Delta\delta_{sat}$) could not be obtained for the **3**·naphthalene complex. The association constant in methanol-d_4 was, however, known from a fluorescence titration (Table I).[51] At $[H_0] = 5.38 \times 10^{-3}$ mol·L^{-1} and $[G_0] = 4.99 \times 10^{-3}$ mol·L^{-1}, we observed in methanol-d_4 complexation shifts $\Delta\delta$ of the protons of naphthalene of +0.62 (1-H) and +0.51 (2-H). From the known K_a value, we calculated that the observed $\Delta\delta$ values correspond to a degree of complexation of 29.18%. From this percentage, the complexation shifts at saturation binding ($\Delta\delta_{sat}$) were calculated as +2.12 (1-H) and +1.75 (2-H). With these $\Delta\delta_{sat}$ values, the binding constants of the **3**·naphthalene complexes in other solvents could be estimated. We applied this method also to estimate K_a of the **2**·perylene complexes in organic solvents (Tables I and II).

The estimation of association constants from the degree of complexation in a single ^{1}H NMR experiment represents a fast method to screen the binding between a host and a guest in a multitude of solvents. The complexes in the various solvents must have similar geometry, and the complexation shifts at saturation binding ($\Delta\delta_{sat}$) of the protons of each binding partner must be close to identical in all solvents. Under these circumstances, only the complexation shifts at saturation binding ($\Delta\delta_{sat}$) in one solvent have to be known. Smaller quantities of the very expensive deuterated organic solvents are needed than in NMR titrations. The margin of error of the K_a values in presumably larger than if they were determined from optical or NMR titrations. Errors can especially arise from slight differences in the geometry of complexes and from resulting differences in the complexation shifts at saturation binding ($\Delta\delta_{sat}$) in the various solvents.[52] That the K_a values obtained from the degree of complexation in a single ^{1}H NMR experiment are good estimates is shown by the comparison with the K_a values from optical titrations. For the **3**·perylene and **3**·pyrene complexes in acetone and the **2**·pyrene complex in methanol, the K_a values from optical titrations and from single ^{1}H NMR experiments are in good agreement (Table I).

The complexation between host **1** and perylene in aqueous solution was studied previously in solid–liquid extraction experiments.[7] The highest association constant for a complex between apolar binding partners, reported to date, was determined to be $K_a = 1.6 \times 10^7$ L·mol^{-1}. However, due to the low solubility of perylene in water, the amount of perylene extracted into the aqueous phase was too small for NMR studies, despite the strong binding. In aqueous solution, we could not prove by NMR that the cavity of host **1** is complementary to a large arene such as perylene. Such evidence has now been obtained with host **16** in organic solution. With $[H_0] = 6.46 \times 10^{-3}$ mol·L^{-1} and $[G_0] = 5.02 \times 10^{-3}$ mol·L^{-1}, the following complexation shifts $\Delta\delta$ were observed in methanol.[53] For perylene: $\Delta\delta$ = +0.73 (1-H), +0.38 (2-H), and +0.72 (3-H); for **3**: $\Delta\delta$ = +0.19 (O–CH_2–CH_2–), +0.33 (O–CH_2–CH_2–), and −0.16 (aryl-*H*).

C. Discussion of the Association Constants K_a of Complexes in Organic Solvents. According to ^{1}H NMR, the highly favored geometry of a specific complex of **2**, **3**, or **16** and an arene is very similar in a large variety of organic solvents. All complexed arenes that are considered in this study are enclosed in specific planes of the cavities of the hosts. The "aromatic guest plane" passes through the three spiro carbon atoms of **2** and **3**. It runs through the two spiro carbon atoms of the diphenylmethane units of **16**, perpendicular to the mean molecular plane of **16**. The geometry of complex in organic and aqueous solution is also very similar. Major differences in the strength of complexation in various solvents are therefore not a consequence of different geometries of complexes.

The studies especially with host **3** clearly demonstrate that efficient complexation between apolar hosts and arenes can take place in organic solvents. Compound **3** binds perylene, pyrene, and fluoranthene even in benzene. The association constants of the complexes of **3** and arenes are the highest reported to date for complexes between apolar binding partners in organic solvents. The binding is strongest in alcohols. Weaker binding is observed in dipolar aprotic solvents such as acetone, Me_2SO, DMF, and THF. The complexation is weakest in chloroform, benzene, and CS_2. The same dependency of the strength of complexation on the solvent is also observed for the complexes of hosts **2** and **16**. The binding ability of hosts **1** or **16** and of host **2** is considerably smaller in organic than in aqueous solution. The binding of host **3** in weakly acidic aqueous solution and in organic solution cannot be compared as this host, in acidic aqueous solution, contains two protonated nitrogen atoms in its cavity. These ionic centers reduce considerably the binding ability of **3** in acidic aqueous solution. The binding in organic solvents is strongly dependent on temperature. Complexation at higher temperatures is always weaker than at lower temperatures. For the **3**·perylene complex in ethanol,

(50) Especially the lower solubility of **16** in organic solvents did not allow the determination of complexation shifts at saturation binding ($\Delta\delta_{sat}$) of the guest.

(51) To date, we have found in all our complexation studies that the H/D isotope effect of the solvent on the strength of complexation can be neglected. Therefore, a K_a value determined in a protonated solvent can be used to calculate the saturation shifts ($\Delta\delta_{sat}$) in a deuterated solvent.

(52) The geometry of the complexes of fluoranthene seems to be less similar in the various solvents. The degrees of complexation that are calculated from the observed $\Delta\delta$ values of the various protons of host and guest in a selected solvent and from the saturation shifts $\Delta\delta_{sat}$ in methanol-d_4 are in less good agreement. Fluoranthene with its lower molecular symmetry can possibly take more than one favored orientation in the aromatic guest plane of the host (see ref 8). Also the K_a values of the **16**·pyrene complexes have larger margins of error. For their estimation, the saturation shifts of the protons of pyrene in the **1**·pyrene complex in D_2O were used. The observed saturation shifts ($\Delta\delta_{sat}$) of the protons of pyrene in the **1**·pyrene complex in D_2O and the observed complexation shifts ($\Delta\delta$) of the protons of pyrene in the **16**·pyrene complex in organic solvents indicate, however, some differences in the geometry of the complexes of the two hosts. In the cavities of both hosts, pyrene is located in the same aromatic guest plane. The protons 2,7-H of pyrene seem, however, to be oriented more outside the cavity of **1** in D_2O than outside the cavity of **16** in organic solvents.

(53) Perylene was not completely dissolved in this solution of complex, which accounts for the rather small observed $\Delta\delta$ values of the protons of the host. The concentrations given are calculated from the weighing-ins.

the enthalpic and entropic contributions to the free energy of binding (ΔG_{303K} = −6.65 kcal·mol^{-1}) are ΔH = −10.7 kcal·mol^{-1} and ΔS_{303K} = −13.4 cal·mol^{-1}·K^{-1}.

The complementarity between host and guest is crucial for efficient complexation in organic solvents. Perylene has the highest complementarity to the binding cavities of **2**, **3**, and **16** and forms the strongest complex, followed by pyrene and fluoranthene. The complexation of naphthalene and durene is considerably weaker. Complexation of durene could only be observed with host **3**. Only the largest arenes can completely fill the binding cavity and provide a high number of tight van der Waals contacts. Naphthalene binds significantly stronger than durene. This difference suggests that van der Waals interactions are a major driving force of complexation. Naphthalene and durene are two guests of very similar size and shape; the polarizability of naphthalene, however, is larger than that of durene. The difference in the binding of naphthalene and durene had also been observed in the studies with host **1** in aqueous solution.[7]

Host **3** is a considerably better binder than compounds **2** and **16** (Table I). The large difference in binding between the two spherical hosts **2** and **3** demonstrates that minor structural changes in the shape of the host can reduce considerably the binding ability. This large and unexpected difference shows that we are still far away from a good understanding of designing powerful hosts for apolar guests in organic solvents. Many additional studies with hosts and guests of different size and shape are needed.

On the basis of the difference observed between **2** and **3** in organic solvents, we predict that a host similar to **3**, but with two *exo*-C–CH_3 residues instead of the two tertiary nitrogen atoms in the cavity, will have a considerably stronger complexation ability in aqueous solution than hosts **1** and **2**. The lone pairs of the two nitrogen atoms in the cavity of **3** do not contribute significantly to the binding in organic solvents, not even in the excited state. The fluorescence spectra of the guests are very similar in the solutions of complexes of all three hosts. For an excited complex (exciplex) between host **3** and encapsulated pyrene, considerable changes in the emission spectrum of the complexed pyrene could be clearly expected.

All three hosts showed the same dependency of their binding ability on the nature of the solvent. We propose a possible explanation for the observed differences in complexation strength in the various organic solvents. A large number of van der Waals contacts are presumably the major attractive binding interaction in the complexes in organic solvents. The attractive van der Waals interactions between host and guest in the complex can be estimated to be of similar strength in all solvents. The difference in binding observed in the various solvents seems therefore to be due mainly to solvation–desolvation phenomena. The solvents can be divided into three classes depending on how they affect complexation.

(1) Strong complexation occurs in protic solvents like alcohols, as energy can be gained from desolvation phenomena similar to the hydrophobic effect in water.[22]

(2) Chloroform, benzene, and carbon disulfide seem to interact favorably with the cavity of **3**, and these solvent molecules act as competitive inhibitors. The binding of arenes in these solvents is weak. The large affinity of carbon disulfide for suitably sized apolar binding cavities has also been observed by Cram.[27] According to CPK molecular models, at least three molecules of CS_2 can be arranged in the plane of the cavity of **3** passing through the three spiro carbon atoms. The specific aromatic solvent-induced shifts (ASIS) observed for the three hosts in benzene seem to indicate an interaction of the aromatic solvent molecules with the cavity.[9,15a] The protons of the aliphatic bridges, which connect the three diphenylmethane units of **3**, are shifted upfield in benzene as solvent, and the protons aryl-*H* as well as N–CH_2–CH_2–C(Ar)$_2$ are shifted considerably downfield (see Experimental Section, Table IV). According to the models, two benzene rings can occupy the cavity of **3** in a way leading to the observed ASIS. Although two molecules of chloroform seem to fit into the cavity of **3**, the encapsulation of only one molecule might be more favorable. According to the CPK models, one chloroform molecule can occupy the cavity in a way leading to a N···H–CCl_3 hydrogen bond as an additional interaction.

(3) Considerable binding is observed in dipolar aprotic solvents like acetone, Me_2SO, DMF, and THF. At the present stage, it is difficult to evaluate whether energy is gained from desolvation during complexation in these solvents. We also do not know if these solvent molecules arrange themselves favorably in the cavity of the hosts and we are unable to estimate the energy cost of their displacement by the entering guest. In further studies, we want to elucidate the importance of solvation–desolvation processes for complexation in dipolar aprotic solvents. If these solvents play a minor role in the complexation process, the binding energy in dipolar aprotic solvents would represent a good estimate for the attractive van der Waals interactions in the complex. These early stage estimations and conclusions on the effect of solvation–desolvation phenomena on the complexation between apolar hosts and guests in organic solvents need to be supported by further extensive studies with new hosts. Molecular dynamics calculations in combination with computer-graphic representations will be of increasing importance in the future for a better understanding of host–guest interactions. Our results clearly show how important it is to take into account solvation free energies in any computer modeling of host–guest interactions.

Besides an understanding of binding, two other interests in the efficient complexation between apolar binding partners in organic solvents should be mentioned. Although enzymes are water-soluble and take their substrates mostly from aqueous environment, the catalytical processes occur in rather nonaqueous conditions at their active sites. The dipolar aprotic character of the active sites contributes to the observed high rates of enzymatic reactions. Complete shielding from water of the reacting and binding sites of synthetic enzyme models, that are active in aqueous solution, requires the construction of very sophisticated, large molecules. An easier alternative could be the design and construction of hosts that bind and catalyze in organic solutions.

Efficient solubilization of arenes through complexation in aqueous solution was observed with hosts **1** and **2**. We found during the present study that host **3** enhances considerably the solubility of perylene, pyrene, and fluoranthene in alcohols and, to some extent, also in dipolar aprotic solvents like THF. It is often encountered in polycyclic aromatic chemistry that an organometallic reaction in THF or ether does not work due to the insolubility of the aromatic compound in these solvents. Solubilization in organic solvents through complexation by suitable, nonreactive hosts might be a way in the future to overcome these problems.

Experimental Section

Instrumentation. ^{1}H NMR spectra: Bruker WP80 and HX360 spectrometer. All δ values (ppm) in the spectra to characterize new compounds refer to Me_4Si as internal standard. If not stated otherwise, the spectra were recorded at 303 K. Mass spectra: Dupont CEC 21-492 instrument (EI, 70 eV). Electronic absorption spectra: Cary 17. Uncorrected fluorescence spectra were measured with a SLM 8000 spectrofluorometer. Melting points (uncorrected): Büchi (Dr. Tottoli). Elemental analysis: Carlo Erba Elemental Analyzer 1106, Max-Planck-Institut für medizinische Forschung, Heidelberg. IR: Beckmann IR-4240.

Syntheses. 1-Acetyl-4,4-bis[4-(ethoxycarbonylmethoxy)-3,5-dimethylphenyl]piperidine (6). 1-Acetyl-4,4-bis(4-hydroxy-3,5-dimethylphenyl)piperidine (36.7 g, 0.1 mol), 14.49 g (0.22 mol) of potassium hydroxide (85%), and 0.6 g of 18-crown-6 in 500 mL of absolute tetrahydrofuran were heated to reflux for 1 h under Ar. A solution of 100 g (0.6 mol) of ethyl α-bromoacetate in 300 mL of absolute tetrahydrofuran was then added dropwise over a period of 6 h. After the reaction mixture was heated to reflux for 2 days, the solvent was evaporated in vacuo. The residue was partitioned between water and chloroform. The aqueous phase was extracted two more times with chloroform. The combined organic phases were dried over magnesium sulfate and the solvent was distilled off. The crude product was chromatographed on silica with dichloromethane to recover the excess of ethyl α-bromoacetate. Elution with ethyl acetate gave a mixture of the diester **6**, the formed monoester, and the starting compound. Chromatography of this mixture on silica from chloroform/ether (20:1) afforded 36.15 g (67%) of **6** as an oil, which eventually crystallized. mp: 108–109 °C. IR (NaCl):

Table III. Typical Concentrations of Host [H_0], Guest [G_0], and Inhibitor [I_0] Used in the Titrations To Determine the Association Constants Shown in Table I

complex	solvent	method[a]	$[G_0]$, mol·L^{-1}	$[H_0]$, mol·L^{-1}
3·perylene	MeOH	A	9.9×10^{-7}	1.1×10^{-4}–1.1×10^{-5}
	EtOH	A	1.2×10^{-6}	1.2×10^{-4}–1.2×10^{-5}
	Acetone	A	3.4×10^{-6}	3.9×10^{-4}–3.9×10^{-5}
3·pyrene	MeOH	A	1.0×10^{-6}	1.0×10^{-4}–1.0×10^{-5}
	MeOH	B	3.0×10^{-6}	3.1×10^{-4}–3.1×10^{-5}
	MeOH-d_4	D	2.0×10^{-3}	2.0×10^{-2}–6.2×10^{-4}
	EtOH	A	2.9×10^{-6}	3.0×10^{-4}–3.0×10^{-5}
	EtOH	B	2.9×10^{-6}	3.0×10^{-4}–3.0×10^{-5}
	EtOH-d_6	D	2.0×10^{-3}	2.0×10^{-2}–6.2×10^{-4}
	Acetone	A	1.0×10^{-5}	1.0×10^{-3}–1.0×10^{-4}
	Acetone	B	1.0×10^{-5}	1.0×10^{-3}–1.0×10^{-4}
3·fluoranthene	MeOH	A	2.5×10^{-7}	2.7×10^{-5}–2.7×10^{-6}
2·perylene	MeOH	B	2.2×10^{-5}	4.2×10^{-3}–4.2×10^{-4}
2·pyrene	MeOH	B	2.0×10^{-5}	4.2×10^{-3}–4.2×10^{-4}
16·perylene	MeOH	B	2.2×10^{-5}	2.2×10^{-3}–2.2×10^{-4}
3·naphthalene[b]	MeOH	C	1.0×10^{-6}	1.1×10^{-4}–1.1×10^{-5}
3·durene[c]	MeOH	C	1.0×10^{-6}	1.1×10^{-4}–1.1×10^{-5}

[a] For the meaning of A, B, and C, see Table I. [b] $[I_0] = 1.1 \times 10^{-2}$ mol·L^{-1}. [c] $[I_0] = 1.0 \times 10^{-1}$ mol·L^{-1}.

Table IV. Chemical Shifts of the Protons of Free Host **3** and of Free Guests in Deuterated Organic Solvents (360 MHz, $T = 303$ K, $c \approx 5 \times 10^{-3}$ mol·L^{-1})

	host **3**						
solvent	N-CH_2-CH_3 (t)	aryl-CH_3 (s)	N-CH_2-CH_3 (q)	N-CH_2-CH_2-C(Ar)$_2$[a] (m)	N-CH_2-CH_2-C(Ar)$_2$ (m)	N-CH_2-CH_2-O (t)	N-CH_2-CH_2-O (t)	aryl-H (s)
MeOH[b]	1.10	2.13	2.38	2.40	2.56	3.01	3.70	6.82
EtOH[b]	1.05	2.11	2.31	2.37	2.50	3.05	3.69	6.77
acetone[c]	0.96	2.11	2.20	2.34	2.40	3.06	3.62	6.86
Me_2SO[b]	0.99	2.13	2.23	2.35	2.41	3.04	3.51	6.90
DMF[c]	0.97	2.12	2.23	2.38	2.42	3.05	3.59	6.94
$CDCl_3$[c]	1.04	2.12	2.32	2.33	2.47	3.01	3.61	6.72
THF[c]	0.96	2.10	2.19	2.32	2.39	3.02	3.54	6.81
benzene[c]	1.03	2.10	2.25	2.54	2.54	2.81	3.39	7.04
CS_2[d]	1.03	2.12	2.31	2.32	2.44	3.05	3.52	6.71

	guests														
	perylene			pyrene			fluoranthene					naphthalene		durene	
solvent	1-H (d)	2-H (t)	3-H (d)	1-H (d)	2-H (t)	4-H (s)	1-H (d)	2-H (t)	3-H (d)	7-H (m)	8-H (m)	1-H (m)	2-H (m)	CH_3 (s)	aryl-H (s)
MeOH[b]	7.74	7.52	8.31	8.21	8.02	8.10	7.94	7.60	7.81	7.90	7.34	7.89	7.51	2.13	6.81
EtOH[b]				8.19	7.99	8.08	7.95	7.62	7.83	7.91	7.35				
acetone[c]	7.53	7.77	8.35	8.28	8.06	8.17	8.06	7.67	7.90	7.99	7.38	7.90	7.51		
Me_2SO[b]	7.60	7.85	8.41	8.38	8.16	8.27	8.20	7.78	8.02	8.12	7.49	7.97	7.57		
DMF[c]	7.57	7.83	8.41	8.34	8.10	8.23	8.17	7.74	7.79	8.10	7.45	7.95	7.54		
THF[c]	7.55	7.77	8.35	8.18	7.98	8.08	7.97	7.62	7.83	7.93	7.34	7.83	7.44		
$CDCl_3$[c]	7.46	7.66	8.17	8.18	8.00	8.07	7.94	7.63	7.84	7.91	7.30	7.83	7.47		
benzene[c]	7.20	7.44	7.89	7.93	7.76	7.82						7.63	7.25		
CS_2[d]				8.18	8.02	8.08									

[a] This signal of host **3** is broadened considerably in each solution as a consequence of the inversion of the piperidine ring slowing on the 360-MHz NMR time scale; see ref 8. [b] The reference is TSP ext. in the same solvent. [c] The reference is TMS ext. in the same solvent. [d] The reference is TMS ext. in benzene-d_6. All external standards are placed in capillary tubes inside the NMR tube.

ν(C=O) 1755, 1640 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.30 (t, J = 7.1 Hz, 6 H), 2.06 (s, 3 H), 2.1–2.5 (m, 4 H), 2.25 (s, 12 H), 3.35–3.85 (m, 4 H), 4.27 (q, J = 7.1 Hz, 4 H), 4.37 (s, 4 H), 6.83 (s, 4 H). MS: m/z 539 (100%, M$^+$). Anal. Calcd for $C_{31}H_{41}NO_7$ (539.7): C, 68.99; H, 7.66; N, 2.60. Found: C, 68.80; H, 7.50; N, 2.68.

1-Acetyl-4,4-bis[4-(carboxymethoxy)-3,5-dimethylphenyl]piperidine (7). **6** (34 g, 63 mmol) and 250 mL of a 1 N aqeuous solution of sodium carbonate were stirred in 250 mL of ethanol at 20 °C for 2 days. The ethanol was removed in vacuo and the remaining solution was acidified with 2 N HCl. The dicarboxylic acid **7**, which precipitated in analytically pure form, was collected by filtration, washed several times with water until the washing liquor showed neutral pH, and dried at 100 °C (20 torr): 29.87 g (98%) of **7**, mp 236 °C. IR (KBr): ν (O–H) 2400–3600; ν(C=O) 1765, 1700 cm^{-1}. ^{1}H NMR (80 MHz, Me_2SO-d_6): δ 1.97 (s, 3 H), 2.0–2.5 (m, 4 H), 2.19 (s, 12 H), 3.05–3.55 (m, 4 H), 4.31 (s, 4 H), 6.97 (s, 4 H), 13.12 (br s, 2 H). MS: m/z 483 (M$^+$). Anal. Calcd for $C_{27}H_{33}NO_7$ (483.6): C, 67.06; H, 6.88; N, 2.90. Found: C, 67.07; H, 7.03; N, 2.79.

1-Acetyl-4,4-bis[4-(succinimidyloxycarbonylmethoxy)-3,5-dimethylphenyl]piperidine (8). A solution of 37 g (0.18 mol) of *N,N'*-dicyclohexylcarbodiimide in 80 mL of dioxane was added to a solution of 41.6 g (86.02 mmol) of **7** and 20.7 g (0.18 mol) of *N*-hydroxysuccinimide in 450 mL of dioxane. After the mixture was stirred for 24 h at room temperature, the *N,N'*-dicyclohexylurea, which had precipitated, was collected by filtration and washed once with dioxane. The combined dioxane solutions were evaporated in vacuo. Dichloromethane was added to the oily residue and an additional amount of *N,N'*-dicyclohexylurea, which precipitated, was removed by filtration. The dichloromethane was distilled off and the residual oil was dissolved in 600 mL of hot 2-propanol/chloroform (4:1). After cooling, 49.1 g (84%) of colorless compound **8** crystallized. The crystals contained 2-propanol even after drying at 100 °C (10^{-3} torr) for 2 days (^{1}H NMR). After dissolving the crystals in dichloromethane and reprecipitation with ether, colorless crystals of **8** without included solvent were obtained: mp 156 °C dec. IR (KBr): ν(C=O) 1825, 1785, 1735, 1632 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$): δ 2.05–2.55 (m, 4 H), 2.08 (s, 3 H), 2.27 (s, 12 H), 2.87 (s, 8 H), 3.2–3.7 (m, 4 H), 4.74 (s, 4 H), 6.83 (s, 4 H). Anal. Calcd for $C_{35}H_{39}N_3O_{11}$ (677.7): C, 62.03; H, 5.80; N, 6.20. Found: C, 62.15; H, 5.80; N, 6.04.

1-Acetyl-4,4-bis[4-(carbamoylmethoxy)-3,5-dimethylphenyl]piperidine (9). A solution of the bis(*N*-hydroxysuccinimide ester) **8** was prepared from 41.6 g (86.02 mmol) of **7** as mentioned above. Dry gaseous ammonia was introduced for 30 min into the stirred reaction mixture of **8** in dioxane, from which the precipitated *N,N'*-dicyclohexylurea had been removed by filtration. After stirring for additional 30 min, the solvent was removed in vacuo and the residue was partitioned between a 2 N aqueous solution of sodium carbonate and dichloromethane. The aqueous phase was extracted two more times with dichloromethane. The combined organic phases were washed once with a 2 N aqueous solution of sodium carbonate, once with 1 N HCl, and twice with water. The solvent was distilled off and the crude product was recrystallized from ethanol/toluene: 34.82 g (84%) of **9**, mp 240–241 °C. IR (KBr): ν(C=O) 1680, 1630 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$): δ 2.0–2.5 (m, 4 H), 2.07 (s, 3 H), 2.23 (s, 12 H), 3.3–3.8 (m, 4 H), 4.26 (s, 4 H), 5.83 (br s, 4 H), 6.86 (s, 4 H). MS: m/z 481 (M$^+$). UV (methanol): λ_{max}(log ϵ) = 275 (2.90), 268 (2.99), 230 (4.15, sh), 197 (4.90). Anal. Calcd for $C_{27}H_{35}N_3O_5$ (481.6): C, 67.34; H, 7.33; N, 8.73. Found: C, 67.10; H, 7.52; N, 8.64.

1-Ethyl-4,4-bis[4-(2-aminoethoxy)-3,5-dimethylphenyl]piperidine (10). A 1 M solution of borane in tetrahydrofuran (468 mL, 0.486 mol) was added dropwise under Ar to 17.3 g (35.9 mmol) of **9** in 350 mL of absolute tetrahydrofuran. After being stirred at room temperature for 14 h, the reaction mixture was heated to reflux for 16 h. After being cooled in an ice bath, the reaction mixture was carefully hydrolyzed with water. After addition of 500 mL of 6 N HCl, the solution was heated to reflux for 3 h. The acidic aqueous solution was cooled to room temperature, extracted three times with ether, and evaporated to dryness. The residue was dissolved in 2 N NaOH and the basic solution was extracted exhaustively with dichloromethane. The combined organic phases were dried over sodium sulfate and, after evaporation of the solvent, 15.2 g (96%) of **10** was obtained as colorless glass, which was used without further purification in the cylization reaction to give **4**. IR (NaCl): ν(N–H) 3360 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.17 (t, J = 7.1 Hz, 3 H), 2.03 (s, 4 H), 2.15–2.7 (m, 10 H), 2.23 (s, 12 H), 3.04 (t, J = 5.0 Hz, 4 H), 3.79 (t, J = 5.0 Hz, 4 H), 6.84 (s, 4 H). HRMS: m/z (M$^+$, $C_{27}H_{41}N_3O_2$) calcd 439.3119, obsd 439.3131.

1-Benzyloxycarbonyl-4,4-bis[4-(carboxymethoxy)-3,5-dimethylphenyl]piperidine (11). A solution of 10 g (20.68 mmol) of **6** in 100 mL of 2 N NaOH was heated to reflux for 6 h. The reaction mixture was cooled in an ice bath to 0 °C and 4.24 g (24.87 mmol) of benzyl chloroformate and 100 mL of 2 N NaOH were added dropwise and simultaneously from two dropping funnels. After being stirred at 0 °C for 10 min, the aqueous solution was extracted five times with ether. The aqueous phase was acidified with 2 N HCl and then extracted three times with dichloromethane. The combined dichloromethane phases were dried over magnesium sulfate and the solvent was distilled off. After addition of water to the remaining residue, **11** crystallized out. Filtration and drying over phosphorus pentoxide at 50 °C (20 torr) yielded 10.83 g (92%) of **11** as colorless crystals, mp 95 °C dec. IR (KBr): ν (C=O) 1735, 1680 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$): δ 2.05–2.55 (m, 4 H), 2.23 (s, 12 H), 3.3–3.75 (m, 4 H), 4.42 (s, 4 H), 5.11 (s, 2 H), 6.82 (s, 4 H), 7.32 (s, 5 H). Anal. Calcd for $C_{33}H_{37}NO_8$ (575.7): C, 68.85; H, 6.48; N, 2.43. Found: C, 68.73; H, 6.47; N, 2.43.

1-Benzyloxycarbonyl-4,4-bis[4-(chloroformylmethoxy)-3,5-dimethylphenyl]piperidine (12). A solution of 4 g (6.95 mmol) of **11** and of 10 mL of sulfinyl chloride in 40 mL of absolute benzene was stirred overnight at room temperature. The solvent and the excess of sulfinyl chloride were removed at 20 °C in vacuo. Benzene was added twice and removed each time at 20 °C in vacuo. Drying for 1 day at 20 °C (10^{-3} torr) yielded 3.99 g (94%) of **12** as colorless foam, which was pure according to ^{1}H NMR and which was used without further purification in the cyclization reaction to give **13**. ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.0–2.4 (m, 4 H), 2.21 (s, 12 H), 3.35–3.7 (m, 4 H), 4.66 (s, 4 H), 5.05 (s, 2 H), 6.78 (s, 4 H), 7.27 (s, 5 H).

1-Acetyl-1'-ethyl-9,13,17,19,29,33,37,39-octamethyl-3,25-dioxodispiro[1,7,21,27-tetraoxa-4,24-diaza[7.1.7.1]paracyclophane-14,4':34,4''-bispiperidine](4). From two dropping funnels, a solution of 6.77 g (10 mmol) of **8** in 500 mL of dichloromethane and a solution of 4.39 g (10 mmol) of **10** in 500 mL of dichloromethane were added dropwise and simultaneously over a period of 9 h into 2 L of dichloromethane which was maintained at 0 °C. After the mixture was stirred overnight, 2 L of the solvent was distilled off. The remaining solution was extracted once with 2 N NaOH after which the aqueous phase was extracted two more times with dichloromethane. The combined organic phases were dried over sodium sulfate and the solvent was distilled off. Chromatography on neutral alumina (Brockmann, activity II–III) from chloroform/ethyl acetate/methanol (5:4.75:0.25) followed by recrystallization from ethanol/toluene afforded 3.7 g (42%) of **4**, mp 335 °C dec. IR (KBr): ν(C=O) 1670, 1630 cm^{-1}. ^{1}H NMR (360 MHz, Me_2SO-d_6, 393 K): δ 0.94 (t, J = 7.1 Hz, 3 H), 1.95 (s, 3 H), 2.12 (s, 12 H), 2.13 (s, 12 H), 2.25 (q, J = 7.1 Hz, 2 H), 2.2–2.35 (m, 8 H), 2.35–2.45 (m, 4 H), 3.4–3.5 (m, 4 H), 3.55 (q, J = 5.7 Hz, 4 H), 3.85 (t, J = 5.7 Hz, 4 H), 4.23 (s, 4 H), 6.83 (s, 4 H), 6.84 (s, 4 H), 7.52 (t, $J \approx$ 5.7 Hz, 2 H). EI–MS: m/z 886 (M$^+$). UV (methanol): λ_{max}(log ϵ) = 275 (3.29, sh), 268 (3.38), 228 (4.39, sh), 198 (5.18). Anal. Calcd for $C_{54}H_{70}N_4O_7$ (887.1): C, 73.11; H, 7.95; N, 6.32. Found: C, 73.16; H, 7.90; N, 6.30.

1',1''-Diethyl-9,13,17,19,29,33,37,39-octamethyldispiro[1,7,21,27-tetraoxa-4,24-diaza[7.1.7.1]paracyclophane-14,4':34,4''-bispiperidine] (5). A 1 M solution of borane in tetrahydrofuran (253 ml, 253 mmol) was added dropwise to a solution of 16.8 g (18.94 mmol) of **4** in 580 mL of absolute tetrahydrofuran. After being stirred for 1 h at 20 °C, the reaction mixture was heated to reflux for 3 h. After being cooled in an ice bath, the solution was hydrolyzed carefully with water. The solvent was removed in vacuo; the remaining residue was dissolved in 750 mL of 6 N HCl and heated to reflux for 3 h. After being cooled, the acidic solution was extracted three times with ether and then evaporated to dryness. Upon addition of 2 N NaOH to the remaining solid residue, the free tetraamine **5** crystallized out. The product was collected by filtration, washed with water until the washing liquor showed neutral pH, and dried at 100 °C (20 torr): 15.3 g (96%) of **5** which was shown to be pure by ^{1}H NMR and which was used without further purification in the cyclization reaction to give **13**. For the elemental analysis, **5** was recrystallized from ethanol/ether/petroleum ether (40 °C); mp 240–241 °C. IR (KBr): ν(N–H) 3355 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.06 (t, J = 7.1 Hz, 6 H), 1.7 (br s, 2 H), 2.17 (s, 24 H), 2.25–2.4 (m, 8 H), 2.34 (q, J = 7.1 Hz, 4 H), 2.4–2.55 (m, 8 H), 3.04 (t, J = 4.9 Hz, 8 H), 3.94 (t, J = 4.9 Hz, 8 H), 6.71 (s, 8 H). Anal. Calcd for $C_{54}H_{76}N_4O_4$ (845.2): C, 76.74; H, 9.06; N, 6.63. Found: C, 76.66; H, 8.93; N, 6.71.

1'-Benzyloxycarbonyl-1'',1'''-diethyl-6,12,22,28,37,43,48,51,52,55,56,59-dodecamethyl-2,16-dioxotrispiro[4,14,20,30,35,45-hexaoxa-1,17-diazaoctacyclo[15.15.15.2^{5,8}.2^{10,13}.2^{21,24}.2^{26,29}.2^{36,39}.2^{41,44}]nonapentaconta-5,7,10,12,21,23,26,28,36,38,41,43,48,50,52,54,56,58-octadecaene-9,4':25,4'':40,4'''-trispiperidine] (13). From two dropping funnels, a solution of 8.45 g (10 mmol) of **5** in 500 mL of absolute toluene and a solution of 6.12 g (10 mmol) of **12** in 500 mL of absolute toluene were

added dropwise and simultaneously under argon over a period of 9 h to 2 L of absolute toluene, which was maintained at 0 °C. After being stirred at 20 °C for two more hours, the solvent was evaporated in vacuo. The residue was taken up in 2 N NaOH and the alkaline solution was extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and the solvent was distilled off. Chromatography on silica from ethyl acetate/triethylamine (9.5:0.5) followed by recrystallization from ethanol yielded 5.24 g (38%) of **13**, mp 189 °C. IR (KBr): ν(C=O) 1695, 1675, 1655 cm^{-1}. ^{1}H NMR (360 MHz, Me_2SO-d_6, 393 K): δ 0.93 (t, J = 7.1 Hz, 6 H), 2.01 (s, 24 H), 2.10 (s, 12 H), 2.2–2.3 (m, 12 H), 2.24 (q, J = 7.1 Hz, 4 H), 2.35–2.45 (m, 8 H), 3.2–3.3 (m, 4 H), 3.35–3.45 (m, 4 H), 3.65–3.75 (m, 4 H), 3.75–3.9 (m, 4 H), 3.9–4.05 (m, 4 H), 4.51 (s, 4 H), 5.05 (s, 2 H), 6.77 (s, 8 H), 6.79 (s, 4 H), 7.25–7.30 (m, 5 H). EI-MS: m/z 1384 (M^+). FAB-MS: m/z 1385 [100% (M^+ + H)], 929 (37), 693 (30), 553 (24), 465 (55); no signals appeared above the molecular ion of **13** up to m/z 4000. Anal. Calcd for $C_{87}H_{109}N_5O_{10}$ (1384.9): C, 75.46; H, 7.93; N, 5.06. Found: C, 75.35; H, 7.91; N, 5.12.

1″,1‴-Diethyl-6,12,22,28,37,43,48,51,52,55,56,59-dodecamethyl-2,16-dioxotrispiro[4,14,20,30,35,45-hexaoxa-1,17-diazaoctacyclo-[15.15.15.2^{5,8}.2^{10,13}.2^{21,24}.2^{26,29}.2^{36,39}.2^{41,44}]nonapentaconta-5,7,10,12,21,23,26,28,36,38,41,43,48,50,52,54,56,58-octadecaene-9,4′:25,4″:40,4‴-trispiperidine] (14). A solution of 8.95 g (6.46 mmol) of **13** in 200 mL of absolute ethanol, which was brought to pH 1–2 by addition of concentrated hydrochloric acid, was hydrogenated for 3 h at 20 °C and ambient pressure in the presence of 2 g of palladium (10%) on charcoal. The catalyst was removed by filtration and washed several times with chloroform. After drying of the combined organic phases over sodium sulfate and evaporation of the solvent, **14** was obtained as crystalline product, which was dried at 100 °C (10^{-3} torr): 7.91 g (98%). For the elemental analysis, **14** was recrystallized from ethanol/water: mp 185 °C dec. IR (KBr): ν(C=O) 1655 cm^{-1}. ^{1}H NMR (360 MHz, Me_2SO-d_6, 393 K): δ 0.93 (t, J = 7.1 Hz, 6 H), 2.00 (s, 24 H), 2.09 (s, 12 H), 2.15–2.25 (m, 4 H), 2.2–2.3 (m, 8 H), 2.23 (q, J = 7.1 Hz, 4 H), 2.3–2.4 (m, 8 H), 2.62 (br s, 1 H), 2.7–2.8 (m, 4 H), 3.15–3.3 (m, 4 H), 3.65–3.75 (m, 4 H), 3.75–3.85 (m, 4 H), 3.9–4.05 (m, 4 H), 4.50 (s, 4 H), 6.77 (s, 12 H). MS: m/z 1250 (M^+). Anal. Calcd for $C_{79}H_{103}N_5O_8$ (1250.7): C, 75.87; H, 8.30; N, 5.60. Found: C, 75.60; H, 8.27; N, 5.44.

1-Acetyl-1″,1‴-diethyl-6,12,22,28,37,43,48,51,52,55,56,59-dodecamethyl-2,16-dioxotrispiro[4,14,20,30,35,45-hexaoxa-1,17-diazaoctacyclo[15.15.15.2^{5,8}.2^{10,13}.2^{21,24}.2^{26,29}.2^{36,39}.2^{41,44}]nonapentaconta-5,7,10,12,21,23,26,28,36,38,41,43,48,50,52,54,56,58-octadecaene-9,4′:25,4″:40,4‴-trispiperidine] (15). A solution of 5.9 g (4.72 mmol) of **14** in 50 mL of acetic anhydride was heated to reflux for 1 h. After evaporation of the excess of acetic anhydride in vacuo, the residue was taken up in 2 N NaOH. The alkaline solution was extracted three times with chloroform. After drying of the combined organic phases over sodium sulfate, the solvent was distilled off. Chromatography on neutral alumina (Brockmann, activity II–III) from chloroform/ethyl acetate/methanol (5:4.75:0.25) followed by recrystallization from ether/petroleum ether (40 °C) afforded 5.2 g (85%) of **15**, mp 200 °C. IR (KBr): ν(C=O) 1645 cm^{-1}. ^{1}H NMR (360 MHz, Me_2SO-d_6, 393 K): δ 0.94 (t, J = 7.1 Hz, 6 H), 1.94 (s, 3 H), 2.01 (s, 24 H), 2.11 (s, 12 H), 2.2–2.3 (m, 12 H), 2.24 (q, J = 7.1 Hz, 4 H), 4 H), 2.35–2.45 (m, 8 H), 3.2–3.3 (m, 4 H), 3.35–3.45 (m, 4 H), 3.65–3.75 (m, 4 H), 3.75–3.85 (m, 4 H), 3.9–4.1 (m, 4 H), 4.52 (s, 4 H), 6.78 (s, 8 H), 6.81 (s, 4 H). MS: m/z 1292 (M^+). UV (methanol): λ_{max}(log ϵ) = 277 (3.46, sh), 269 (3.51), 232 (4.36, sh), 199 (5.30). Anal. Calcd for $C_{81}H_{105}N_5O_9$ (1292.8): C, 75.26; H, 8.19; N, 5.42. Found: C, 74.98; H, 8.20; N, 5.15.

1′,1″,1‴-Triethyl-6,12,22,28,37,43,48,51,52,55,56,59-dodecamethyl-2,16-dioxotrispiro[4,14,20,30,35,45-hexaoxa-1,17-diazaoctacyclo-[15.15.15.2^{5,8}.2^{10,13}.2^{21,24}.2^{26,29}.2^{36,39}.2^{41,44}]nonapentaconta-5,7,10,12,21,23,26,28,36,38,41,43,48,50,52,54,56,58-octadecaene-9,4′:25,4″:40,4‴-trispiperidine] (2). A stirred solution of 1.25 g (1.0 mmol) of **14** in 10 mL of glacial acetic acid was heated to 50–55 °C. Sodium borohydride (1.1 g, 29.07 mmol) was added portionwise under Ar over a period of 30 min. The reaction mixture was stirred at 50–55 °C for 9 h. After being cooled, the solution was acidified with 2 N HCl and then stirred for 10 min. NaOH (2 N) was added, and the resulting alkaline solution was extracted exhaustively with dichloromethane. After drying of the combined organic phases over sodium sulfate, the solvent was distilled off. The crude product was chromatographed on silica from ethyl acetate/triethylamine (9.5:0.5). Recrystallization from ether and drying at 150 °C (10^{-3} torr) yielded 700 mg (55%) of **2** as colorless needles, mp 180 °C. IR (KBr): ν(C=O) 1650 cm^{-1}. EI-MS: m/z 1278 (M^+). FAB-MS: m/z = 1279 [29%, (M^+ + H)], 929 (100), 465 (70). ^{1}H NMR (360 MHz, Me_2SO-d_6, 393 K): δ 0.93 (t, J = 7.1 Hz, 6 H), 0.94 (t, J = 7.1 Hz, 3 H), 2.01 (s, 24 H), 2.10 (s, 12 H), 2.23 (q, J = 7.1 Hz, 6 H), 2.2–2.35 (m, 12 H), 2.35–2.5 (m, 12 H), 3.15–3.3 (m, 4 H), 3.6–3.75 (m, 4 H), 3.75–3.9 (m, 4 H), 3.9–4.1 (m, 4 H), 4.51 (s, 4 H), 6.78 (s, 8 H), 6.80 (s, 4 H). UV (methanol): λ_{max}(log ϵ) = 278 (3.42, sh), 269 (3.48), 232 (4.38, sh), 198 (5.26). Anal. Calcd for $C_{81}H_{107}N_5O_8$ (1278.8): C, 76.08; H, 8.43; N, 5.47. Found: C, 75.82; H, 8.36; N, 5.64.

1′,1″,1‴-Triethyl-6,12,22,28,37,43,48,51,52,55,56,59-dodecamethyl-trispiro[4,14,20,30,35,45-hexaoxa-1,17-diazaoctacyclo-[15.15.15.2^{5,8}.2^{10,13}.2^{21,24}.2^{26,29}.2^{36,39}.2^{41,44}]nonapentaconta-5,7,10,12,21,23,26,28,36,38,41,43,48,50,52,54,56,58-octadecaene-9,4′:25,4″:40,4‴-trispiperidine] (3). (a) By Reduction of 15. A 1 M solution of borane in tetrahydrofuran (55 mL, 55 mmol) was added dropwise under Ar into a solution of 5.13 g (3.97 mmol) of **15** in 150 mL of absolute tetrahydrofuran. The mixture was stirred at 20 °C for 3 h and then heated to reflux for 2 h. After being cooled, the solution was carefully hydrolyzed by addition of water and the solvent was distilled off. The residue was heated to reflux for 3 h in 150 mL of 6 N HCl. After being cooled, the acidic solution was extracted three times with ether and then evaporated to dryness in vacuo. Upon addition of 2 N NaOH to the residue, **3** was obtained as crystalline product. The crystals were collected by filtration, washed with water until the washing liquor showed neutral pH, and dried at 80 °C (20 torr). Chromatography on silica from ethyl acetate/triethylamine (9.5:0.5) followed by recrystallization from *n*-hexane afforded after drying at 100 °C (10^{-3} torr) 3.9 g (79%) of **3**, mp 146 °C. EI-MS: m/z 1250 (M^+). FAB-MS: m/z 1251 [100%, (M^+ + H)], 627 (63), 553 (35), 461 (56). ^{1}H NMR (360 MHz, $CDCl_3$, 303 K): δ 1.04 (t, J = 7.1 Hz, 9 H), 2.12 (s, 36 H), 2.32 (q, J = 7.1 Hz, 6 H), 2.25–2.4 (m, 12 H), 2.4–2.55 (m, 12 H), 3.01 (t, J = 6.8 Hz, 12 H), 3.61 (t, J = 6.8 Hz, 12 H), 6.72 (s, 12 H). UV (methanol): λ_{max}(log ϵ) 278 (3.48), 269 (3.54), 197 (5.29). Anal. Calcd for $C_{81}H_{111}N_5O_6$ (1250.8): C, 77.78; H, 8.95; N, 5.60. Found: C, 77.66; H, 8.83; N, 5.58.

(b) By Reduction of 2. The same procedure was used as in the preparation of **3** starting from **15**. **2** (430 mg, 0.336 mmol) reacted with 5 mL (5 mmol) of the 1 M solution of borane in tetrahydrofuran to give 350 mg (83%) of **3**. The identity of this product with the product obtained by reduction of **15** was demonstrated by EI-MS, ^{1}H NMR, and melting point.

Complexation Studies. The synthesis of host **16** is reported in ref 10. The purification of the arenes that are used as guests is described in ref 7. The determination of association constants from solid–liquid and liquid–liquid extractions *and* from optical and ^{1}H NMR titrations is described in detail in ref 7 and 8.

Optical and ^{1}H NMR Titrations. ^{1}H NMR Spectra of Pure Hosts and Guests in Organic Solvents. In Table II, only the changes of the chemical shifts ($\Delta\delta$) upon complexation are given. The ^{1}H NMR data of the pure host **3** and of all guests used in this study are given in Table IV. The concentration of the host and the guest in each experiment was $\approx 5 \times 10^{-3}$ mol·L^{-1}. Multiplet centers are given for better comparison. With the δ values of Table IV and the complexation shifts of Table II, the exact position of the signals of the protons of the guest in the solutions of complex can be calculated. The solvent dependency of the signals of the free hosts **2** and **16** is similar to the solvent dependency of the resonances of host **3**. The chemical shifts of the protons of the guests in various organic solvents will be useful for the evaluation of complexation shifts ($\Delta\delta$) in future studies.

Association constants were not only calculated from the degree of complexation of the guest in the solution of complex. K_a values were also obtained from the degree of complexation of the host in the solution of complex. The K_a values obtained from both the evaluation of the complexation shifts of host and guest were generally in good agreement. Table V shows the complexation shifts of the protons of **3** in solutions

Table V. Complexation Shifts ($\Delta\delta$) of Selected Protons of **3** in Solutions of the **3**·Pyrene Complex (360 MHz, T = 303 K)[a]

solvent	N-CH_2-CH_2-O (t)	aryl-H (s)
MeOH-d_4	+2.14 ($\Delta\delta_{sat}$)	−0.60 ($\Delta\delta_{sat}$)
EtOH-d_6	+2.13	−0.60
acetone-d_6	+1.43	−0.39
Me_2SO-d_6	+1.17	−0.34
DMF-d_7	+0.78	−0.20
THF-d_8	*b*	−0.17
$CDCl_3$	+0.36	−0.10
benzene-d_6	+0.12	−0.03
CS_2	+0.10	−0.03

[a] For the concentrations of host and guest, see Table II; for the external standards in the various solvents, see Table IV. From the ($\Delta\delta$) and ($\Delta\delta_{sat}$) values of Table V, K_a values can be calculated that are in good agreement with the K_a values (Table I) calculated from the data of Table II for the same complexes. [b] Resonance masked by other signals of the host.

of the 3·pyrene complex (for the concentrations of host and guest see Table II).

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Registry No. 2, 92816-67-6; **2**·perylene, 100928-41-4; **2**·pyrene, 92816-68-7; **2**·naphthalene, 100928-42-5; **3**, 92787-69-4; **3**·perylene, 100928-38-9; **3**·pyrene, 100928-39-0; **3**·fluoranthene, 100938-76-9; **3**·naphthalene, 100928-40-3; **3**·durene, 100938-77-0; **4**, 92787-65-0; **5**, 92787-66-1; **6**, 92787-58-1; **7**, 92787-59-2; **8**, 92787-60-5; **9**, 92787-61-6; **10**, 92787-62-7; **11**, 92787-63-8; **12**, 92787-64-9; **13**, 92816-66-5; **14**, 92787-67-2; **15**, 92787-68-3; **16**·perylene, 100928-43-6; **16**·pyrene, 100928-44-7; **16**·fluoranthene, 100928-45-8; **16**·naphthalene, 100928-46-9; 1-acetyl-4,4-bis(4-hydroxy-3,5-dimethylphenyl)piperidine, 86748-12-1; ethyl α-bromoacetate, 105-36-2; *N*-hydroxysuccinimide, 6066-82-6; benzyl chloroformate, 501-53-1.

Carbon Dioxide Chemistry. Synthesis, Properties, and Structural Characterization of Stable Bis(carbon dioxide) Adducts of Molybdenum

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Abstract: The bis(carbon dioxide) adduct, *trans*-$Mo(CO_2)_2(PMe_3)_4$, **1**, has been prepared from the reaction of *cis*-$Mo(N_2)_2(PMe_3)_4$ with CO_2 under pressure (4–5 atm). The interaction of **1** with several small molecules has been studied. In particular, reaction with COS affords a seven-coordinate *S,S'*-dithiocarbonate, $Mo(S_2CO)(CO)_2(PMe_3)_3$, **2**, while interaction with various isocyanides yields the new carbon dioxide complexes *trans,mer*-$Mo(CO_2)_2(CNR)(PMe_3)_3$, **3** (R = Me, **3a**; *i*-Pr, **3b**; *t*-Bu, **3c**; Cy, **3d**; $CH_2C_6H_5$, **3e**). The new compounds have been characterized by analytical and spectroscopic (IR and ^1H, ^{13}C, and ^{31}P NMR) studies. The molecular structures of **2**, **3b**, and **3e** have been determined by X-ray crystallography. Compound **2** is orthorhombic and belongs to the space group $Pna2_1$ with $a = 14.003$ (2) Å, $b = 9.767$ (2) Å, $c = 15.127$ (2) Å, $D_c = 1.52$ g·cm^{-3}, and $Z = 4$. Refinement was achieved on 1939 independent observed reflections, leading to a final R value of 0.038. **3b** crystallizes in the monoclinic space group $C2/c$ with unit cell parameters $a = 24.47$ (3) Å, $b = 13.01$ (1) Å, $c = 16.77$ (1) Å, $\beta = 132.41$ (3)°, and $D_c = 1.35$ g·cm^{-3} for $Z = 8$. Least-squares refinement based on 3493 independent observed reflections led to a final R value of 0.076. Crystals of **3e** are monoclinic, space group $P2_1/c$ with $a = 11.563$ (8) Å, $b = 11.792$ (7) Å, $c = 18.57$ (1) Å, $\beta = 90.42$ (4)°, $D_c = 1.39$ g·cm^{-3}, and $Z = 4$, 1907 reflections were considered observed ($I \geq 3\sigma(I)$), and the final R value based on them was 0.093. **3b** and **3e** are isostructural, with the Mo atom bonded to two trans, staggered CO_2 molecules, the overall molecular geometry being approximately octahedral.

Molecular carbon dioxide complexes of transition metals have received considerable attention in the past years, in the hope of discovering model systems for the activation of CO_2 and its subsequent transformation into organic chemicals of commercial interest. Despite considerable and intensive research, attested by the number of review articles published in this subject in recent years,[2] only a few compounds have been authenticated as true carbon dioxide complexes. These include species containing side-on η^2-coordinated[3] and η^1,C-coordinated[4] CO_2, as well as two examples of what is usually referred to as assisted coordination of carbon dioxide.[5] In addition, numerous reports have appeared[6] on CO_2 complexes whose structures have been proposed on the basis of spectroscopic and chemical evidences. A closer examination of these complexes[7] discredited many of the initial formulations, and this, the difficulty in the spectroscopic characterization (due in part to the paucity of information on IR and NMR data for authentic CO_2 complexes), and other factors led Ibers to propose[2d,8] structural determination by diffraction methods as the only criterion to adequately characterize transition metal–carbon dioxide complexes.

The continuous interest in carbon dioxide chemistry, and the existence of only a brief report on the reaction of this molecule with dinitrogen complexes of molybdenum,[9] prompted us to investigate its interaction with the complex *cis*-$Mo(N_2)_2(PMe_3)_4$,

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(2) (a) Darensbourg, D. J.; Kudaroski, R. A. *Adv. Organomet. Chem.* **1983**, *22*, 129. (b) Palmer, D. A.; Eldik, R. V. *Chem. Rev.* **1983**, *83*, 651. (c) Ziessel, R. *Nouv. J. Chim.* **1983**, *7*, 613. (d) Ibers, J. A. *Chem. Soc. Rev.* **1982**, *11*, 57. (e) Sneeden, R. P. A. "Comprehensive Organometallic Chemistry"; Pergamon Press: Oxford, 1982. For other reviews, see ref 1 of ref 13, this paper.

(3) (a) Aresta, M.; Nobile, C. F.; Albano, V. G.; Forni, E.; Manassero, M. *J. Chem. Soc., Chem. Commun.* **1975**, 36. Aresta, M.; Nobile, C. F. *J. Chem. Soc., Dalton Trans.* **1977**, 708. (b) Bristow, G. S.; Hitchcock, P. B.; Lappert, M. F. *J. Chem. Soc., Chem. Commun.* **1981**, 1145. (c) Gambarotta, S.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *J. Am. Chem. Soc.* **1985**, *107*, 2985.

(4) Calabrese, J. C.; Herskovitz, T.; Kinney, J. B. *J. Am. Chem. Soc.* **1983**, *105*, 5914.

(5) Gambarotta, S.; Arena, F.; Floriani, C.; Zanazzi, P. F. *J. Am. Chem. Soc.* **1982**, *104*, 5082. (b) Herskovitz, T.; Guggenberger, L. J. *J. Am. Chem. Soc.* **1976**, *98*, 1615.

(6) See for instance: Ito, T.; Yamamoto, A. *J. Chem. Soc., Dalton Trans.* **1975**, 1398. Bochkarev, M. N.; Fedorova, E. A.; Radkov, Yu. F.; Korshev, S. Ya.; Kalinina, G. S.; Razuvaev, G. A. *J. Organomet. Chem.* **1983**, *258*, C29. For other examples, see ref 7.

(7) Eisenberg, R.; Hendriksen, D. E. *Adv. Catal.* **1979**, *28*, 119.

(8) Mason, M. G.; Ibers, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 5153.

(9) Chatt, J.; Kubota, M.; Leigh, G. J.; March, F. C.; Mason, R.; Yarrow, D. J. *J. Chem. Soc., Chem. Commun.* **1974**, 1033.

0002-7863/86/1508-2286$01.50/0