Guest-Induced Organization of a Three-Dimensional Palladium(II) Cagelike Complex. A Prototype for "Induced-Fit" Molecular Recognition

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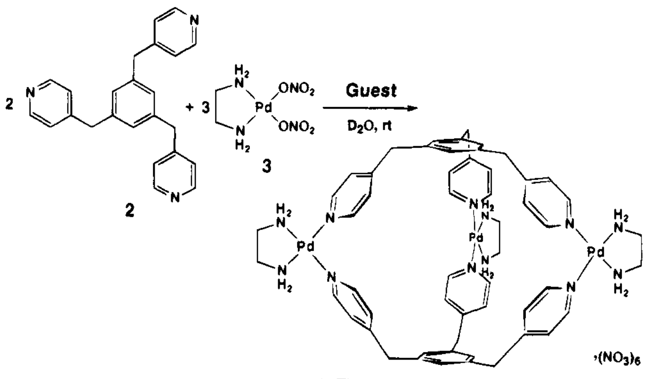
Instead of the lock-and-key model, current understanding of molecular recognition in a biological system is based on the "induced-fit" mechanism, in which specific substrates induce the organization of the recognition site of a receptor. Although models for induced-fit have been provided by flexible artificial hosts which have restricted conformations only if they recognize a specific guest,[1] there are few examples of induced-fit models in which a guest induces the organization of a host itself.[2,3] Reported here is the successful demonstration of such a phenomenon in a coordination approach to a three-dimensional cagelike Pd(II) complex **1**.[4−6] *Thus, the complex 1 assembles in high yields only in the presence of specific guest molecules* (Scheme 1).

A tridentate ligand 1,3,5-tris(4-pyridylmethyl)benzene[7] (**2**, 6 mM) was treated with (en)Pd$(NO_3)_2$[8] (**3**, 9 mM) and sodium 4-methoxyphenylacetate (**4**·Na, 15 mM) at ambient temperature in water. The NMR spectrum, obtained by a control experiment carried out in D_2O, showed the assembly of a single component in a high yield (>90%). Characterization of this component as the cagelike complex **1** mainly follows from its electrospray ionization mass spectroscopy (ESI-MS)[9,10] and NMR.[11] In particular, the extremely simple spectrum showed high symmetry of the product and the expected 2:3 stoichiometry of the components (**2**:(en)Pd^{2+} moiety), ruling out the other assignments for its structure.

Scheme 1



1 (The guest is included in the cavity.)

More significant information derived from ESI-MS, elemental analysis, and NMR shows that the cagelike host **1** binds the guest **4** in a 1;1 stoichiometry in aqueous solution. Thus, a molecular ion corresponding to the **1**·**4** complex (minus NO_3^-) was shown by ESI-MS with a series of prominent $[(M + H) - NO_3 - (HNO_3)_n]^{2+}$ and $[(M + H) - (NO_3)_2 - (HNO_3)_{n-1}]^{3+}$ peaks ($n = 1-4$).[10] Elemental analysis of the product, isolated as its ClO_4 salt in 94% yield by adding aqueous $NaClO_4$, was also consistent with the **1**·**4** (1:1) complex,[12] in spite of an initial 1;5 molar ratio[13] in the solution. Furthermore, the 1;1 binding of **1** and **4** was confirmed by ^1H NMR titration experiments,[14] from which the association constant between **1** and **4** was estimated to be $>10^4$ at least.[15]

Outstanding upfield shift of the signals of **4** was observed on complexation with **1** (Table 1). While the methoxyl and aromatic protons significantly shifted, $\Delta\delta$ of CH_2COO^- signal was little. This observation is ascribable to the complexation of **4** in the cagelike cavity of **1**, with a proposed inclusion geometry in which the hydrophobic moiety is located inside while hydrophilic COO^- is outside,

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(1) (a) Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 2426−2431. (b) Hamilton, A. D.; Engen, D. V. *J. Am. Chem. Soc.* **1987**, *109*, 5035−5036. (c) Sijbesma, R. P.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1991**, *113*, 6695−6696. (d) Conn, M. M.; Deslongchamps, G.; Mendoza, J. de; Rebek, J., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 3548−3557. (e) Güther, R.; Nieger, M.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 601−603.

(2) (a) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *Acc. Chem. Res.* **1993**, *26*, 469−475. (b) Also see: Lofthagen, M.; Chadha, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 8785−8790.

(3) Self-organization is characterized by the spontaneous generation of a well-defined molecular architecture under thermodynamic control. In this sense, our work can be distinguished from the guest-templated preorganization of host precursors[2] since the following cyclizing step proceeds kinetically and the host never dissociates into its components if the guest is removed.

(4) For reviews of three-dimensional cagelike compounds, see the following: (a) Evmeyer, F.; Vögtle, F. *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic Press: London, 1991; Vol. 4, Chapter 6, pp 263−282. (b) Seel, C.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 528−549.

(5) Cu(I)-directed organization of a cylindrical cagelike complex: Baxter, P.; Lehn, J.-M.; DeCian, A.; Fischer, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 69−72.

(6) Metal-directed assembly of macrocyclic host compounds: (a) Maverick, A. W.; Buckingham, S. C.; Yao, Q.; Bradbury, J. R.; Stanley, G. G. *J. Am. Chem. Soc.* **1986**, *108*, 7430−7431. (b) Bradbury, J. R.; Hampton, J. L.; Martone, D. P.; Maverick, A. W. *Inorg. Chem.* **1989**, *28*, 2392−2399. (c) Fujita, M.; Yazaki, J.; Ogura, K. *J. Am. Chem. Soc.* **1990**, *112*, 5645−5647. (d) Fujita, M.; Nagao, S.; Iida, M.; Ogata, K.; Ogura, K. *J. Am. Chem. Soc.* **1993**, *115*, 1574−1576. (e) Kobuke, Y.; Sumida, Y.; Hayashi, M.; Ogoshi, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1496−1498. (f) Kobuke, Y.; Satoh, Y. *J. Am. Chem. Soc.* **1992**, *114*, 789−790. (g) Al-Resayer, S. I.; Hitchcock, P. B.; Nixon, J. F. *J. Chem. Soc., Chem. Commun.* **1991**, 78−79. (h) Scrimin, P.; Tecilla, P.; Tonellato, U.; Vignana, N. *J. Chem. Soc., Chem. Commun.* **1991**, 449. (i) Mackay, L. G.; Anderson, H. L.; Sanders, J. K. *J. Chem. Soc., Chem. Commun.* **1992**, 43−44. (j) Schwabacher, A. W.; Lee, J.; Lei, H. *J. Am. Chem. Soc.* **1992**, *114*, 7597−7598. (k) Cole, K. L.; Farran, M. A.; Deshayes, K. *Tetrahedron Lett.* **1992**, *33*, 599−602. (l) Rüttimann, S.; Bernardinelli, B.; Williams, A. F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 392−394.

(7) Easily prepared by the addition of 1,3,5-trilithiobenzene, derived from 1,3,5-tribromobenzene and *n*-BuLi (4.5 molar equiv, −78 °C, THF), to isonicotinaldehyde (4.8 molar equiv, −78 °C, 18%) followed by hydrogenolysis (H_2, Pd/C, EtOH, HCl, 50 °C, 56%).

(8) Prepared from (en)$PdCl_2$ and $AgNO_3$ (2 molar equiv): Drew, H. D. K.; Pinkard, F. W.; Preston, G. H.; Wardlaw, W. *J. Chem. Soc.* **1932**, 1895.

(9) ESI-MS is effective for obtaining molecular weights of transition-metal complexes: (a) Bitsch, F.; Dietrich-Buchecker, C. O.; Khémiss, A.-K.; Sauvage, J,-P.; Van Dorsselaer, A. *J. Am. Chem. Soc.* **1991**, *113*, 4023−4025. (b) Leize, E.; Van Dorsselaer, A.; Krämer, R.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1993**, 990−993.

(10) ESI-MS data of **1**·**4** (minus NO_3^-) complex (major peaks are shown): *m/z* 777 ($[(M + H) - NO_3 - HNO_3]^{2+}$), 746 ($[(M + H) - NO_3 - (HNO_3)_2]^{2+}$), 715 ($[(M + H) - NO_3 - (HNO_3)_3]^{2+}$), 684 ($[(M + H) - NO_3 - (HNO_3)_4]^{2+}$), 518 ($[(M + H) - (NO_3)_2]^{3+}$), 497 ($[(M + H) - (NO_3)_2 - HNO_3]^{3+}$), 477 ($[(M + H) - (NO_3)_2 - (HNO_3)_2]^{3+}$), 456 ($[(M + H) - (NO_3)_2 - (HNO_3)_3]^{3+}$). Besides these peaks, there are several ascribable to the molecular ion of **1**·(**4**)$_2$ (minus $(NO_3^-)_2$). In this species, however, the second molecule of **4** probably exists as the counterion in place of one nitrate ion. No peaks derived from free **1** were observed. The spectrum was obtained on a TSQ700 with ESI source (Finnigan MAT, San Jose, CA) with a *m/z* range of 2000. The electrospray interface was heated to 100 °C. The sampling cone voltage was 31.3 V. An aqueous solution of **1** (4 mM) was injected into the spectrometer. The flow rate was 2.00 $\mu L\ min^{-1}$.

(11) ^1H NMR of **1** from the mixture of **1** (1.0 mM) and **4** (1.5 mM) (400 MHz, D_2O, TMS in $CDCl_3$ as external standard): δ 2.87 (s, 12 H, NH_2CH_2-), 3.97 (s, 12 H, $PyCH_2Ar$), 7.20 (s, 6 H, Ar*H*), 7.30 (d-like, 12 H, $J = 6.5$ Hz, PyH_β), 8.36 (d-like, 12 H, $J = 6.5$ Hz, PyH_α).

(12) Anal. Calcd for $C_{63}H_{75}N_{12}O_{23}Cl_5Pd_3 \cdot 5H_2O$ ($[[(en)Pd]_3(\mathbf{2})_2]\cdot\mathbf{4}\cdot(ClO_4)_5)\cdot 5H_2O$): C, 38.71; H, 4.38; N, 8.60. Found: C, 38.48; H, 4.17; N, 8.85.

(13) [**1**] at equilibrium is approximately 3 mM. Thus the ratio **1**:**4** in the solution is 1:5.

(14) Hanna, M. W.; Ashbaugh, A. L. *J. Phys. Chem.* **1964**, *68*, 811−816. Also see ref 6c.

(15) Association constants were estimated by a nonliner least-squares fitting for $\Delta\delta$(guest) in ^1H NMR vs [**1**]/[**4**]. Since we had to estimate the concentration of host from the NMR integral ratio of the mixture of the host and oligomers, accurate determination of the association constant was difficult.

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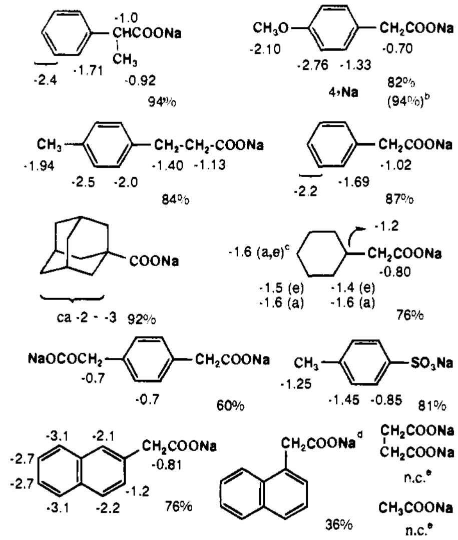
Table 1. Guest-Induced Organization of **1**[a]



[a] The guest compounds are shown. The NMR yield of **1** is determined at $[\mathbf{2}]_0 = 2$ mM, $[\mathbf{3}]_0 = 3$ mM, and [guest] = 1.5 mM unless otherwise noted and is shown below each structure. The negative values shown with each structure present upfield shift ($\Delta\delta$ in ppm) in ^{1}H NMR measured at $[\mathbf{2}]_0 = 6$ mM, $[\mathbf{3}]_0 = 9$ mM, and [guest] = 1.5 mM. At these conditions, titration experiments showed that the $\Delta\delta$ values of the guests (except $C_6H_4(COONa)_2$) were saturated. [b] The yield at $[\mathbf{2}]_0 = 2$ mM, $[\mathbf{3}]_0 = 3$ mM, and [guest] = 5 mM. [c] Axial and equatorial protons are donated by a and e, respectively. [d] $\Delta\delta$ values could not be analyzed due to overlap with uncharacterized signals. [e] Not complexed (no significant upfield shift was observed).

Worth noting is that the host **1** assembled in high yields only in the presence of specific guests. In the absence of a guest, the reaction of **2** and **3** gave rise to a considerable amount of oligomeric products, These oligomers, however, disappeared upon addition of **4**.[16] Interestingly, this guest-induced assembly process was monitored by a time-dependent ^{1}H NMR measurement (Figure 1). After addition of **4** to a reaction mixture derived from **2** and **3**, the oligomers gradually disappeared and the signals of **1** became stronger, accompanying the upfield shifting of the guest signals (a and b), The assembly of **1** was complete within several hours,

Various anionic guests having a hydrophobic moiety induced the organization of **1** (Table 1). The relative ability of the guests to induce the host organization was evaluated by comparing the yields of **1** at a given low concentration,[17] From the yields of **1** at $[\mathbf{2}]_0 = 2$ mM, $[\mathbf{3}]_0 = 3$ mM, and [guest] = 1,5 mM (Table 1), the following characteristics of the complexation are noted; (i) At this set of conditions, **1** assembles in 60% yield without guest.[16] (ii) The host **1** assembles in the highest yields (>90%) when the guests have a bulky hydrophobic moiety such as 1-phenylethyl or adamantyl group. Molecular modeling showed that the size of these groups is comparable to that of the spherical inner cavity of **1**.[18] (iii) Monocarboxylates having a phenyl, substituted phenyl, or cyclohexyl group as well as *p*-toluenesulfonate also induce the assembly of **1** effectively (76–87%). (iv) Less hydrophobic substrates such as dicarboxylates or acetate are poorly or hardly complexed, (v) It is particularly interesting that (1-naphthyl)acetate negatively decreased the yield of **1** (36%). Probably, this guest is too large to induce the host organization but is able to stabilize a partially dissociated or oligomeric structure through hydrophobic contact,

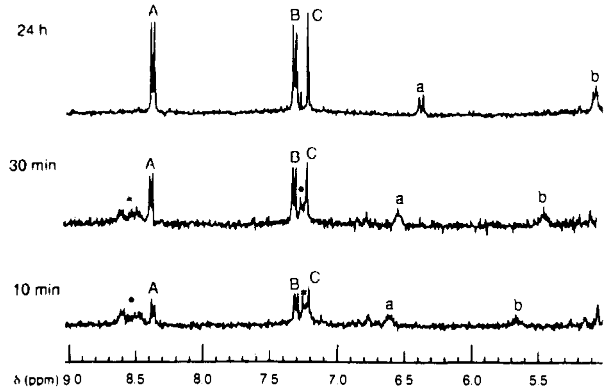


Figure 1. Monitoring of the guest-induced self-organization of **1** by ^{1}H NMR (270 MHz, D_2O, 25 °C). Spectra were collected at 10 min, 30 min, and 24 h after the addition of **4**·Na to a oligomeric mixture arising from **2** and **3** in D_2O ($[\mathbf{2}]_0 = 2.4$ mM, $[\mathbf{3}]_0 = 3.6$ mM, $[\mathbf{4}] = 1.2$ mM). Signals A, B, and C are referred to aromatic protons of **1** (A, Py$H\alpha$; B, PyH_β; C, ArH), while signals a and b correspond to aromatic protons of **4**. The signal b at 24 h is overlapping with a side band of H_2O signal. Complicated signals appearing at δ 7.1–7.3 and 8.4–8.7 (indicated by asterisks) are attributed to oligomeric components. ArCH_2 signals of **1** appeared as a singlet (δ 3.97), showing that twisting of the three-dimensional framework of **1** is rapid on the NMR time scale. A singlet signal at δ 7.3 is referred to $CHCl_3$, slightly contained in the external TMS/$CDCl_3$ solution.

Besides anionic hosts, a neutral hydrophobic guest was also effective. For example, when *p*-xylene was saturated (0.3 mM), the host assembled in 72% yield at $[\mathbf{2}]_0 = 2$ mM and $[\mathbf{3}]_0 = 3$ mM ($\Delta\delta_{ArCH_3} = 1{,}20$; $\Delta\delta_{ArH} = 1.80$). Thus ion-pairing in the binding of anionic guest, though effective, is not essential, On the other hand, a less hydrophobic neutral guest, *p*-dimethoxybenzene, hardly induced the organization of the host. Cationic guest trimethylbenzylammonium bromide did not interact with the host. Upfield shifts of guest signals in the presence of excess host are also shown in Table 1, Titration showed that these values are saturated, except those of 1,4-$(NaOCO)_2C_6H_4$,

In summary, metal-directed assembly of molecular architecture[19] has proven to be effective for the construction of a three-dimensional cagelike complex **1**, It is particularly interesting that the spontaneous manner in which the framework of **1** assembles only in the presence of specific guests can be regarded as a prototype for "induced-fit" molecular recognition.

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Supplementary Material Available: An experimental procedure for the preparation of **2**, including spectral and analytical data, the complete ^{1}H NMR spectra (δ 0–9.0 range) from which Figure 1 was delivered, and the MM2 structure of **1** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(16) The oligomeric products are in equilibrium with **1**. At lower concentrations, **1** arises even in the absence of the guest though the yields are low. The yields of **1** (concentration of the net Pd^{2+}) are <5% (27 mM), 23% (12 mM), 43% (6 mM), and 60% (3 mM). Further dilution did not increase the yield.

(17) Note that the increase of yields of **1** by the addition of guests became more dramatic at higher concentrations, as shown in Figure 1. However, we carried out these experiments at a low concentration, since at higher concentrations the yield of **1** became so high in most cases that the estimation of the relative induction ability was difficult. The yields quoted in Table 1 have little quantitative significance because of the reason cited in footnote 15.

(18) MM2 parameters supplied by CAChe system (Ver. 3.5, Sony/Tektronicx Corp.) were used for the refinement of the molecular modeling (see supplementary material). It was shown that adamantyl and 1-phenylethyl groups are bulky enough to fit the cavity of the host, while (1-naphthyl)acetate is too bulky.

(19) For reviews, see: Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89–112; **1990**, *29*, 1304–1319.