Guest-Selected Formation of Pd(II)-Linked Cages from a Prototypical Dynamic Library

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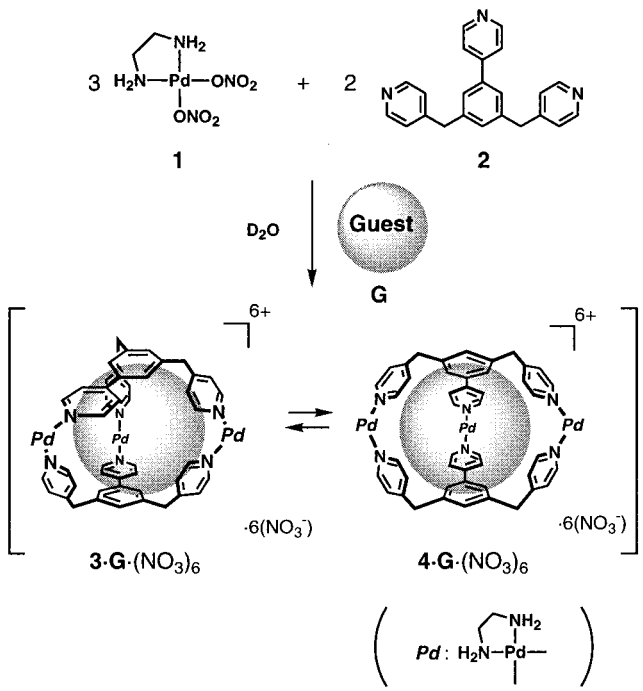
Biological receptors modulate the shape and size of their recognition sites to bind substrate molecules,[1] generating numerous receptor structures from which the most suitable one is selected (or induced-fit) by their substrates. Modeling such a system is particularly important to develop a new receptor design wherein artificial receptors are constructed through a selection process by their own guests. Although previous examples dealt with the induced-fit control of receptor conformations, there are only several reports on the control of receptor linkages.[2] Here we report the guest-selected formation of its optimal cage-like receptor from an equilibrium mixture of receptors.[3,4] In Scheme 1, Pd(II)-linked cages, **3** and **4**, and some oligomeric compounds,[5] accessible from the same components **1** and **2**, are in equilibrium. We show that, from this thermodynamic mixture, each cage structure is selected upon the addition of appropriate guest molecules. The phenomenon described herein is a prototype for a "dynamic receptor library",[2] which represents one of important goals in the field of molecular recognition.

The treatment of **1** with **2** in a 3:2 ratio first resulted in the formation of a mixture of oligomeric compounds[5] (Figure 1a). From this mixture, however, cage complex **3** was selectively formed upon the addition of 1,3,5-benzenetricarboxylic acid (**5**).[6] ^{1}H NMR revealed the desymmetrization of both the host and the guest frameworks (Figure 1b), in good agreement with the asymmetric structure of **3**. Namely, H^c and H^d of the host C_6H_3 ring, as well as Py^1 and Py^2 rings, were inequivalent and guest

Scheme 1



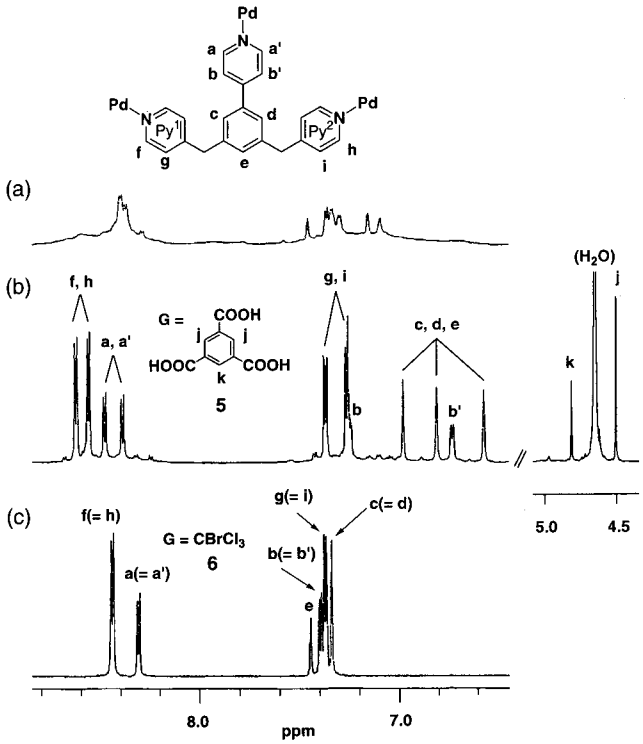


Figure 1. ^{1}H NMR observation of the guest-selected formation of cage complexes (500 MHz, D_2O, 25° C): (a) oligomeric mixtures obtained from **1** and **2** in D_2O ($[\mathbf{1}]_0 = 90$ mM, $[\mathbf{2}]_0 = 60$ mM); (b) **3·5** complex assembled upon the addition of **5** ($[\mathbf{1}]_0 = 90$ mM, $[\mathbf{2}]_0 = 60$ mM, $[\mathbf{5}]_0 = 30$ mM); (c) **4·6** complex assembled upon the addition of an excess amount of **6** (suspended) ($[\mathbf{1}]_0 = 12.5$ mM, $[\mathbf{2}]_0 = 8.3$ mM).

C_6H_3 protons were observed at δ 4.50 ($\Delta\delta = 4.08$, s, 2 H) and δ 4.81 ($\Delta\delta = 3.77$, s, 1 H).[7] These observations strongly suggested the formation of **3** which tightly accommodated **5** in its cavity. The formation of host−guest complex **3·5** was also supported by ESI-MS which showed prominent peaks for [**3·5**-

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(1) Koshland, D. E., Jr. *FEBS Lett.* **1976**, *62*, E47.

(2) Several recent reports deal with the dynamic receptor library: (a) Rowan, S. J.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1407. (b) Brady, P. A. Sanders, J. K. M. *J. Chem. Soc., Perkin Trans .1* **1997**, 3237. (c) Hasenknopf, B.; Lehn, J.-M.; Boumediene, N.; Dupont-Gervain, A.; Dorsselaer, A. V.; Kneisel, B.; Fenske, D. *J. Am. Chem. Soc.* **1997**, *119*, 10956. (d) Rivera, J. M.; Martín, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 819. (e) Lee, S. B.; Hwang, S.; Chung, D. S.; Yun, H.; Hong, J.-I. *Tetrahedron Lett.* **1998**, *39*, 873. (f) Klekota, B.; Hammond, M. H.; Miller, B. L. *Tetrahedron Lett.* **1997**, *38*, 8639. (g) Still, W. C. *J. Org. Chem.* **1998**, *63*, 904. (h) Also see: Goodman, M. S.; Jubian, V.; Linton, B.; Hamilton, A. D. *J. Am. Chem. Soc.* **1995**, *117*, 11610.

(3) Guest-induced assembly of receptors: (a) Fujita, M.; Nagao, S.; Ogura, K. *J. Am. Chem. Soc.* **1995**, *117*, 1649. (b) Bilyk, A.; Harding, M. M. *J. Chem. Soc., Chem. Commun.* **1995**, 1697.

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(5) Our preliminary result implies that, in addition to M_3L_2-type structures (**3** and **4**), dimeric M_6L_4 compounds is involved.

(6) Experimental details: see Supporting Information.

(7) (a) Host behavior: Although protons a and a′ do not exchange on the NMR chemical shift time scale, they are correlated by NOESY, showing the rapid fliping of the pyridine ring (which has protons a and a′) on the NOESY time scale (mixing time: 300 ms). On the other hand, no NOESY corelation is observed between Py^1 and Py^2, suggesting the exchange of these rings does not take place even on the NOESY time scale. NOEs are not observed between the host and the guest by NOESY. (b) Guest behavior: desymmetrization of the guest C_6H_3 ring also shows that the rotation of the guest molecule in the cavity is not allowed on the NMR time scale. On the other hand, only one singlet signal is observed for benzene guest, suggesting the rapid spining of the bernzene molecule in the **4**·benzene complex on the NMR time scale.

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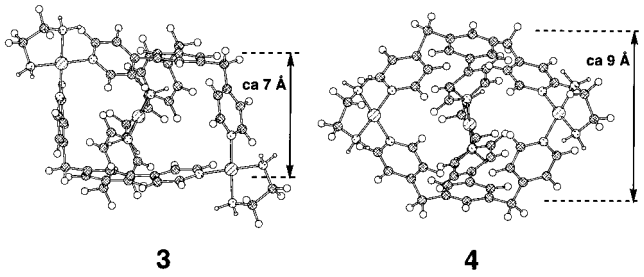

Figure 2. Optimized geometry of (a) **3** and (b) **4**.

$(NO_3)_n]^{n+}$ (e.g., m/z = 861.1 and 523.2 for n = 2 and 3, respectively).[6] Several aromatic guests, including water-immiscible compounds such as benzene and *p*-xylene, were also found to be effective for organization of cage **3**, that accommodated the guest in a 1:1 stoichiometry.

The selective formation of symmetrical host **4** was induced by the addition of spherical guests such as $CBrCl_3$ (**6**) and CBr_4. Thus, the addition of **6** to the initial oligomeric mixture resulted in the selective formation of **4·6** complex in ~85% yield. Minor product (probably, **3·6** complex in ~15% yield) could be removed after crystallization of the reaction mixture giving pure **4·6** complex (Figure 1c).[8] In NMR, the ligand framework maintains its symmetry ($Py^1 = Py^2$, $H^c = H^d$) in good accordance with the symmetrical structure of **4**. Encapsulated $CBrCl_3$ was observed by the ^{13}C NMR with a remarkable upfield shift ($\Delta\delta$ −2.9 ppm).[6]

Molecular modeling, refined by Cerius[2] program,[9] explains the origin of the selectivity in the formation of host **3** and **4**. As shown in Figure 2, cage **3** has a flat cavity, whereas cage **4** has a spherical one. The host frameworks should be organized so that maximum hydrophobic interaction can be gained. Therefore, flat guests select host **3**, whereas spherical guests prefer host **4**.

Molecular chirality existing in the framework of host **3** is worthy of special attention. Despite the symmetrical structure of component ligand **2**, cage structure **3** is chiral because of asymmetric orientation of two ligands in the cage framework.[10] Interestingly, the chirality of the cage was observed by diastereomeric complexation with (*R*)-mandelic acid ((*R*)-**7**). Thus, (*R*)-**7** induced the organization of a diastereomer mixture of {(*P*)-**3**}·{(*R*)-**7**} and {(*M*)-**3**}·{(*R*)-**7**}.[11] As a consequence, two sets of asymmetric cages were observed by NMR (Figure 3a). The observation of the two diastereomers also evidenced that racemization ((*P*)-**3** ⇄ (*M*)-**3**), which requires the cleavage of at least two Pd−N bonds, did not take place on the NMR time scale. Interestingly, diastereomers were not observed when racemic **7** was employed (Figure 3b). This result indicated a very rapid exchange of (*R*)- and (*S*)-**7** on the NMR time scale, making no difference in the situation of (*P*)- and (*M*)-hosts. As a preliminary result, chiral induction was observed to some extent for a few guests.[10a] For example, (*S*)-1-acetoxyethylbenzene (**8**) induced the organization of **3·8** in a 3:2 diastereomer ratio.

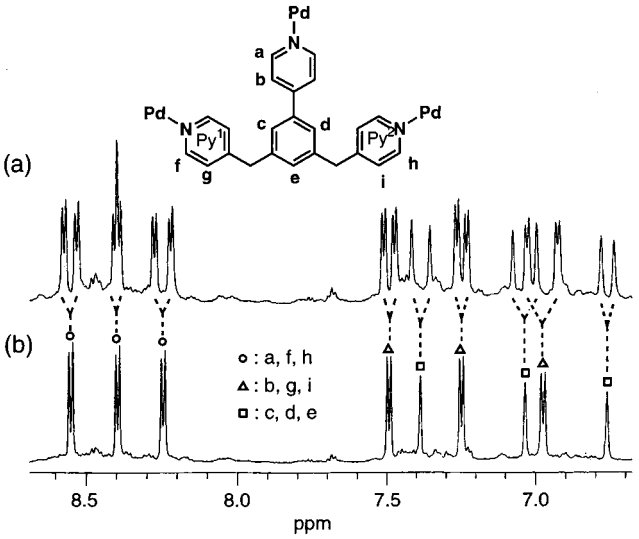

Figure 3. ^1H NMR spectra of (a) **3**·((*R*)-**7**) and (b) **3**·((*rac*)-**7**) (500 MHz, D_2O, 25° C, $[\mathbf{1}]_0$ = 12.5 mM, $[\mathbf{2}]_0$ = 8.3 mM, $[\mathbf{7}]_0$ = 21 mM).

Reversible conversion between two cage structures **3** and **4** particularly featured the thermodynamic formation of the cages. When **3**·(*p*-xylene) was treated with excess amount of $CBrCl_3$, the guests were exchanged, and host framework **3** was slowly converted to **4**, giving more stable **4**·($CBrCl_3$) complex within 24 h. The cage framework was, of course, reconverted into **3** within 2 h when thus obtained **4**·($CBrCl_3$) was subsequently treated with an excess amount of *p*-xylene.[12] Competition experiments were also carried out: in the presence of 1:1 mixture of *p*-xylene and $CBrCl_3$ (5 equiv), the ratio **3**:**4** was 65:35, showing a slight preference for the dissymmetric form.

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Supporting Information Available: Experimental details of the preparation of **2**, self-assembly of **3·G** and **4·G** complexes, and ESI-MS data of **3·5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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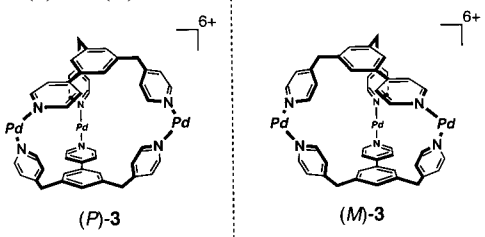
(8) The interconversion process is very slow and is negligble within hours if the complex is treated at low temperature and at low concentration. Therefore, pure **4·6** complex can be isolated if it is crystallized and carefully dissolved in water without heating. Upon heating, pure **4·6** complex is again converted into the original 85:15 mixture.

(9) Energy minimization was performed using Cerius[2] with Universal force field: Rappé, A. K.; Cosewit, C. J.; Colwell, K. S.; Goddard, W. A., III; Skiff, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 10024.

(10) Chiral receptors assembled from achiral building blocks: (a) Rivera, J. M.; Martín, T.; Rebek, J., Jr. *Science* **1998**, *279*, 1021. (b) Tokunaga, Y.; Rebek. J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 66.

(11) The (*P*)- and (*M*)-**3** can be defined as follows:



(12) Guest exchange in encapsulation complexes: (a) Santamaría, J.; Martín, T.; Hilmersson, G.; Craig, S. L.; Rebek. J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 8344. (b) Szabo, T.; Hirmersson, G.; Rebek. J., Jr. *J. Am. Chem. Soc*. **1998**, *120*, 6193.