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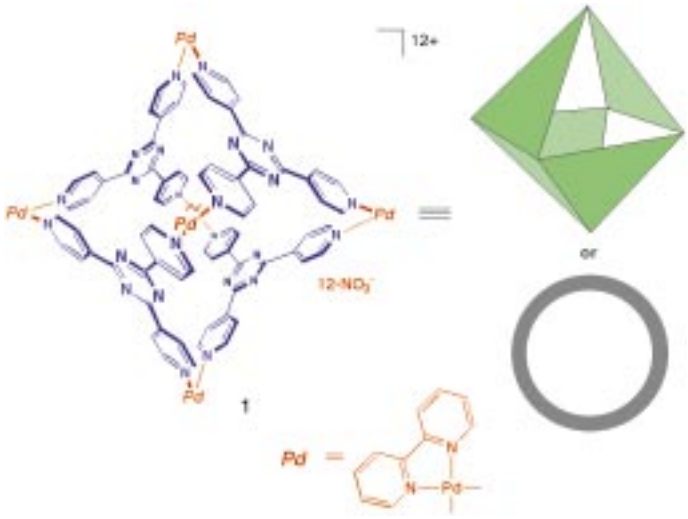
Probing Guest Geometry and Dynamics through Host – Guest Interactions**

Takahiro Kusukawa, Michito Yoshizawa, and Makoto Fujita*

Conformational freedom of molecules is restricted when they are enclathrated within the limited interior space of hollow compounds.[1] Analysis of the inclusion geometry of guest molecules is important because molecules in a specific geometry or aggregation are expected to show unique properties and reactivities which do not appear when they are in solution. The restricted conformations are in general analyzed by observing guest molecules themselves. On the other hand, information on the geometry of guests can be read out by the spectroscopic analysis of host frameworks provided the host and the guest communicate with each other through subtle host – guest interactions. Several reports have dealt with the conformational analysis of guests by the observation of host frameworks.[2, 3] However, the observed spectra of the hosts are often not sufficiently simple to analyze details.

Coordination nanocage **1** has recently been shown to strongly bind a variety of neutral substrates within its nanosized cavity.[4] As a result of the high symmetry of cage



1 (T_d) the twelve pyridine rings in **1** are all equivalent, and the NMR spectrum of the empty cage displays only a set of pyridine protons at $\delta = 9.47$ (PyH^{α}) and 8.92 (PyH^{β}) (Figure 1a). When the cage accommodates guest molecule(s) with lower symmetry the T_d symmetry of the cage is desymmetrized and the symmetry of the entity follows that of the guest(s) if the cage and the guest(s) strongly interact. For example, if the guest has C_1 symmetry then 48 pyridine protons of **1** become inequivalent and, in principle, 48 independent pyridine protons should be observed in the ^{1}H NMR spectrum. Scheme 1 summarizes the relationship between the guest symmetry and the maximum number of pyridine protons which should appear in the NMR spectra. Thus, an analysis of the symmetry of the cage probes how guests are accommodated in the cavity. We show in the following discussions some examples of probing the guest geometry by NMR analysis of the host symmetry, where all predicted structures have been confirmed by X-ray analyses. The analysis of the symmetry by NMR spectroscopic analysis also elucidates the dynamic motion of included guests.

The 1:2 complexation of cage **1** with 4,4′-dimethoxydibenzoyl (**2a**) provides a fine example. The 1:2 inclusion complex $(\mathbf{2a})_2 \subset \mathbf{1}$ was easily prepared by mixing a solution of **2a** in hexane (saturated, 1 mL) and a solution of **1** in D_2O (5.3 mM, 2 mL), and stirring the mixture at 80 °C for 0.5 h. After

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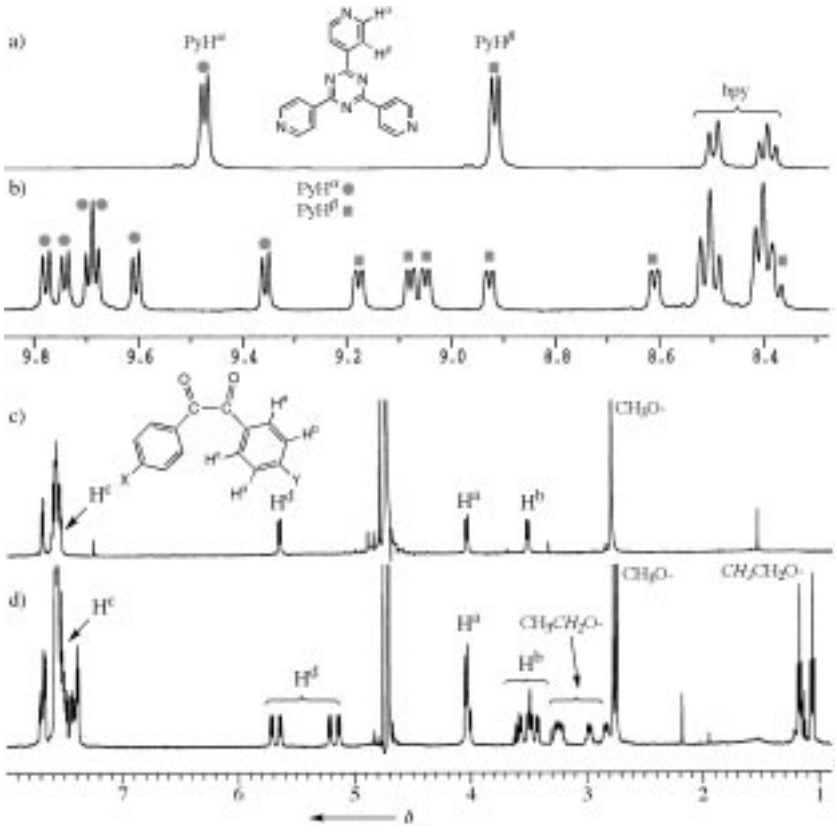
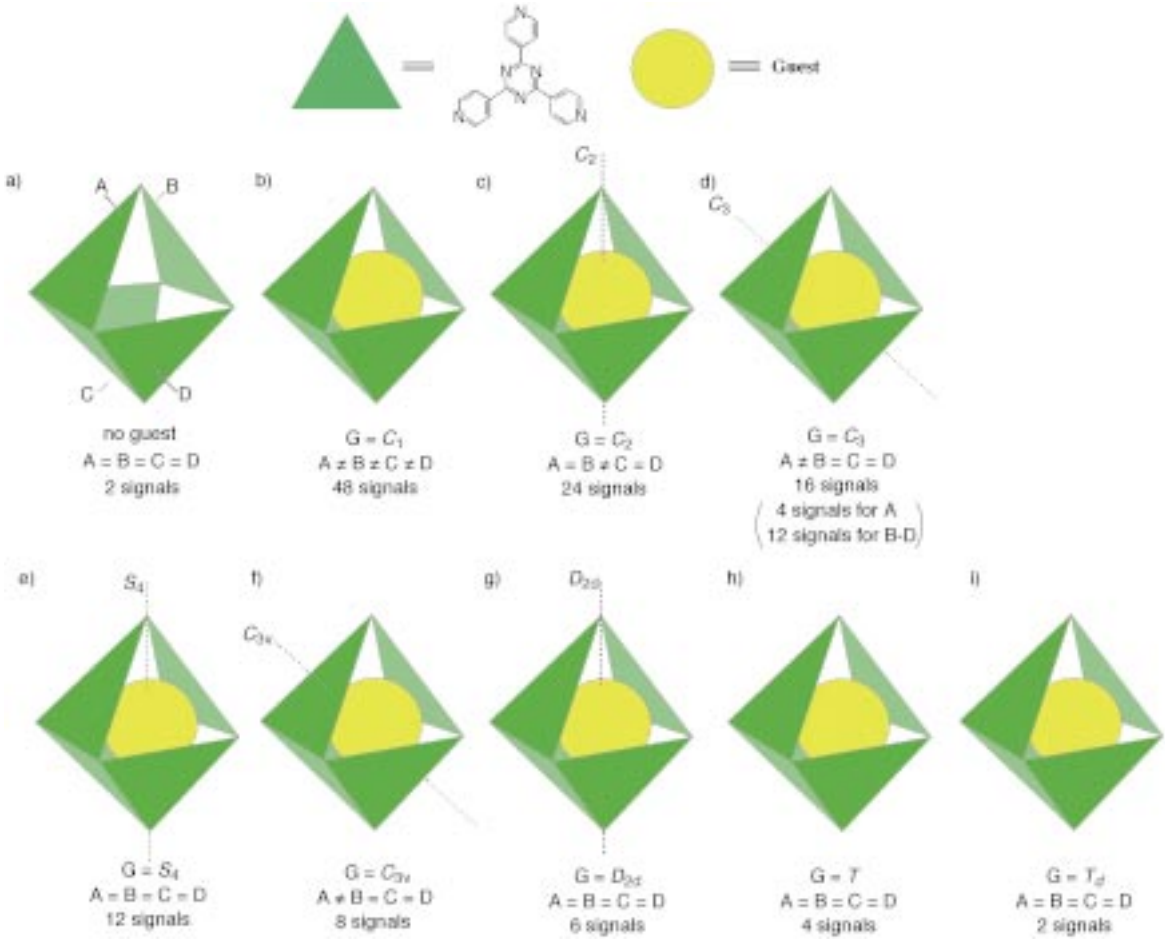


Figure 1. ^{1}H NMR observations of the enclathration of **2a** in nanocage **1**. a) Empty **1**. b) and c) $(\mathbf{2a})_2 \subset \mathbf{1}$. d) $(\mathbf{2b})_2 \subset \mathbf{1}$.



Scheme 1. The relationships between the guest symmetry and the maximum number of pyridine protons that should appear in the NMR spectra.

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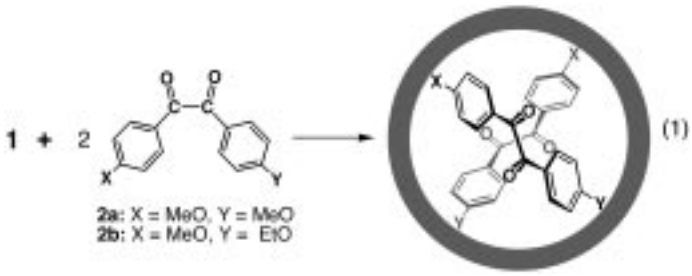
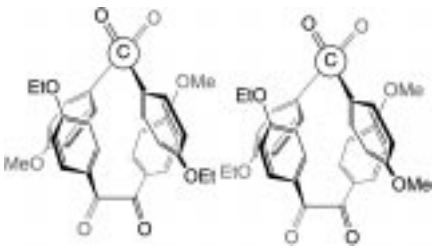
complexation was complete, the pyridine protons of the host were split into six pairs: six PyH^{α} protons at $\delta = 9.35 - 9.8$ and six PyH^{β} protons at $\delta = 8.35 - 9.2$ (Figure 1b). This observation suggested the desymmetrization of the host into an S_4 symmetric entity with 12 inequvalent protons on each ligand (see case e of Scheme 1 where ligands A – D are all equivalent but each ligand possesses no symmetry element). The S_4 symmetry can originate from a specific orientation of two guest molecules in the cavity and will be generated only if they aggregate orthogonally and adopt a chiral, twisted conformation with opposite screw senses [Eq. (1)].[5]



The S_4 orientation of the guests was also supported by the guest signals in the ^{1}H NMR spectrum. A tight contact of the two guest molecules was shown by NOEs (1.2 – 18.4 %) between the methoxy protons and other aromatic protons. These interactions must be intermolecular because the corresponding NOEs were not observed in the NMR spectrum of free **2** in $CDCl_3$. The twisted conformation of **2** was consistent with the observation of four different chemical shifts for the four aromatic protons on the phenylene groups (Figure 1c). The observation of the chirality of each guest demonstrated that two conformations of enclathrated **2a** were completely frozen at room temperature, while those of free **2a** are in rapid equilibrium in solution. With the asymmetric substituted analogue **2b**, a diastereomeric pair (see below) was observed in a 1:1 ratio (Figure 1d).



The proposed orientation of **2a** was confirmed by an X-ray analysis (Figure 2). As expected, two molecules were packed orthogonally and each of them adopted a twisted conformation with a dihedral angle (ψ) of 80.6 – 80.8° between the two carbonyl groups. This angle is considerably smaller than that of dibenzoyl in its crystal structure ($\psi = 124.6°$),[6] but very close to that of an optimized conformation ($\psi = -83.27°$).[7] Thus, each guest adopts its optimal geometry without influence from crystal-packing effects.

The dynamics of the guest were studied using variable temperature NMR spectroscopy. Upon heating the sample,

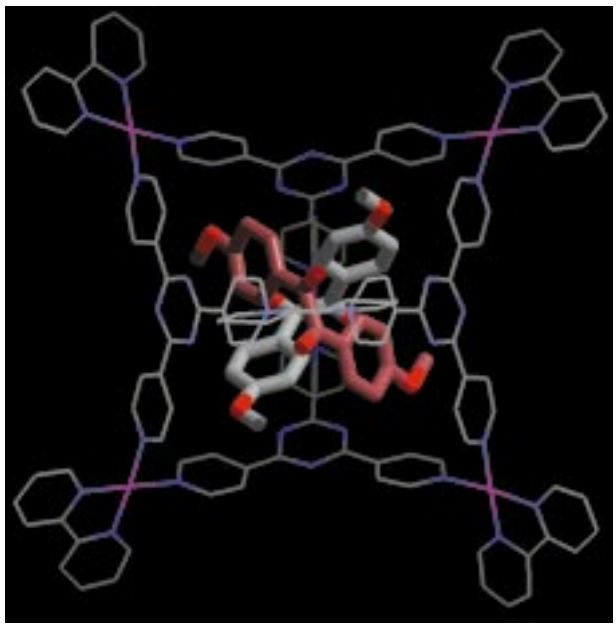
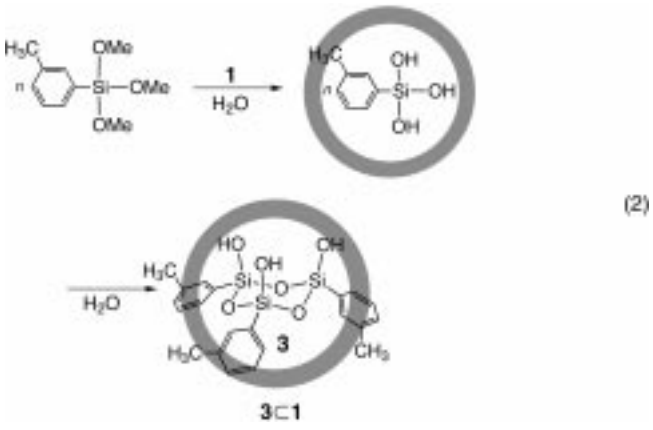


Figure 2. Crystal structure of $(\mathbf{2a})_2 \subset \mathbf{1}$.

the signals for the PyH^{α} and PyH^{β} protons coalesced at 343 K into a broad pair of signals around $\delta = 9.6$ and 9.0, respectively. Since the average chemical shifts of the pyridine protons did not change significantly, the coalescence of the signals can be explained by the rapid P/M interconversion of the guest to give the apparent T_d-symmetric environment of the host.

The enclathration of a cyclic siloxane trimer (**3**) with C_{3v} symmetry was also studied. This guest molecule was synthesized in situ within the cavity of **1** by a hydrolysis of trimethoxy(*m*-tolyl)silane followed by condensation [Eq. (2)].[8] Eight pyridine signals were observed in the



aromatic region of the ^{1}H NMR spectrum for cage **1**, which is in good agreement with C_{3v} symmetry (see case f in Scheme 1). Thus, the observed ^{1}H NMR spectrum suggests one C_{3v}-symmetrized ligand (A) and three C_{2v}-symmetrized ligands (B). Ligand A gave a pair of doublets (H^a and H^b; 6H integral for each) while ligand B gave three pairs of doublets (H^c and H^d, H^e and H^f, and H^g and H^h; 2H integral for each, Figure 3). Indeed, the spectrum of guest **3** was consistent with

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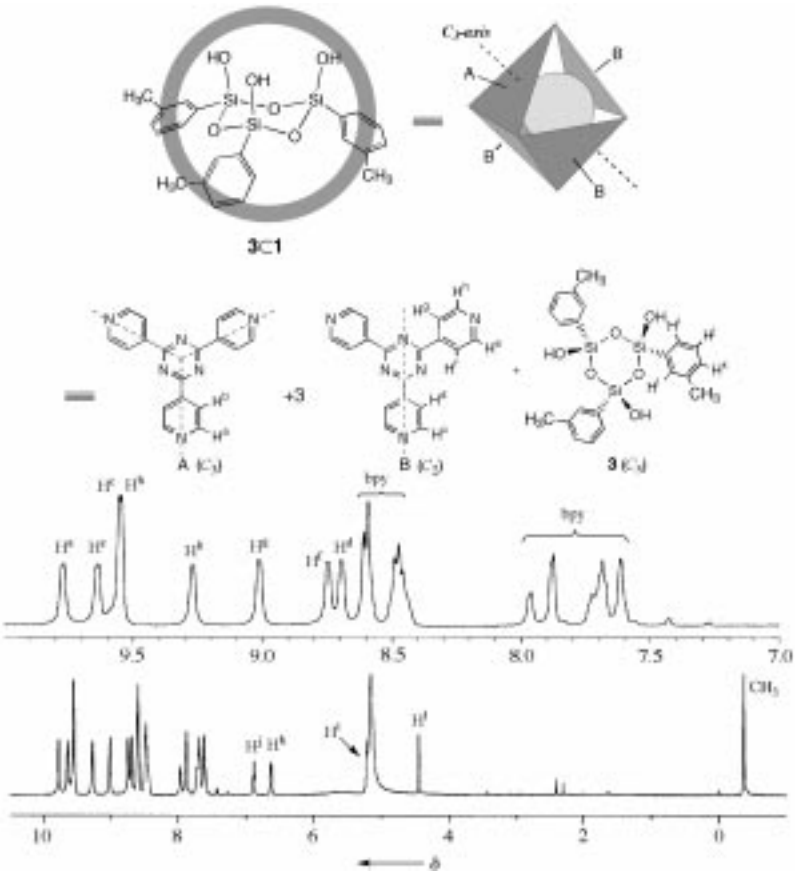

Figure 3. ^{1}H NMR spectra of $\mathbf{3}\subset\mathbf{1}$ at 278 K.

the strong binding of **3** in the cavity: highly upfield-shifted methyl protons at $\delta = -0.37$ and aromatic protons at $\delta = 6.88$, 6.63, 5.21, and 4.45 were observed.

The C_{3v} inclusion geometry was also evident from an X-ray analysis (Figure 4). A C_3-axis passes through both the host and the guest frameworks as expected. The all-*cis* configuration of **3** with respect to an almost planer six-membered siloxane ring was confirmed. The guest conformation in the solid structure is in fact C_3 (not C_{3v}) as a consequence of the presence of asymmetric *m*-tolyl groups. Thus, the observation of C_{3v} symmetry for the host framework probes the rapid flipping of *m*-tolyl groups in solution which gives an apparent C_{3v} structure. While guest **3** is frozen or allowed to only spin around the C_{3v} axis at room temperature, its motion becomes random at elevated temperatures. The host signals coalesced at 313 K in variable-temperature NMR measurements (Figure 5), which showed that the guest turned around rapidly within the cage above this temperature.

The present study has shown that the specific conformation and orientation of guest molecules in cagelike host **1** can be predicted in a dynamic fashion by analyzing not the guest but the host framework as a result of the simple, highly symmetric structure of **1**. The facile probe of guest information by this method will make possible the design of new properties and reactivities of molecules.[9]

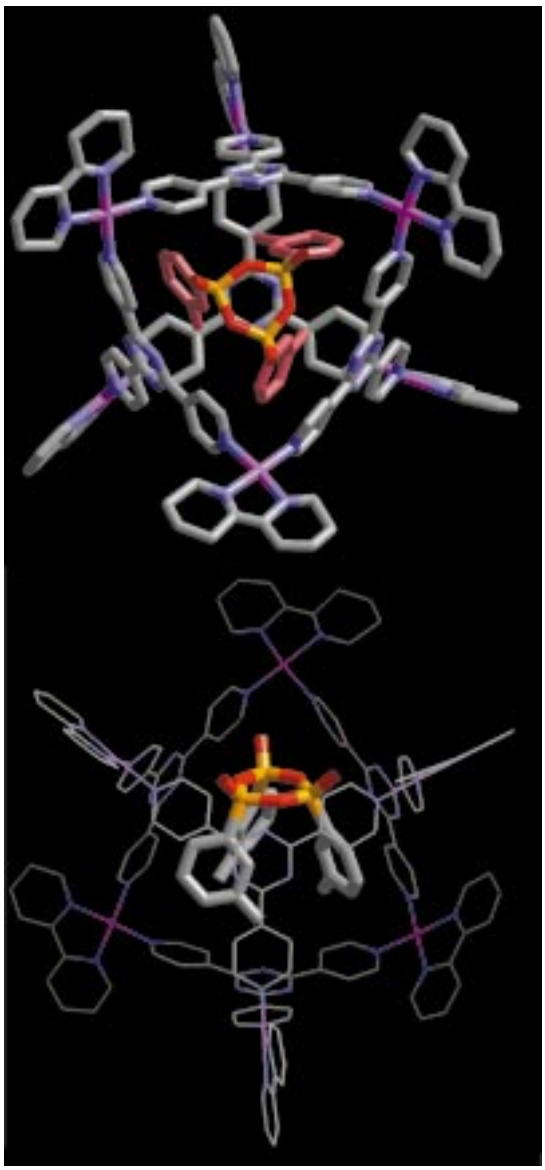

Figure 4. The top and side views of the $\mathbf{3}\subset\mathbf{1}$.

Experimental Section

Typical procedure: A suspension of **2a** (61.1 mg, 0.226 mmol) in hexane (1 mL) was stirred with a solution of **1** in D_2O (7.5 mM, 1.5 mL) for 0.5 h. The two phases were then separated. Analysis of the aqueous phase by NMR spectroscopy showed the stoichiometric formation of $(\mathbf{2a})_2\subset\mathbf{1}$. The aqueous solution was condensed to give $(\mathbf{2a})_2\subset\mathbf{1}$ as a pale yellow powder (44.5 mg) in 97% yield.

$(\mathbf{2a})_2\subset\mathbf{1}$: ^{1}H NMR (500 MHz, D_2O, 300 K, TMS as external standard): $\delta =$ 9.78 (d, $J = 6.0$ Hz, 4H, PyH^{α}), 9.74 (d, $J = 5.9$ Hz, 4H, PyH^{α}), 9.74 (d, $J =$ 5.9 Hz, 4H, PyH^{α}), 9.61 (d, $J = 5.4$ Hz, 4H, PyH^{α}), 9.36 (d, $J = 6.0$ Hz, 4H, PyH^{α}), 9.18 (d, $J = 6.0$ Hz, 4H, PyH^{β}), 9.08 (d, $J = 5.9$ Hz, 4H, PyH^{β}), 9.05 (d, $J = 5.9$ Hz, 4H, PyH^{β}), 8.93 (d, $J = 5.9$ Hz, 4H, PyH^{β}), 8.61 (d, $J =$ 5.4 Hz, 4H, PyH^{β}), 8.50 (t, $J = 8.6$ Hz, 12H, bpy), 8.40 (t, $J = 8.4$ Hz, 12H, bpy), 8.37 (d, $J = 6.0$ Hz, 4H, PyH^{β}), 7.7–7.5 (m, 28H, 24H for bpy, 4H for diketone ArH), 5.66 (d, $J = 8.9$ Hz, 4H, diketone ArH), 4.05 (d, $J =$ 8.9 Hz, 4H, diketone ArH), 3.52 (d, $J = 8.8$ Hz, 4H, diketone ArH), 2.80 (s, 12H, diketone CH_3O-); ^{13}C NMR (125 MHz, D_2O, 300 K): $\delta = 193.0$ (s, diketone CO), 169.6 (s, triazine), 169.5 (s, triazine), 169.3 (s, triazine), 163.0 (s, diketone), 157.14 (s, bpy), 157.08 (s, bpy), 153.5 (d, py), 153.3 (d, py), 153.2 (d, py), 153.0 (d, py), 152.9 (d, py), 152.8 (d, py), 150.6 (d, bpy), 150.4

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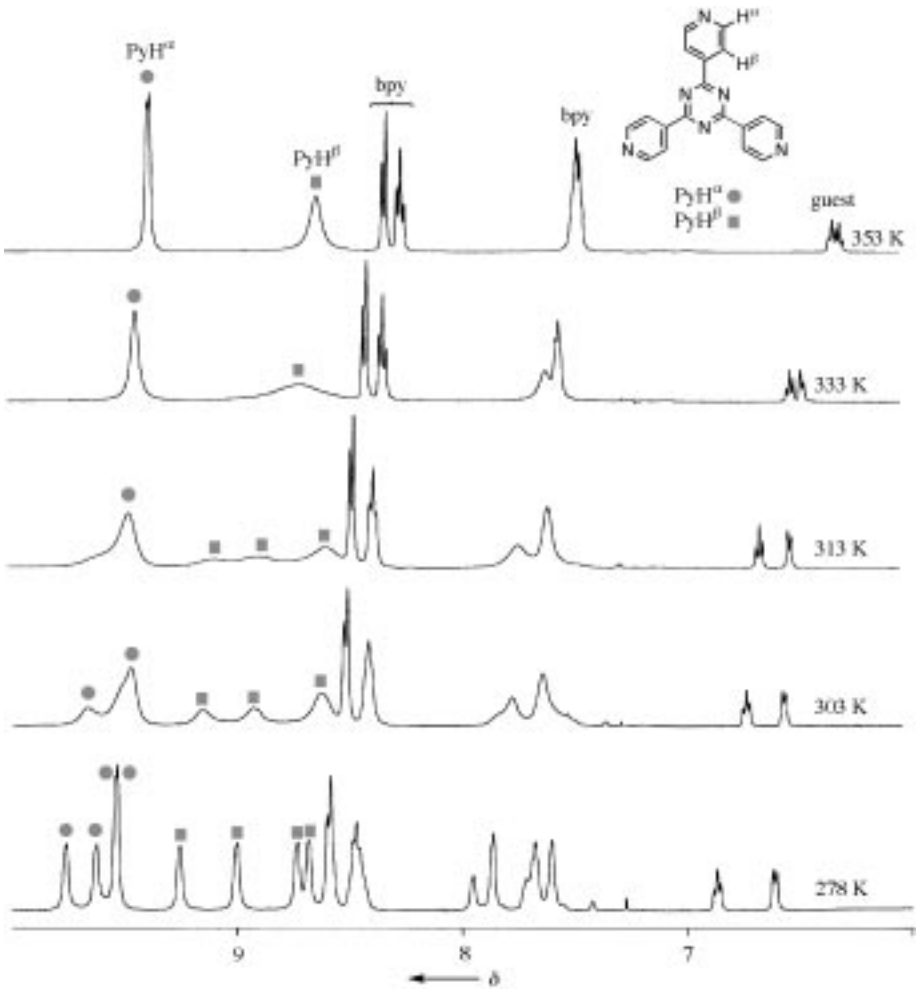

Figure 5. Variable-temperature ^{1}H NMR spectra of $\mathbf{3}\subset\mathbf{1}$ in D_2O. PyH$^{\alpha}$ and PyH$^{\beta}$ protons are marked with a circle (●) and a square (■). The coalescence at 313 K indicates the random movement of the guest above this temperature, which results in the loss of the apparent C_{3v} symmetry of the cage.

(d, py), 150.3 (d, py), 146.3 (s, py), 145.3 (s, py), 145.0 (s, py), 143.3 (d, bpy), 143.2 (d, bpy), 132.3 (d, diketone Ar), 132.3 (d, diketone Ar), 129.7 (d, diketone Ar), 128.5 (d, py, bpy), 127.8 (d, py), 127.6 (d, py), 126.5 (d, py), 126.2 (d, py), 124.9 (d, bpy), 124.8 (d, bpy), 124.1 (s, diketone Ar), 120.4 (s, diketone Ar), 107.4 (d, diketone Ar), 56.5 (q, diketone CH_3O-).

An aqueous solution of $(\mathbf{2a})_2\subset\mathbf{1}$ (7.5 mM, 0.5 mL) was allowed to stand at ambient temperature for a few days to give single crystals of $(\mathbf{2a})_2\subset\mathbf{1}$. A pale yellow crystal was selected under ambient conditions, attached to the tip of a glass fiber, and transferred to a Bruker SMART CCD diffractometer. Crystal data for $(\mathbf{2a})_2\subset\mathbf{1}$: $C_{164}H_{124}N_{48}O_{44}Pd_6$, $M_r = 4109.51$, crystal dimensions $0.50\times0.50\times0.50$ mm^3, tetragonal space group $P4_32_12$ (no. 96), $a = b = 29.535(3)$, $c = 31.351(4)$ Å, $V = 27349(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 0.998$ g cm^{-3}, $F(000) = 8288$, radiation, $\lambda(Mo_{K\alpha}) = 0.71073$ Å, $T = 298$ K, reflections collected/unique 88739/12358 ($R_{int} = 0.0615$). The structure was solved by direct methods (SHELXL-97) and refined by full-matrix least-squares methods on F^2 with 865 parameters. $R_1 = 0.1080$ ($I > 2\sigma(I)$), $wR_2 = 0.2809$, GOF 2.151; max./min. residual density 1.000/$-$0.655 e Å^{-3}. Further refinement was unsuccessful because of the high degree of disorder of the counterions and water molecules.

Preparation of $\mathbf{3}\subset\mathbf{1}$: *m*-Tolyltrimethoxylsilane (17.9 mg; 8.45×10^{-2} mmol, 5 equiv) was suspended in a solution of **1** (60.3 mg; 16.9×10^{-3} mmol, 6.5 mM) in H_2O (2.6 mL) at 100 °C and the mixture was stirred at the same temperature for 1 h. After the mixture was cooled down to room temperature, the solution was filtered, and evaporated to dryness. The crude product was purified by crystallization from H_2O to give $\mathbf{3}\subset\mathbf{1}$ as a pale yellow powder (61.5 mg; 15.3×10^{-3} mmol) in 90% yield. Physical data of $\mathbf{3}\subset\mathbf{1}$: m.p. >300 °C; ^{1}H NMR (500 MHz, D_2O, 278 K, TMS as external standard): $\delta = 9.77$ (d, 6H, PyH^a), 9.63 (d, 6H, PyH^e), 9.55 (d, 12H, PyH^{c,h}), 9.27 (d, 6H, PyH^b), 9.02 (d, 6H, PyH^g), 8.75 (d, 6H, PyH^f), 8.70 (br s, 6H, PyH^d), 8.61 (d, 12H, bpy), 8.48 (t, 12H, bpy), 7.9–7.8 (m, 3H, bpy), 7.87 (m, 6H, bpy), 7.68–7.72 (m, 9H, bpy), 7.61 (m, 6H, bpy), 6.88 (t, J = 7.0 Hz, 3H, Ar*H*), 6.63 (d, $J = 7.0$ Hz, 3H, ArH), 5.21 (d, $J = 7.0$ Hz, 3H, ArH), 4.45 (s, 3H, ArH), -0.37 (s, 18H, CH_3); ^{13}C NMR (125 MHz, D_2O, 278 K, TMS as external standard): $\delta = 169.8$ (s), 169.4 (s), 168.3 (s), 156.7 (s), 152.9 (d), 152.4 (d), 152.2 (d), 151.7 (d), 150.3 (d), 150.1 (d), 146.1 (s), 145.9 (s), 142.8 (d), 134.4 (s), 132.9 (d), 130.4 (d), 130.2 (d), 129.3 (s), 128.0 (d), 127.7 (d), 127.1 (d), 126.9 (d), 126.5 (d), 126.2 (d), 124.6 (d), 18.5 (q, CH_3); ^{29}Si NMR (99 MHz, D_2O, 278 K, TMS as external standard): $\delta = -63.9$; IR (KBr, cm^{-1}): 3400 (br s), 3030 (br s), 1603, 1576, 1520, 1375, 1313, 1249, 1032 (O-Si-O), 958, 869, 826, 802, 771, 744, 722, 701, 641, 520, 458; elemental analysis (%) calcd for $C_{153}H_{120}O_{42}N_{48}Pd_6Si_3\cdot16H_2O$: C 42.60, H 3.55, N 15.58; found: C 42.77, H 3.44, N 15.35.

An aqueous solution of $\mathbf{3}\subset\mathbf{1}$ (16.9×10^{-2} mmol, 2.6 mL) was allowed to stand at ambient temperature for a few days to give single crystal of $\mathbf{3}\subset\mathbf{1}$. A colorless crystal was selected under ambient conditions, attached to the tip of a glass fiber, and transferred to a Bruker SMART CCD diffractometer. Crystal data for $\mathbf{3}\subset\mathbf{1}$: $C_{153}H_{120}N_{48}O_{42}Pd_6Si_3$, $M_r = 4025.64$, crystal dimensions $0.40\times0.20\times0.20$ mm^3, trigonal space group $P\bar{3}c1$ (no. 165), $a = b = 27.6231(9)$, $c = 34.1541(17)$ Å, $V = 22569.3(15)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.185$ g cm^{-3}, $F(000) = 8112$, radiation, $\lambda(Mo_{K\alpha}) = 0.71073$ Å, $T = 105$ K, reflections collected/unique 70124/6814 ($R_{int} = 0.0568$). The structure was solved by direct methods (SHELXL-97) and refined by full-matrix least-squares methods on F^2 with 667 parameters. $R_1 = 0.1307$ ($I > 2\sigma(I)$), $wR_2 = 0.3578$, GOF 3.012; max./min. residual density 2.250/$-$0.874 e Å^{-3}. Owing to the high degree of disorder of the counterions and water molecules, further refinement was unsuccessful. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-155770 ($(\mathbf{2a})_2\subset\mathbf{1}$) and CCDC-155771 ($\mathbf{3}\subset\mathbf{1}$). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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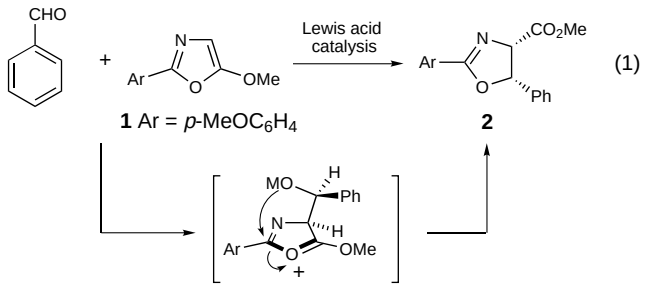
Chiral Salen – Aluminum Complexes as Catalysts for Enantioselective Aldol Reactions of Aldehydes and 5-Alkoxyoxazoles: An Efficient Approach to the Asymmetric Synthesis of *syn* and *anti* β-Hydroxy-α-amino Acid Derivatives**

David A. Evans,* Jacob M. Janey, Nabi Magomedov, and Jason S. Tedrow

The stereoselective synthesis of α-amino-β-hydroxy acids is a topic of ongoing interest as these structures are found in numerous peptide-based natural products including the vancomycin antibiotics.[1] The stereoselective synthesis of *trans*-5-substituted 2-oxazoline-4-carboxylates has been reported using an aldol reaction between aldehydes and methyl isocyanoacetate,[2] and the enantioselective version of this reaction has subsequently been developed by Ito and Hayashi et al.[3] A related aldol addition/acyl transfer process wherein 5-methoxyoxazole **1** functions as the glycine enolate synthon has been described by Suga and Ibata et al. [Eq. (1)].[4] In

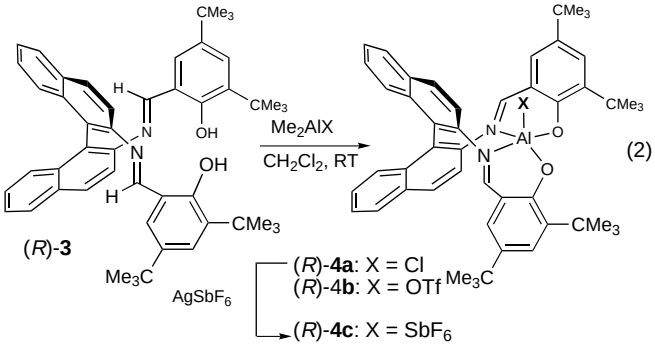


(1)

contrast to the Hayashi – Ito reaction, this addition affords the more versatile *cis*-2-oxazoline-4-carboxylates **2**. These substrates may be cleanly isomerized to their *trans* counterparts, thus providing access to both α-amino-β-hydroxy acid diastereomers from the same reaction sequence.

In the current rendition, the Suga – Ibata reaction [Eq. (1)] is mediated by an uncharacterized metal complex derived from trimethylaluminum and (*R*)- or (*S*)-BINOL. This chiral complex affords *cis*-**2** with good diastereoselection (4:1 – 20:1) but variable enantioselectivities. As described, this reaction suffers from high catalyst loading (30 %), long reaction times, and the requirement of excess aldehyde to drive the reactions to completion.[4] Here we describe the synthesis and characterization of the chiral aluminum complexes (*R*)-**4** and their use in the catalysis of this *cis*-diastereoselective aldol reaction with enantioselectivities in excess of 90 % for a range of aromatic aldehydes.

Chiral aluminum complex (*R*)-**4a** was prepared in quantitative yield by reaction of the enantiomerically pure diaminobinaphthyl-derived ligand[5] (*R*)-**3** with dimethylaluminum chloride [Eq. (2); CH_2Cl_2, 25 °C]. Complex (*R*)-**4a** was



(2)

isolated as a yellow, bench-stable amorphous solid. The structure of *rac*-**4a** was determined by X-ray crystallography.[6] The complex exhibits a distorted trigonal bipyramidal geometry with the chlorine atom located in the equatorial plane (Figure 1). The dihedral angle between the two naphthyl planes is 62°, creating a chiral environment around the aluminum metal center. The corresponding triflate complex (*R*)-**4b** was prepared by the reaction of (*R*)-**3** with dimethylaluminum triflate[7] (CH_2Cl_2, 0 → 25 °C) in 94 % yield. The structure of *rac*-**4b** was also determined by X-ray analysis. In contrast to the aluminum chloride complex *rac*-**4a**, the triflate complex *rac*-**4b** crystallized as the diaqua aluminum complex *rac*-**5**, and exhibited a distorted octahedral geometry with two *cis* water molecules coordinated to the metal center (Figure 1). According to the triflate – aluminum distance of 4.5 Å the triflate anion is fully dissociated. Inspection of the X-ray structure of *rac*-**5** indicates that the (*R*)-**3** ligand is bound to the aluminum center of (*R*)-**4b** in a Δ-*cis*-β configuration.[8]

Initial experiments revealed that $[Al(OH_2)_2\{(R)\text{-}\mathbf{3}\}][OTf]$ (**5**) (20 mol %) catalyzes the reaction of oxazole **1** with benzaldehyde (1.2 equiv, CH_2Cl_2, 3 Å MS, 25 °C, 20 h) to furnish (4*S*,5*S*)-oxazoline **2** in 98 % *ee* and with high diastereoselection (93:7 *dr*) favoring *cis*-**2**. However, catalyst turn-

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