Selective Enclathration of Linear Alkanols by a Self-assembled Coordination Cage. Application to the Catalytic Wacker Oxidation of ω-Alkenols

Michito Yoshizawa, Naoko Sato, and Makoto Fujita*
Department of Applied Chemistry, School of Engineering, The University of Tokyo and CREST,
Japan Science and Technology Agency (JST), 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656

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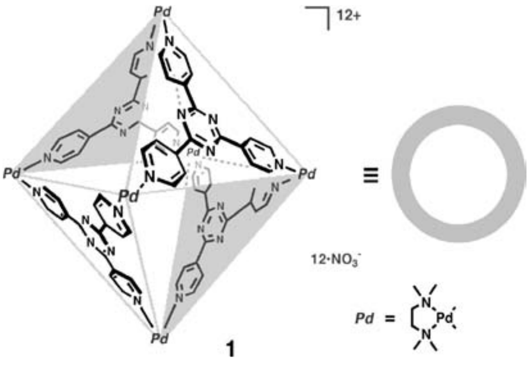
Linear alkanols were efficiently enclathrated by a self-assembled cage (**1**) to give a 1:2 host–guest complex as confirmed by NMR and crystallographic analyses. Cage **1** also enclathrated an ω-alkenol, 8-nonen-1-ol, and, upon heating, Wacker-type oxidation took place with a catalytic amount of **1** to give 9-hydroxynonan-2-one in a good yield.

Because of their flexible conformation, long alkyl chain compounds are poorly recognized by synthetic receptors.[1,2] Therefore, subsequent chemical transformation within the receptors has been hardly explored.[3] In nature, lipoxygenases[4] demonstrate both the selective recognition and the chemical reaction (oxidation) of long alkyl chain compounds within their binding pockets. To mimic the nature's system, we have examined the binding and the subsequent reaction of long alkyl chain compounds within self-assembled coordination cage **1**, which we have developed as a molecular flask during the last decade.[5] We have found that cage **1** binds linear alkanols and ω-alkenols quite efficiently and, in case of the ω-alkenols, subsequent Wacker-type oxidation is smoothly catalyzed by cage **1** (Scheme 1).

While binding a variety of relatively rigid organic compounds,[6] cage **1** hardly recognizes simple linear alkanes mainly because of a large entropy cost for binding these substrates. By simply attaching a hydroxyl group, we found the efficient binding of long alkyl chain compounds by cage **1**. When an excess amount (ca. 20 equiv.) of 1-nonanol (**2**) was suspended in an aqueous solution of **1** (5 mM) at 80 °C for 1 h, the quantitative formation of $\mathbf{1} \supset (\mathbf{2})_2$ complex was observed by ^{1}H NMR (Figure 1). The proton signals of **2** were significantly shifted upfield ($\Delta\delta$ = ca. $-0.8\sim-2.4$ ppm). Protons $H_{a\text{–}i}$ were fully assigned by H–H COSY NMR. From the integral ratio, the formation of a 1:2 host–guest complex was indicated. Similarly, longer alkanols (C_{10}–C_{13}) as well as decanoic acid (**3**) were also enclathrated within **1** giving rise to 1:2 complexes.[7] Since linear alkanes such as *n*-nonane were hardly enclathrated by cage **1**, the hydroxyl group is essential for binding linear alkyl chain compounds.



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Scheme 1.

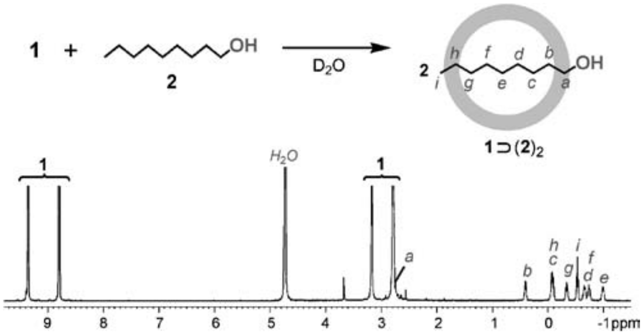

Figure 1. ^{1}H NMR spectrum (500 MHz, rt, D_2O, TMS as external standard) of $\mathbf{1} \supset (\mathbf{2})_2$ complex.

The formation of $\mathbf{1} \supset (\mathbf{2})_2$ complex was clearly displayed by crystallographic analysis. Pale yellow crystals suitable for X-ray crystallographic analysis grew from an aqueous solution of $\mathbf{1} \supset (\mathbf{2})_2$ by the very slow evaporation of water for two months.[8] The crystal structure revealed the orthogonal packing of two molecules of **2** in the cavity of cage **1** (Figure 2). The terminal hydroxyl group was situated at the opening of **1** being away from a Pd(II) center of **1** by ca. 5.1 Å. This distance indicated no interaction between the hydroxyl group and the cage. Probably, the hydroxyl group stabilized the $\mathbf{1} \supset (\mathbf{2})_2$ complex through hydrogen bonding with outside water molecules at the opening.[8] This

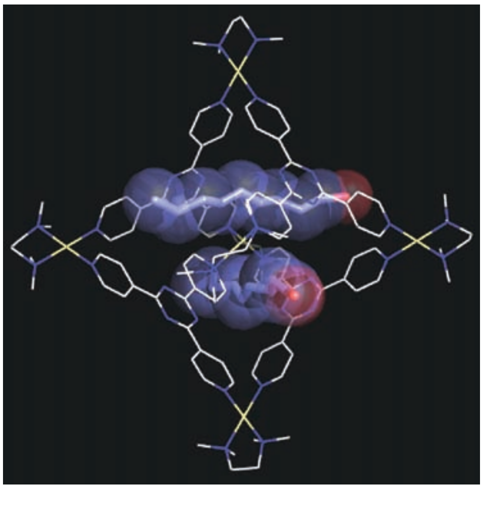

Figure 2. Crystal structure of $\mathbf{1} \supset (\mathbf{2})_2$ complex. Two molecules of **2** are orthogonally packed in the cavity of **1**.

agreed with the fact that the structural isomers, 3- and 4-nonanols, were poorly enclathrated by **1**.

We paid our attention to the proximity of the terminal methyl group to a Pd(II) corner of the cage, and examined the enclathration of ω-alkenols in expectation of the interaction of the olefin moiety with the Pd(II) center. When a large excess of 8-nonen-1-ol (**4**) (20 equiv. mol) was suspended in the aqueous solution of **1** at 80 °C for 5 h, we observed the Wacker-type oxidation of **4**. Namely the $CH_2{=}CH$– group of **4** was catalytically converted into a CH_3CO– group to give 9-hydroxynonan-2-one (**5**) in 66% yield.[9] Since the substrate **4** was insoluble in water, the reaction proceeded in an organic-aqueous two-phase system. ^1H NMR monitoring of the aqueous phase clearly revealed the efficient binding of **4** by the cage followed by the smooth transformation of **4** into **5**. At the beginning, the formation of inclusion complex $\mathbf{1} \supset (\mathbf{4})_2$ was confirmed (Figure 3a). Upon heating, new signals assignable to **5** appeared around 3.5–0.9 ppm (Figure 3b). The chemical shifts of **5** were not shifted upfield, indicating that **5** was excluded and replaced by more hydrophobic **4**. Large integral ratio of **5** in Figure 3b showed moderate water solubility of **5**.

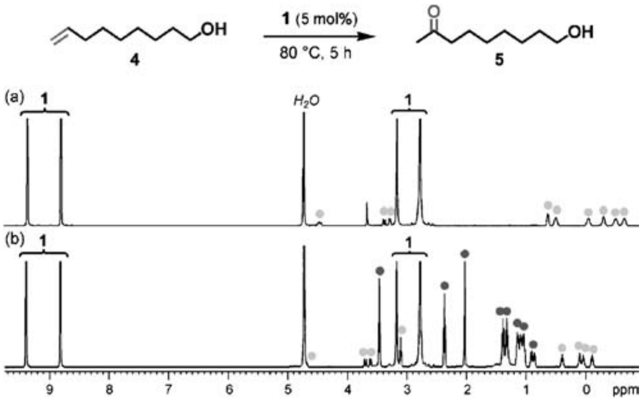

Figure 3. Catalytic Wacker oxidation of 8-nonen-1-ol (**4**) into 9-hydroxynonan-2-one (**5**) in the aqueous solution of **1** (5 mol %) at 80 °C for 5 h. ^1H NMR spectra (500 MHz, rt, D_2O, TMS as external standard) of the aqueous phase (a) before and (b) after the reaction (light gray circle: **4**, dark gray circle: **5**).

The observed catalytic turnover indicated the involvement of both inclusion and exclusion steps in the catalytic cycle. The inclusion step should be driven by the efficient hydrophobic interaction between substrate **4** and cage **1** as revealed by the X-ray structure (Figure 2). The exclusion step should be driven by the reduced host–guest hydrophobic interaction due to the conversion of the hydrophobic $CH_2{=}CH$– moiety into the hydrophilic CH_3CO– moiety. Since the Pd(II) component, (tmed)$Pd(NO_3)_2$,[10] hardly showed the catalytic activity (only 2% yield), the present reaction was obviously catalyzed by the Pd(II)-containing cage **1** itself. Interestingly, Pd(0) species that should be formed in the Wacker-type oxidation seemed to be aerobically reoxidized into Pd(II) without using reoxidizing coreagent such as a Cu(II) salt.

Previously, we reported the catalytic Wacker oxidation of styrene promoted by cage $\mathbf{1'}$ and (en)$Pd(NO_3)_2$.[11,12] Since $\mathbf{1'}$ did not show any catalysis, co-existence of (en)$Pd(NO_3)_2$ was essential. In the present case, the oxidation was efficiently promoted by cage **1** alone. The catalysis of cage **1** itself is ascribed to the geometry fixation of **4** in the cavity. In analogy to the X-ray geometry of **2**, the terminal $CH_2{=}CH$– group is expected to be very close to the Pd(II) center of the cage to facilitate the reaction. Under the same conditions, 9-decen-1-ol and 10-undecen-1-ol were less efficiently oxidized into 10-hydroxydecan-2-one and 11-hydroxyundecan-2-one in only 32 and 9% yields, respectively,[9] due probably to wrong orientation of the olefin moiety with respect to the Pd(II) center.

In summery, we have achieved the recognition of long alkyl chain compounds at a fixed position of the hydrophobic cavity of **1**. The subsequent catalytic oxidation of ω-alkenols is reminiscent of nature's system, where a substrate is recognized at the binding pocket and a metal center promotes a reaction at a specific position, and the product is excluded from the pocket.[4]

References and Notes

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7 $\mathbf{1} \supset (\mathbf{3})_2$, $\mathbf{1} \supset$ (1-decanol)$_2$, $\mathbf{1} \supset$ (1-undecanol)$_2$, $\mathbf{1} \supset$ (1-dodecanol)$_2$, and $\mathbf{1} \supset$ (1-tridecanol)$_2$ were formed in ca. 100, 80, 80, 55, and 30% yields, respectively, under the same conditions.

8 Crystal data for $\mathbf{1} \supset (\mathbf{2})_2$: $C_{113}H_{161}N_{45}O_{97}Pd_6$, MW = 4344.40, tetragonal, space group $I4_1/a$, $a = b = 26.1979(14)$ Å, $c = 31.687(3)$ Å, $V = 21747(3)$ Å^3, $T = 80(2)$ K, $Z = 4$, $D_{\rm calcd} = 1.327$ g cm^{-3}, λ (Mo Kα) = 0.71073 Å, 125649 reflections measured, 12513 unique ($R_{\rm int} = 0.0295$) which were used in all calculations. The structure was solved by direct method (SHELXL-97) and refined by full-matrix least-squares methods on F^2 with 582 parameters. $R_1 = 0.0758$ ($I > 2\sigma(I)$) and $wR_2 = 0.2173$, GOF 1.134; max./min. residual density 1.531/−1.049 eÅ^{-3}. Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-279341. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk). Near the hydroxyl group of **2**, a water molecule was observed within a hydrogen bonding distance (O···O: 2.85 Å).

9 The yield was estimated by NMR after **4** and **5** were extracted with $CDCl_3$ from the reaction mixture.

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