Synthesis and Cavity Size Effect of Pd-Containing Macrocycle Catalyst for Efficient Intramolecular Hydroamination of Allylurethane

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S *Supporting Information*

ABSTRACT: Palladium-containing macrocycle catalysts (**PdMCs**) with different ring sizes ranging from 24 to 30 members were synthesized. The intramolecular hydro-amination of an allylurethane (**AU**) catalyzed by **PdMCs** proceeded efficiently to afford the corresponding oxazolidinone (**OZ**) in 95% isolated yield. The dependence of the hydroamination of **AU** to **OZ** on the cavity size indicated that the reaction rate was clearly controlled by both substrate uptake and product release steps.

Development of supramolecular catalysts exhibiting elegant and efficient catalytic activity is an interesting and attractive topic for chemists.[1] Among those supramolecular catalysts, macrocycle catalysts represented by Cu-modified *β*-cyclodextrins[2] are characterized by facile preparation of a flexible framework and easy cavity control through the choice of reaction type. Because of the specific space for reactions around the metals in these catalysts, the catalysts often exhibit size-selective catalysis.[3−5] Nolte, Rowan, and co-workers performed detailed studies of metalloporphyrin-containing macrocycles that effectively catalyze the epoxidation of polymeric alkenes via a pseudorotaxane intermediate. This reaction mimics the reaction mode of *λ*-exonuclease,[6] which also proceeds via a pseudorotaxane intermediate with DNA. Meanwhile, we reported the intramolecular cyclization of allylurethanes to oxazolidinones catalyzed by a Pd-tethering macrocycle catalyst (**PdMC**)[7] after our finding of a similar transformation within a rotaxane molecule with four allylurethane moieties in the axle component.[7b] Interestingly, this catalytic hydroamination of allylurethanes with pyridyl moieties proceeds only when the allylurethane can form a pseudorotaxane complex with **PdMC**, suggesting that the reaction takes place in the catalyst cavity.[7] Although such macrocycle catalysts are expected to have a potential utility as a highly active and selective catalyst, to the best of our knowledge the characteristic features of their catalysis have not yet been investigated. We have studied the functions of **PdMCs** and recently found a unique catalysis specific to their macrocyclic structures that is disclosed in this paper. This **PdMC**-catalyzed intramolecular hydroamination of allylurethane depends largely upon the cavity size of **PdMC**, which affected not only the initial complexation with substrate followed by the Pd-catalyzed hydroamination but also the elimination of the product from the cavity.

PdMCs with three different ring sizes were prepared via a two-step reaction starting from the pincer-type ligand (**1**), as illustrated in Scheme 1 and according to our previously

**Scheme 1. Synthesis of Macrocycle Catalysts (PdMCs)**
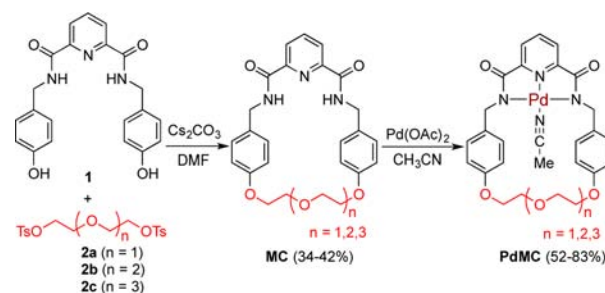
reported method for **PdMC30**.[7a] Namely, initial macrocycle formation from pyridine bisamide ligand **1** and an oligo-(ethylene glycol) (**MC24**, **MC27**, or **MC30**) was followed by palladium insertion into the cavity of the **MCs** using palladium(II) diacetate to afford the corresponding **PdMCs** in good yields. The structures of **PdMCs** were determined using ^{1}H NMR, MALDI-TOF MS and X-ray crystal structure analyses.

The association constant (K_a) between **PdMC** and a pyridine-containing bis(allylurethane) (**AU**) was evaluated by ^{1}H NMR spectra in d_6-DMSO at various temperatures (from 40 to 120 °C), as shown in Table 1.[8] The formation of a 1:1 inclusion complex (**AU ⊂ PdMC**) was readily confirmed by the

Table 1. Complexation between PdMCs and AU
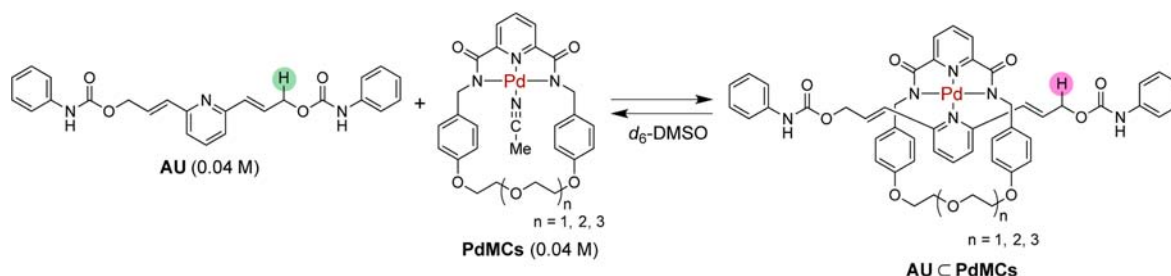
K_a $(M^{-1})^{a,b}$	40 °C	60 °C	80 °C	100 °C	120 °C
PdMC24	0	0	0	0	0
PdMC27	150 ± 59	110 ± 40	65 ± 15	47 ± 6	22 ± 6
PdMC30	880 ± 210	460 ± 60	190 ± 10	120 ± 10	59 ± 6

[a]Estimated by ^{1}H NMR spectrum. [b][**PdMCs**] = [**AU**] = 0.04 M.

upfield shift of the methylene proton peaks of **AU** (Figure S1). This result strongly suggested the formation of a pseudorotaxane complex on the basis of the similarity of NMR spectra to those obtained in our previous study.[7b] The thermodynamic parameters for pseudorotaxane formation were also determined by van't Hoff plot in d_6-DMSO (Figure S2 and Table S1).

Although no complex was formed with **PdMC24**, complexes were obtained with **PdMC27** and **PdMC30**, which had larger cavity sizes. As can be seen in Table 1, **AU ⊂ PdMC30** exhibited a larger K_a than **AU ⊂ PdMC27** at all temperatures, indicating that **AU ⊂ PdMC30** is more stable than **AU ⊂ PdMC27**. Clear MALDI-TOF-MS peaks corresponding to **AU ⊂ PdMC27** (m/z 1047.77 [M + Na]⁺, m/z 1047.25 calcd for $C_{52}H_{50}N_6O_{10}Pd$) and **AU ⊂ PdMC30** (m/z 1091.63 [M + Na]⁺, m/z 1091.28 calcd for $C_{54}H_{54}N_6O_{11}Pd$) were observed.

The cavity sizes of **PdMCs** have been estimated by X-ray analysis of the acetonitrile complexes or their derivative (Table 2). The structural data revealed that the distances between the Pd atoms and oxyethylene portions of **PdMC24**, **PdMC27**, and **PdMC30** were ca. 8.2, 9.8, and 9.9 Å,[7b] respectively. The cavity-sizes clearly increased as the length of the oxyethylene spacer increased, as expected. Furthermore, two face-to-face benzene rings in **PdMC24** were twisted to shrink its cavity width (5.8 Å), which is likely due to the shorter spacer length, which was not observed in **PdMC27** (7.0 Å) or **PdMC30** (7.1 Å). This constrained structure should control the formation of the pseudorotaxane-type complex with **AU**.

Next, a solution of **AU**, triethylamine (200 mol %), and **PdMC27** (20 mol %) in d_6-DMSO was heated at 80 °C for 95 h to give the corresponding hydroamination product (**OZ**) in 95% isolated yield with a diastereomer ratio of ca. 50:50. With **PdMC30**, the yield of **OZ** was 72%, and no **OZ** was obtained with **PdMC24**. The catalytic activity of **PdMC** was investigated by monitoring the ^{1}H NMR spectral changes during the reaction of **AU** in the presence of **PdMC** (20 mol %) and triethylamine in DMSO (Figure 1). No changes in the ^{1}H NMR spectrum were observed with **PdMC24**, even after 57 h, which was in contrast to **PdMC27** and **PdMC30**; the intramolecular hydroamination of **AU** to **OZ** with these catalysts readily occurred with 100% conversion, as shown in Figure 1a. These results clearly reveal that the complexation of **AU** with **PdMC** plays a key role in the reaction. Interestingly, the initial rate of the reaction with **PdMC30** was greater than that with **PdMC27**, although the reaction with **PdMC30** took longer to reach completion than the reaction with **PdMC27**.[9]

Table 2. Cavity Sizes for PdMCs Estimated by X-ray Analysis

[a]Calculated from the crystal structures of the acetonitrile complexes. [b]Structural parameters have been estimated from the crystal structure of a cyclic tetrameric derivative without acetonitrile ligands. Averaged values in the four crystallographically independent units are shown. See Supporting Information for details.

The time−conversion curves clearly indicate two different reaction stages (early and late). Considering all of the above-described results, a plausible reaction mechanism for the **PdMC**-catalyzed hydroamination of **AU** was proposed and is presented in Scheme 2.

The initial equilibrium formation of a pseudorotaxane complex between **PdMC** and **AU** is followed by the Pd-catalyzed hydroamination of one allylurethane moiety of **AU**. Successive hydroamination of the remaining allylurethane moiety proceeds with retention of the pseudorotaxane structure. Final **PdMC** elimination from the product−**PdMC** complex (**OZ ⊂ PdMC**) concludes a successful reaction cycle. Because no monohydroaminated product was detected in the ^{1}H NMR, the second hydroamination must be faster than the first one. In fact, the faster reaction with **PdMC30** versus **PdMC27** can be explained if the rate-limiting step is the initial monohydroamination from **AU ⊂ PdMC** (see the difference in
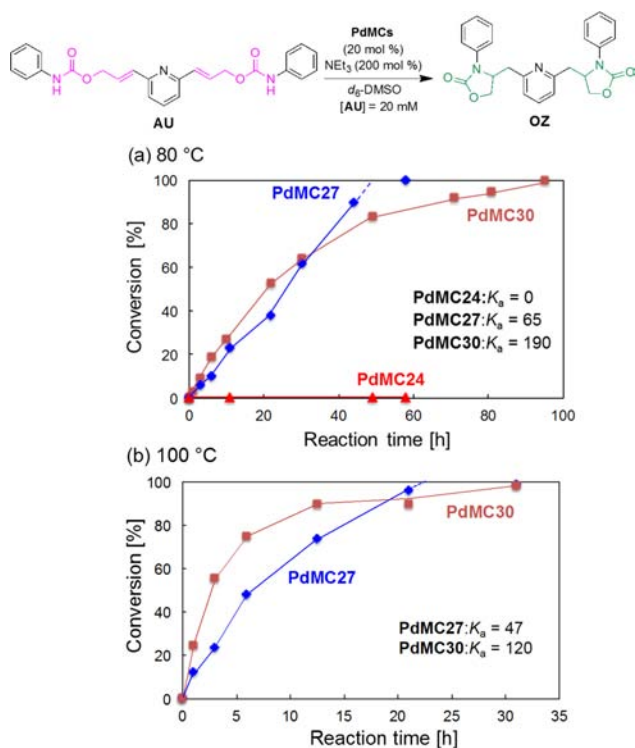
Figure 1. Time−conversion curves for the intramolecular hydroamination of **AU** catalyzed by **PdMCs** at (a) 80 and (b) 100 °C.

Scheme 2. Plausible Reaction Mechanism for the Intramolecular Hydroamination of AU Catalyzed by PdMC
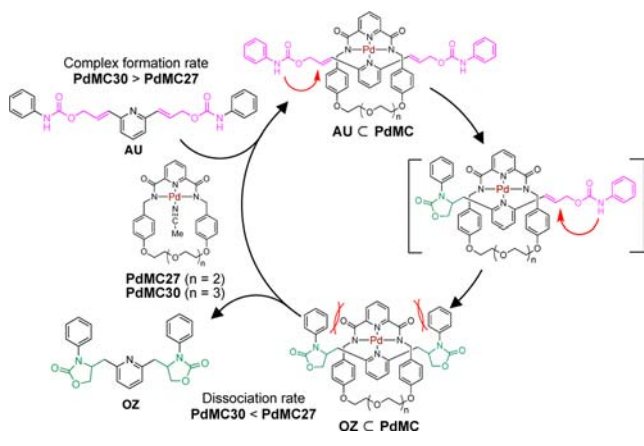
K_a values in Table 1). In addition, the faster completion of the reaction with **PdMC27** can be accounted for if **OZ ⊂ PdMC** dissociates more rapidly to regenerate **PdMC**, which can be attributed to greater steric strain. This conclusion is supported by previous results obtained for **PdMC30**, which cannot translate over the two oxazolidinone moieties formed in the axial positions because of the bulkiness in the rotaxane system.[7b] Next, to examine the complexation between **OZ** and **PdMCs**, the catalysts were each mixed with **OZ** under various conditions. Interestingly, neither **PdMC27** nor **PdMC30** formed a complex with **OZ** in d_6-DMSO at 25−100 °C. This result also supports the conclusion that the rate of the reaction with **PdMC27** in the latter period does not decrease significantly, even though the concentration of substrate **AU** is lower.

To verify our proposed mechanism, density functional theory (DFT) calculations were performed using Gaussian 09.[10] The geometries of **AU**, **OZ**, **PdMCs**, **AU ⊂ PdMCs**, and **OZ ⊂ PdMCs** were optimized without any constraints using DFT method at B3LYP/lanl2dz levels in the presence of DMSO.[11] The initial geometries of **PdMCs** and their derivatives were determined or estimated using the results from the X-ray structure analyses. Figure 2 summarizes the relative energy
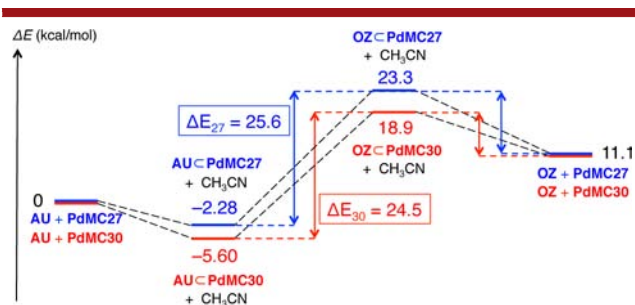
Figure 2. Relative energies for various intermediate structures involved in the **PdMC**-catalyzed intramolecular hydroamination of **AU**, for **PdMCs** with different cavity sizes. The energy values for **AU + PdMC27** (−2 103 116.267 kcal/mol) and **AU + PdMC30** (−2 199 643.318 kcal/mol) were calculated at the B3LYP/lanl2dz levels and set to zero for the **PdMC27** and **PdMC30** derivatives, respectively.

values for each conformation. The energy values for **AU ⊂ PdMCs** are lower than the totals of the individual energy values for **AU** and the corresponding **PdMCs**. Furthermore, **AU ⊂ PdMC30** is more stable than **AU ⊂ PdMC27**, being consistent with the actual K_a values (Table 1). Meanwhile, the relative energy increases dramatically for **OZ ⊂ PdMCs**. Notably, because the energies are even higher than the total values for **OZ** and **PdMCs**, **PdMCs** can form complexes with **AU** remaining in the reaction mixture immediately after dissociation of **OZ ⊂ PdMC** intermediate. In addition, the difference in the relative energies for **AU ⊂ PdMC** and **OZ ⊂ PdMC** intermediates increases for **PdMC27** ($\Delta E_{27} - \Delta E_{30} = 1.1$ kcal/mol), as does the difference for **OZ ⊂ PdMC** and **OZ + PdMC** (4.4 kcal/mol). The lower the concentration of **AU** or **AU ⊂ PdMC**, the larger the contribution of the dissociation of **OZ ⊂ PdMC** to the reaction rate. These calculated results are in good agreement with the experimental results, including the unusual acceleration at the latter reaction stage and the proposed mechanism.

Note that if the proposed mechanism is correct then an increase in both the reaction temperature and catalyst concentration should affect the reaction profile, i.e., reduce the importance of the **OZ ⊂ PdMC** dissociation step. This assumption was confirmed: when the reaction was performed at 100 °C, only a slight difference in the completion time was observed for the catalysts with different ring sizes (Figure 1b). Namely, the difference in the energy differences ΔE_{30} and ΔE_{27} was diminished, leading to a reduction in the difference in the reaction rates for **PdMC30** and **PdMC27**. Meanwhile, when the **PdMC** concentration was increased to 40 mol % (Figure 3), the reaction proceeded more rapidly than that with 20 mol % (Figure 1a), and the reaction with **PdMC30** reached completion sooner than that with **PdMC27**. Thus, a high catalyst concentration appears to weaken the acceleration effect observed with 20 mol % **PdMC27** because the reaction is complete before the effect (i.e., that **PdMC27** was eliminated
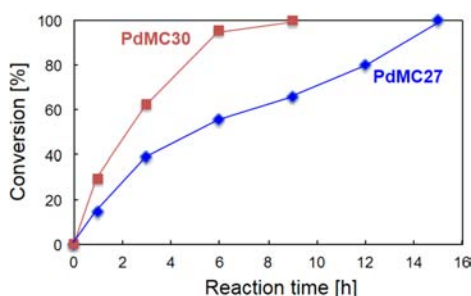
Figure 3. Time−conversion curves for the hydroamination of **AU** catalyzed by **PdMC27** and **PdMC30** (40 mol %) in d_6-DMSO at 80 °C.

from **OZ** faster than **PdMC30** because of the larger steric hindrance (Scheme 2)) can distinctly emerge. The predicted experimental results obtained here indicate that the selection of macrocycle catalysts with appropriate cavity sizes is crucial for reactions that proceed via pseudorotaxane intermediates.

In this study, Pd-containing macrocycle (**PdMC**) complexes with three different cavity sizes were prepared and characterized. In addition, **PdMCs** with an appropriate cavity size efficiently catalyzed the intramolecular hydroamination of **AU** once incorporated into their cavities. Building on our previous report on the size effect of substrates,[7b] the results obtained in the present study clarified the importance of the cavity size of the catalysts. The current results also provide further valuable insight into catalyst structure design.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and analytical and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(9) The reaction orders for hydroamination of **AU** were evaluated. As results, the reaction orders using **PdMC27** and **PdMC30** at 100 °C and **PdMC30** at 80 °C were assumed to be almost one. The reaction with **PdMC27** at 80 °C did not fit a first-order equation. This result also suggested the unique catalytic activity of **PdMC27**.

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