Metallo-Enzyme Model in Pure Water: Cyclodextrin-Lanthanide Tris(perfluoroalkanesulfonyl)methide and Bis(perfluoroalkanesulfonyl)amide Complexes

Joji Nishikido,*[a] Masayuki Nanbo,[a] Akihiro Yoshida,[a] Hitoshi Nakajima,[a] Yousuke Matsumoto,[b] Koichi Mikami*[b]

[a] The Noguchi Institute, Tokyo 173-0003, Japan
[b] Department of Applied Chemistry, Tokyo Institute of Technology, Meguro-ku, Tokyo 152-8552
Fax +81(3)57342776; E-mail: kmikami@o.cc.titech.ac.jp

Received 1 July 2002

Abstract: Inclusion complexes of cyclodextrin/cyclodextrin copolymer and lanthanide tris(perfluorobutanesulfonyl)methide/bis(perfluorobutanesulfonyl)amide, namely metallo-enzyme model, are efficient and recyclable super Lewis acid catalysts, which can promote Diels–Alder and Mukaiyama-aldol reactions in pure water.

Key words: cyclodextrin, Lewis acids, catalysis, lanthanides, aqueous reactions

Enzymes are gigantic proteins that function as catalysts for biological reactions particularly in water. These enzymes include the structure of the hydrophobic pocket for inclusion of organic apolar substrates, and the reaction kinetics increased at the hydrogen bonding or metallo-complexation sites. A wide variety of Lewis acid metal complexes have thus been developed to realize unique reactivities and high selectivities close to those attained by enzymes, however, without any hydrophobic pocket.[1,2] Here we report a metallo-enzyme model consisting of hydrophobic pocket and Lewis acid metal complex, as a recyclable catalyst in pure water.

How can we design a metallo-enzyme model consisting of Lewis acid catalysts and hydrophobic pocket, and immobilization thereof in pure water?[3,4] Cyclodextrin (CD) is a naturally occurring host molecule and can form insoluble crystalline inclusion complexes with organic molecules.[5–8] Thus, we designed CD inclusion complexes of trivalent lanthanide [Ln(III)] tris(perfluoroalkanesulfonyl)methide[9] [abbreviated as Ln(C_n-methide)$_3$] and bis(perfluoroalkanesulfonyl)amide[9] [abbreviated as Ln(C_n-amide)$_3$] as super Lewis acidic and completely recyclable catalysts. Particularly, ytterbium and scandium methide and amide complexes with fluorous pony tails[10–13] (Figure 1) effectively formed the inclusion complex[14] with CD. It was reported that CD forms inclusion complexes with fluorocarbon surfactants, due to hydrophobic interaction.[5,15] Since the chain length of perfluorobutane group is nearly equal to the length of cyclodextrin ring, it is assumed that the metal locates just outside the hydrophobic pockets of CD. Thus, organic substrates are expected to be readily activated by coordination of the center metal in the inclusion complexes.

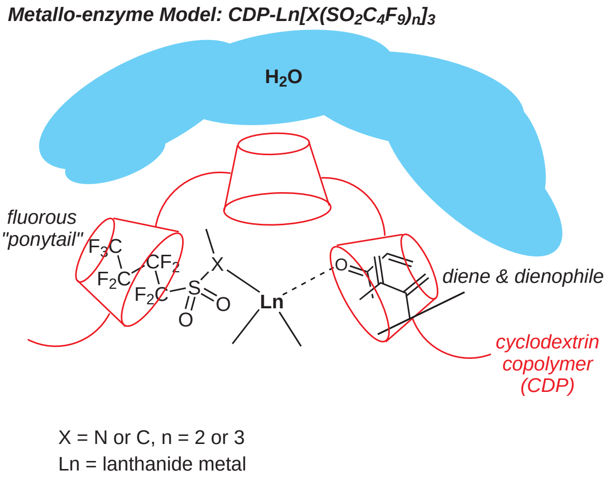


Figure 1

First, the synthesis of CD- and CD copolymer (CDP)-Ln methide and amide inclusion complexes were examined. CD and β-CD/epichlorohydrin copolymer (CDP)[16] were suspended in water at room temperature, and then Ln methide or amide was added to this solution or suspension. The complexes of β- and γ-CD with Ln C_n-methide and C_n-amide (n = 4) were precipitated as inclusion complexes, with the exception of α-CD, washed with water, and dried at 60 °C under 0.1 mmHg.

Scanning transmission electron microscopy (STEM) micrographs[17] or Yb, F, S energy-dispersive X-ray (EDX) maps of CD- and CDP-Yb bis(perfluorobutanesulfonyl)amide [abbreviated as Yb(C_4-amide)$_3$][13] thus obtained are shown in Figure 2 and Figure 3, respectively. The Yb amide was found to be equally dispersed and immobilized in the hydrophobic cavity of CD and CDP, as observed by Yb, F and S mapping. The amount of Ln(C_4-methide)$_3$ or Ln(C_4-amide)$_3$ in the cavity of CDP could be controlled to be ca. 50% by varying the amount of the Ln complexes.[18] Lanthanide triflates, bis(trifyl)amides and tris(trifyl)methides did not form any inclusion complex with β-CD or γ-CD. These results indicate that CD forms inclusion complexes selectively with $Ln[C(SO_2C_nF_{2n+1})_3]_3$ and $Ln[N(SO_2C_nF_{2n+1})_2]_3$, (n = 4).

Synlett 2002, No. 10, Print: 01 10 2002.
Art Id.1437-2096,E;2002,0,10,1613,1616,ftx,en;U03002ST.pdf.

ISSN 0936-5214

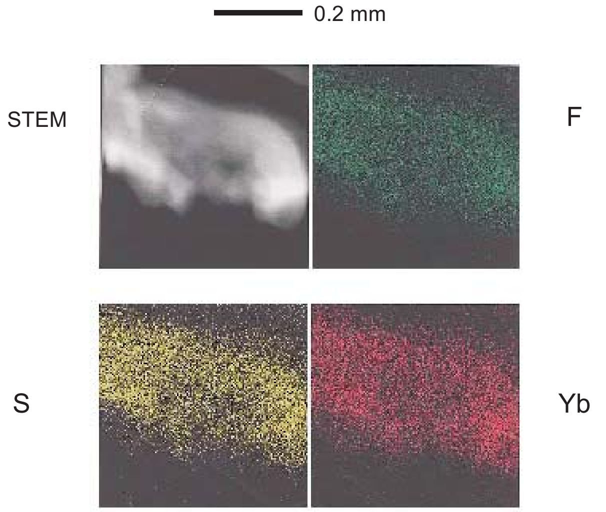


Figure 2 Scanning transmission electron microscopy (STEM); micrograph and Yb, F, S energy-dispersive X-ray (EDX); map of **CD**-Yb bis(perfluorobutanesulfonyl)amide

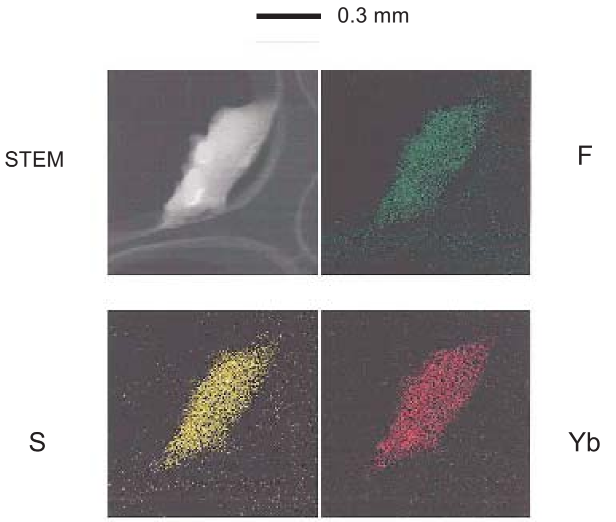
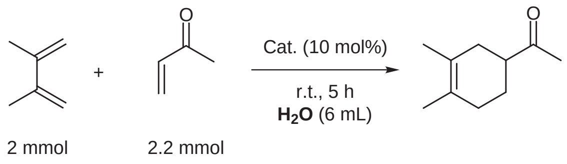


Figure 3 Scanning transmission electron microscopy (STEM); micrograph and Yb, F, S energy-dispersive X-ray (EDX); map of **CDP**-Yb bis(perfluorobutanesulfonyl)amide

The catalytic activities and recycling of the CDP-Ln complexes were then examined for C–C bond-forming reactions such as the Diels–Alder (D–A) reaction (Scheme 1),[19,20] since the D–A reaction catalyzed by CD in water has been reported by Breslow.[21,22] The D–A reaction of 2,3-dimethyl-1,3-butadiene with methyl vinyl ketone was carried out in the presence of a catalytic amount of CDP-Yb C_4-methide complex in pure water (Table 1). Typical experimental procedure is as follows: To a mixture of 2,3-dimethyl-1,3-butadiene (0.16 g, 2 mmol) and methyl vinyl ketone (0.15 g, 2.2 mmol) in water (6 mL) was added 10 mol% of CDP-Yb(C_4-methide)$_3$ [0.2 mmol of Yb(C_4-methide)$_3$] at room temperature. After stirring for 5 hours at that temperature, D–A adduct was extracted by 1,2-dichloroethane. The 1,2-dichloroethane layer was analyzed by GC using *n*-nonane as an internal standard. The chemical yield was 99% (entry 9). Under the same reaction conditions, the adduct was obtained in only low yields (9%, 9%) in the presence of Yb(OTf)$_3$ (entry 5) or Yb(NTf$_2$)$_3$ (entry 6). Both 20 mol% of CDP itself (entry 7) and Yb C_4-methide catalyst (entry 8) gave the adduct in low yields (12% and 39%). Thus, the CDP-Yb methide complex gave a much higher yield than either CDP or Yb methide complex did. These results clearly show that the Yb methide complex-catalyzed reaction is further accelerated by hydrophobic association of the D–A substrates within the inclusion complex in water. The Yb methide complex was completely (>99.9%) recovered as determined by atomic emission spectrometry analysis.



Scheme 1

Table 1 Diels–Alder Reactions in Water

Entry	Catalyst[a]	Yield (%)[d]
1	None	8
2	D-glucose[b]	8
3	β-CD[b]	9
4	γ-CD[b]	9
5	Yb(OTf)$_3$	9
6	Yb(NTf$_2$)$_3$	9
7	CDP[b]	12
8	Yb(C_4-methide)$_3$	39
9	CDP-Yb(C_4-methide)$_3$	99
10	CDP-Yb(C_4-methide)$_3$[c]	25

[a] CDP: β-CD/epichlorohydrin copolymer; Yb(C_4-methide)$_3$: Yb[C(SO$_2$-*n*-C_4F_9)$_3$]$_3$; CDP-Yb(C_4-methide)$_3$: CDP complex of Yb(C_4-methide)$_3$.
[b] Catalyst (20 mol%) was used.
[c] The reaction was carried out in dichloromethane (6 mL).
[d] Calculated by GC analysis using *n*-nonane as an internal standard.

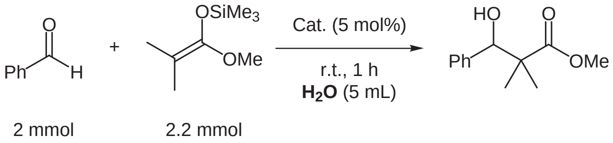
The recycling was then conducted in the D–A reaction at room temperature (25 °C) for 8 hours using the CDP-Sc(C_4-methide)$_3$ complex (5 mol%) in water (Table 2, Scheme 1). The D-A adduct was obtained in good isolated yield (90%). The Sc C_4-methide complex was completely (>99.9%) recovered as determined by atomic emission spectrometry analysis, and used in a recyclable manner without any loss of catalytic activity of CDP-Sc methide complex (yields: 1st run: 95%; 2nd run: 94%; 3rd run: 95%; 4th run: 94%).

Table 2 Diels–Alder Reactions Catalyzed by CDP-Sc(C_4-methide)$_3$[a] in Water

Cycle[b]	Yield (%)[c]
1	95
2	94
3	95
4	94 (90)[d]

[a] CDP-Sc(C_4-methide)$_3$: CDP complex of Sc(C_4-methide)$_3$.
[b] The catalyst was recycled by filtration.
[c] Calculated by GC analysis using *n*-nonane as an internal standard.
[d] Isolated yield.

The CDP-Yb methide complex was also completely recycled for Mukaiyama-aldol reaction of benzaldehyde with ketene silyl acetal (KSA) derived from methyl isobutyrate in water (yields: 1st run: 74%; 2nd run: 72%; 3rd run: 73%) (Scheme 2, Table 3). The inclusion complex is thus an efficient and immobilized Lewis acid catalyst despite unstable KSA in water.



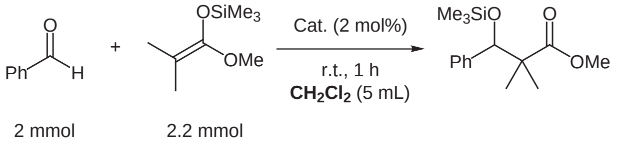
Scheme 2

Table 3 Mukaiyama-aldol Reactions Catalyzed by CDP-Yb(C_4-amide)$_3$ in Water

Cycle[b]	Yield (%)[c,d]
1	74
2	72
3	73

[a] CDP-Yb(C_4-amide)$_3$: CDP complex of Yb(C_4-amide)$_3$.
[b] The catalyst was recycled by filtration.
[c] Based on benzaldehyde.
[d] Calculated by GC analysis using *n*-nonane as an internal standard.

To prevent KSA from decomposing, we attempted Mukaiyama-aldol reaction in organic solvent (Scheme 3, Table 4). Surprisingly, the aldol product was obtained quantitatively in dichloromethane (entry 1), in contrast to D–A reaction product. Moreover, the CDP-Yb amide complex was completely recycled in dichloromethane (yields: 1st run: 99%; 2nd run: 99%; 3rd run: 99%; 4th run: 98%; 5th run: 99%). After the reaction, no Yb complex was detected in dichloromethane by atomic emission spectrometry analysis. The inclusion complex is thus an extremely efficient and immobilized Lewis acid catalyst even in an organic solvent. It is conceivable that Yb amide complex can be immobilized in the hydrophobic cavity of CDP because of its low solubility in dichloromethane.



Scheme 3

Table 4 Mukaiyama-aldol Reactions Catalyzed by CDP-Yb(C_4-amide)$_3$ in Dichloromethane

Cycle[b]	Yield (%)[c,d]
1	99
2	99
3	99
4	98
5	99

[a] CDP-Yb(C_4-amide)$_3$: CDP complex of Yb(C_4-amide)$_3$.
[b] The catalyst was recycled by filtration.
[c] Based on benzaldehyde.
[d] Calculated by GC analysis using *n*-nonane as an internal standard.

Continuous-flow system was finally examined in dichloromethane using a column packed with CDP-Yb(C_4-amide)$_3$ complex (column volume: 5 mL, flow rate: 30 mL/h, contact time: 10 min, the amount of catalyst: Yb(C_4-amide)$_3$, 1 mmol, otherwise in the same concentration as shown in Scheme 3) for the Mukaiyama-aldol reaction (Figure 4).[23,24] The catalytic activity of the present immobilized catalyst did not decrease even after 44 hours (conversion of benzaldehyde: continuously 98–99%). The turn over number of the Lewis acid catalyst [TON: aldol product (mol)/Lewis acid catalyst (mol)] reached up to 517–523 after 44 hours.

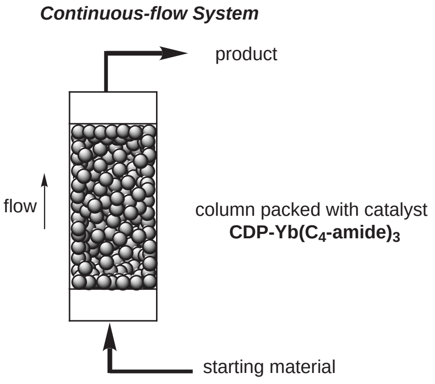


Figure 4

In summary, we have disclosed that Ln methide or amide as CDP or CD inclusion complexes are extremely efficient and immobilized Lewis acid catalysts due to the powerful electron-withdrawing ability of the perfluoroalkyl ponytails effectively included in the hydrophobic cavity of CDP or CD. The inclusion complexes give much higher catalytic efficiency as a metallo-enzyme model than their components independently used in either CDP or simple lanthanide catalyst form. Not only batch system including complete recovery followed by reuse after simple filtration but also advanced continuous-flow system, have thus been established without loss of their catalytic activities.

References

(1) (a) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, **2000**. (b) Santelli, M.; Pons, J. M. *Lewis Acid and Selectivity in Organic Synthesis*; CRC Press: New York, **1996**. (c) *Selectivities in Lewis Acid Promoted Reactions*; Schinzer, D., Ed.; Kluwer Academic Publishers: Dordrecht, **1988**.
(2) (a) Mikami, K.; Nakai, T. In *Kagaku Zokan*, Vol. 124; Kagaku Dojin: Tokyo, **1995**, 177. (b) Mikami, K.; Terada, M.; Matsuzawa, H. *Angew. Chem. Int. Ed.* **2002**, *41*, 5000.
(3) Pugin, B.; Blaser, H.-U. In *Comprehensive Asymmetric Catalysis*, Vol. 3; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **1999**, 1367.
(4) (a) Lubineau, A.; Auge, J. *Top. Curr. Chem.* **1999**, *206*, 1. (b) Sinou, D. *Top. Curr. Chem.* **1999**, *206*, 41. (c) Cornils, B. *Top. Curr. Chem.* **1999**, *206*, 133. (d) *Organic Reactions in Water*; Grieco, P., Ed.; Blackie Academic and Professional: London, **1998**. (e) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, **1997**.
(5) (a) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: Berlin, **1978**. (b) Shannon, R. D. *Acta Crystallogr., Sect. A* **1976**, *32*, 751.
(6) Szejtli, J. *Cyclodextrin and Their Inclusion Complexes*; Akademiai: Kiado, **1982**.
(7) *Cyclodextrin*; Toda, F.; Ueno, A., Eds.; Sangyo-Tosho: Tokyo, **1995**.
(8) (a) *Comprehensive Supramolecular Chemistry*, Vol. 3; Szejtli, J.; Osa, T., Eds.; Pergamon: Oxford, **1996**. (b) Tsuruta, H.; Yamaguchi, K.; Imamoto, T. *Chem. Commun.* **1999**, 1703.
(9) Koppel, I. A.; Taft, R. W.; Anvina, F.; Zhu, S.-Z.; Hu, L.-Q.; Sung, K. S.; DesMarteau, D. D.; Yagupolskii, L. M.; Yagupolsukii, Y. L.; Kondratenko, N. V.; Volkonskii, A. Y.; Vlasov, V. M.; Notario, R.; Maria, P.-C. *J. Am. Chem. Soc.* **1994**, *116*, 3047.
(10) Horvath, I. T.; Rabai, J. *Science* **1994**, *266*, 72.
(11) Gladysz, J. A. *Science* **1994**, *266*, 55.
(12) Curran, D. P. *Angew. Chem. Int. Ed.* **1998**, *37*, 1174.
(13) (a) Sc- and Yb$[N(SO_2C_4F_9)_2]_3$: Nishikido, J.; Nakajima, H.; Saeki, T.; Ishii, A.; Mikami, K. *Synlett* **1998**, 1347. (b) Mikami, K.; Kotera, O.; Motoyama, Y.; Sakaguchi, H. *Synlett* **1996**, 171. (c) Sc- and Yb$[C(SO_2C_8F_{17})_3]_3$: Mikami, K.; Mikami, Y.; Matsumoto, Y.; Nishikido, J.; Yamamoto, F.; Nakajima, H. *Tetrahedron Lett.* **2001**, *42*, 289. (d) Yb$[C(SO_2C_6F_{13})_2SO_2C_8F_{17}]_3$: Barret, A. G. M.; Braddock, D. C.; Catterick, D.; Henshke, J. P.; McKinnell, P. M. *Synlett* **2000**, 847.
(14) Recently, it was reported that CD forms inclusion complexes with fluorocarbon surfactants, due to hydrophobic interaction: Wilson, L. D.; Verrall, R. E. *J. Phys. Chem. B* **1997**, *101*, 9270.
(15) (a) Zhang, B.; Breslow, R. *J. Am. Chem. Soc.* **1997**, *119*, 1676. (b) Otto, S.; Engberts, J. B. F. N.; Kwak, J. C. T. *J. Am. Chem. Soc.* **1998**, *120*, 9517. (c) Tian, H.-Y.; Chen, Y.-J.; Wang, D.; Zeng, C.-C.; Li, C.-J. *Tetrahedron Lett.* **2000**, *41*, 2529. (d) Manabe, K.; Mori, Y.; Wakabayashi, T.; Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 7202.
(16) Comm. available from Aldrich Chemical Company, Inc.: Cat. No. 33, 256-9.
(17) Williams, D. B.; Carter, C. B. *Transmission Electron Microscopy*; Plenum Press: New York, **1996**.
(18) The full percentage of Ln complex/γ-CDP-Ln complex was found to reach only 60% because of the steric repulsion. Indeed, elemental analysis showed that CDP formed a 59% inclusion complex of Ln(C_4-methide)$_3$: Calcd Yb, 3.64%. Found: Yb, 3.61%.
(19) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289.
(20) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.
(21) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.
(22) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1988**, *110*, 5613.
(23) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357.
(24) Bach, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 417.