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Cyclodextrin in Artificial Enzyme Model, Rotaxane, and Nano-material Fabrication

HUI-LAN CHEN*, BIN ZHAO and ZHIBIN WANG
State Key Laboratory of Coordination Chemistry, Nanjing University, 210093, Nanjing, P.R. China

Key words: coenzyme B_{12}, cyclodextrin, holo-enzyme model, nano-metal oxide, rotaxane and pseudorotaxane

Abstract

In this paper, we summarized our recent studies on the holo-enzyme model in mimicry of coenzyme B_{12} by cyclodextrin/alkyl(aqua)cobaloxime supramolecular complexes, the [2] and [3] rotaxanes based on cyclodextrin and bisimidazolyl compound, and nano-metal oxide preparation through thermal decomposition of metal acetates with β-cyclodextrin coating.

Introduction

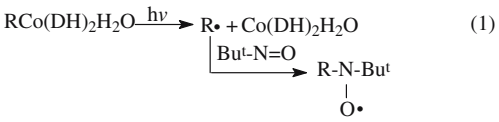
Cyclodextrins are a class of cyclic oligosaccharides consisting of six (α), seven (β) or eight (γ) α-1,4 linked D-glucopyranose units. They contain a toroidal hydrophobic cavity capable of including a variety of inorganic and organic guest species, and show regio- and stereospecificity with respect to the substrate and product during catalytic processing [1]. Other than a great lot of industrial applications, cyclodextrins have been widely employed to construct novel supramolecular assemblies, such as psuedorotaxanes, rotaxanes, and catenens, which have potential applications in molecular switches and molecular mashines [2]. They could also act as artificial enzymes to mimic natural biological systems [3] and apply in fabrication of nano-scale materials to improve morphology, size distribution and characters [4]. Here, we report our recent research works related to the above three areas.

B_{12}-artificial enzyme based on cyclodextrin

Alkylcobaloximes ($RCo(DH)_2L$, where DH = dimethylglyoxime, R = alkyl, L = neutral monodentate axial ligand) are a kind of widely studied coenzyme B_{12} (deoxyadenosylcobalamin 5′-, AdoCbl) model compounds having a σ-type Co–C bond [5]. It has been recognized that the key step of those B_{12}-dependent enzymatic reactions is related to homolysis of the Co–C bond to produce a 5′-deoxyadenosyl radical (Ado·) and a $\cdot B_{12r}(Co^{II})$ species [6]. It is estimated that the rate of Co–C bond cleavage in the holoenzyme complex is at least 10^{12} time faster than in the enzyme-free $AdoB_{12}$ [7, 8]. The enzyme protein probably induces the conformational changes of the coring ligand and causes steric interactions between the axial and equatorial ligands leading to a weakening of the Co–C bond. Therefore, investigation of B_{12} holo-enzyme model has attracted more and more attention [9]. Breslow *et al.* [10] prepared a cyclodextrin-bound B_{12}, in which cyclodextrin is attached to cobalamin by a direct bond. A substrate and B_{12} could be bound together in a receptor site, so that intracomplex atom transfer to the carbon radical can mimic the opening stages of the general mechanism. In the mean time, an adenosyl-cyclodextrin conjugate has been synthesized in the Kraütler group [11].

Recently, a series of alkyl(aqua)cobaloxime/CD inclusion complexes (R = *n*-C_3H_7, *n*-and *i*-C_4H_9, *n*-C_5H_{11}, *n*-C_6H_{13}, *c*-C_6H_{11}, $CH_3CO_2(CH_2)_2$ *et al.*, and CD = α- and β-), in which guest and host associate through non-covalent interaction and CD could act as artificial enzyme, were prepared and characterized by our research group. The ^1H NMR study and crystal structure analysis of these complexes revealed that the alkyl group of alkyl(aqua)cobaloxime enters the cavity of CD from the wider opening, and there are different structural and conformational changes in alkyl(aqua) cobaloximes after the inclusion [12]. Figure 1 illustrated some examples of them.

By using the spin-trapping EPR technique, we studied the anaerobic photolysis of coenzyme B_{12} and its analogs, as well as alkyl(aqua)cobaloximes (R = *n*-, *iso*-, *sec*-butyl, *c*-pentyl, *c*-hexyl, methoxycarbonylethyl, 2,2-(ethoxycarbonyl)propyl) in the absence and presence of β-cyclodextrin.



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* Author for correspondence. E-mail: hlchen@nju.edu.cn

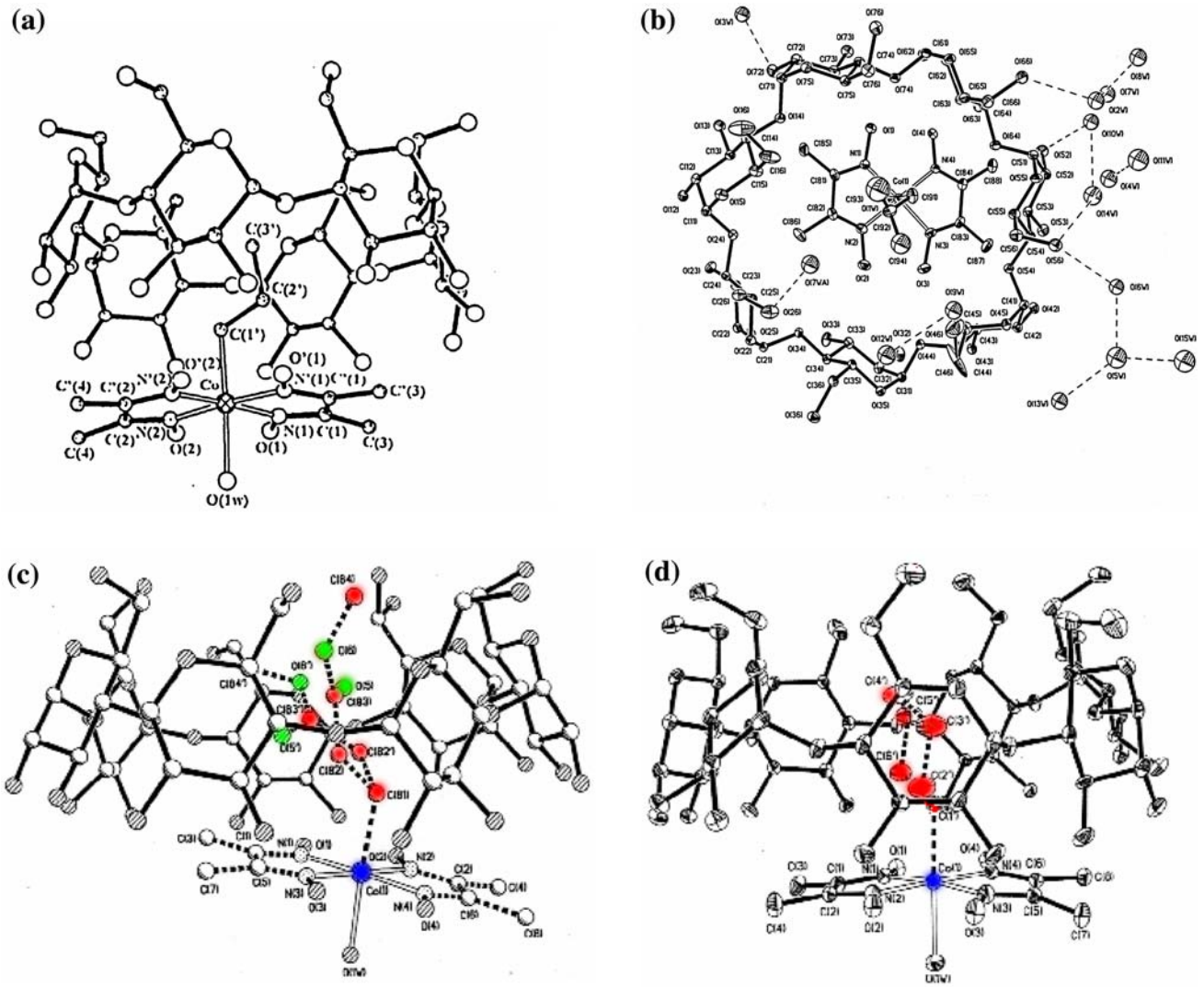
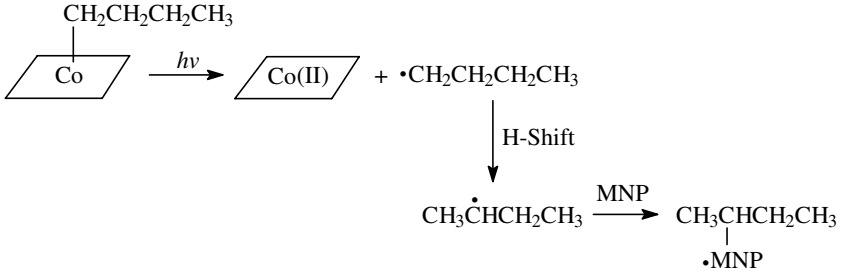


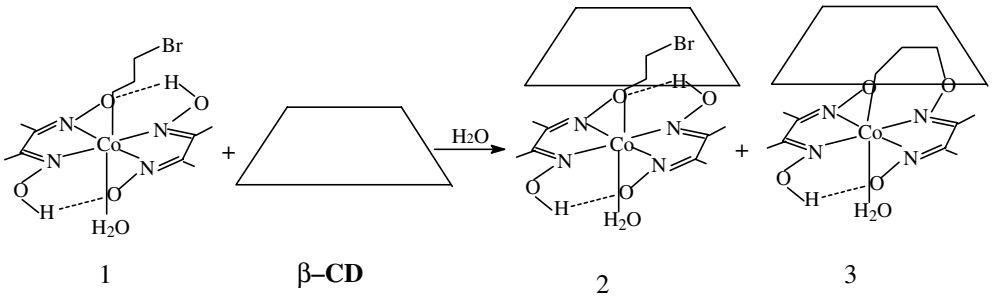
Figure 1. Crystal structures (a) *n*-PrCo(DH)$_2$ H$_2$O/α-CD (b) *i*-Bu Co(DH)$_2$ H$_2$O/*β*–CD (c) CH$_3$COO(CH$_2$)$_2$Co(DH)$_2$H$_2$O/*β*-CD (d) *c*-C$_6$H$_{11}$Co(DH)$_2$H$_2$O/*β*-CD

The 1,2-rearrangement products, which is a short-lived radicals arise from the Co–C bond cleavage of the cobalamins and cobaloximes, have been characterized. The changes of EPR parameters indicate that the formed spin adduct of radical and MNP(2-metyl-2-nitrosopropane) could be included in the *β*-cyclodextrin's cavity [12c, 13]. It has been also found that only the primary alkyl radical, such as *n*-butyl , undergo a 1,2-hydrogen shift solely (see Scheme 1*)* while *i*-butyl exhibits both 1,2-hydrogen and 1,2-metyl shift, and *β*-cyclodextrin could stabilize the primary one to a certain extent [14].

The electrochemical reduction of a series of alkyl(aqua)cobaloximes in the absence and presence of *β*-CD was investigated by means of cyclic voltammetry. It is revealed that *β*-CD facilitates the cleavage of Co–C bond during the reduction process of alkylcobaloxime [15]. In addition, a novel *β*-CD induced elimination were



Scheme 1.



Scheme 2.

found during the process of preparing bromopropyl(aqua)cobaloxime/β-CD inclusion complexes [16]. According to the FAB-MS and single crystal X-ray diffraction one of the product is a new cobalt-to-oxime bridged organocobaloxime inclusion complex (**3** in the Scheme 2). It is suggested that cyclodextrin provides a confined environment in the reaction for HBr elimination, which may has potential application for catalysis and to prepare new type of organo-metallic complexes with novel structure and special reactivity.

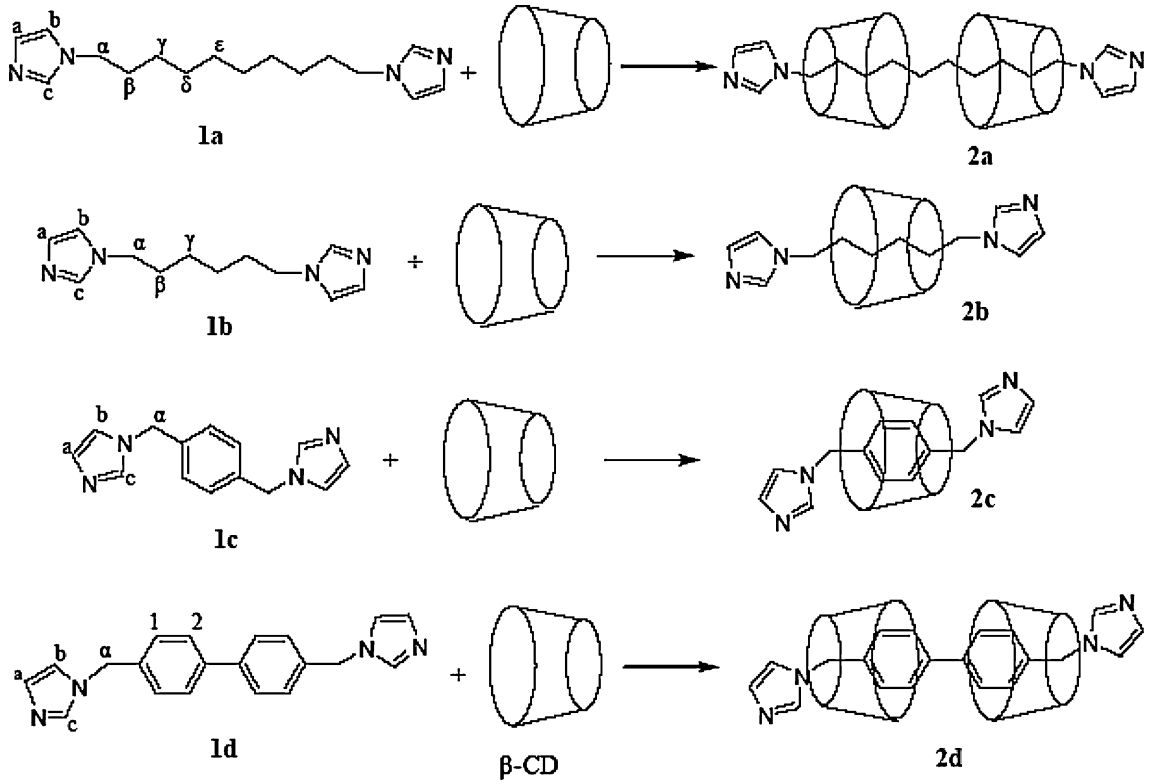
This finding indicates that such inclusion complexes could be a model for the displacement of the benzimodazole residues from Co in the binding of B_{12} coenzyme to the apoenzyme and, thus, could be of interest in developing artificial enzymes, modeling the B_{12}-based ones [5c].

Rotaxane type cyclodextrin supramolecules

Recently, we synthesis and characterize a new type of β-CD pseudorotaxanes, in which bisimidazolyl compounds, i.e. **1a** (1,10-bis(imidazol-1-lyl)decane), **1b** (1,6-bis(imidazol-1-lyl)hexane), **1c** (1,4-bis(imidazol-1-ylmethyl)benzene) and **1d** (4,4′-(bis(imidazol-1-ylmethylene))biphenyl) are employed as guest to thread into β-CD [17, 18]. The pseudorotaxanes of **2a**, **2b**, **2c** and **2d** are prepared by self-assembly of the guest compounds with β-CD in aqueous solution (see Scheme 3).

The products were characterized by ^{1}H NMR spectroscopy, E.A. and ESI-MS, respectively. Two crystal structures of pseudorotaxanes, i.e. **2a** (**1a**/2β-CD) and **2c** (**1c**/β-CD) have been determined for the first time (Figure 2) [17].

It is interested to note that the guests with longer alkylene chain or two benzene rings can thread into two CDs and form [3] pseudorotaxanes, otherwise, [2] pseudorotaxanes were formed. Because of the N atom in terminal imidazole group of the guest molecule could be coordinated with transition metal ion, this type of pseudorotaxanes might be converted to permanently metalo-rotaxanes, which will probably be furnished with



Scheme 3.

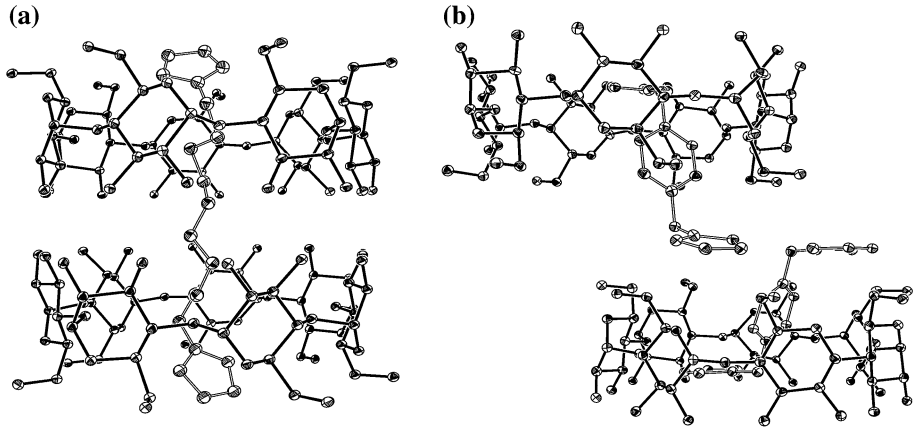


Figure 2. Molecular structures of the [2] and [3] pseudorotaxanes (a) **2a** (b) **2c**.

specific photonic, electric, or magnetic properties. We also found that a reductive type schiff base guest N^1,N^6-bis((pyridin-4-yl)methyl)hexane-1,6-diamine can thread into two β-CDs and form a [3] pseudorotaxane (Zhibin Wang *et al.*, unpublished work). The product was characterized by ^{1}H NMR spectroscopy and E.A., respectively. Further investigations are in progress in our laboratory.

Cyclodextrin in nano-scaled metal oxide fabrication

Thermal decomposition of metal salt, such as $Zn(CH_3COO)_2$ or $Ni(CH_3COO)_2$, is one of the versatile ways to obtain ZnO or NiO metal oxide nano-materials. In our previous investigation we proposed a novel and facile approach to fabricate ZnO nano-particles under the relatively simple and mild conditions, in which zinc acetate is coated by β-cyclodextrin (β-CD). It has been observed that the morphology, dimension, and size distribution of the product ZnO are strongly affected with the presence of β-CD compared to zinc acetate alone (Figure 3) [19]. Besides, the size of ZnO can be controlled by changing the β-CD/zinc acetate concentration ratio [20].

By using this method we also prepare a kind of nano-scaled nickel oxide from thermal decomposition process by β-CD coating $Ni(CH_3COO)_2$. Its XRD, TEM, magnetic property were determinted, respectively (Bin Zhao *et al.*, submitted). The TEM pictures of the two kind as-prepared NiO nano-particles are showed in Figure 4. It can be seen that the size of the NiO particles are approximately in 20–30 nm, and their morphology, shape and distribution of particle size are notable

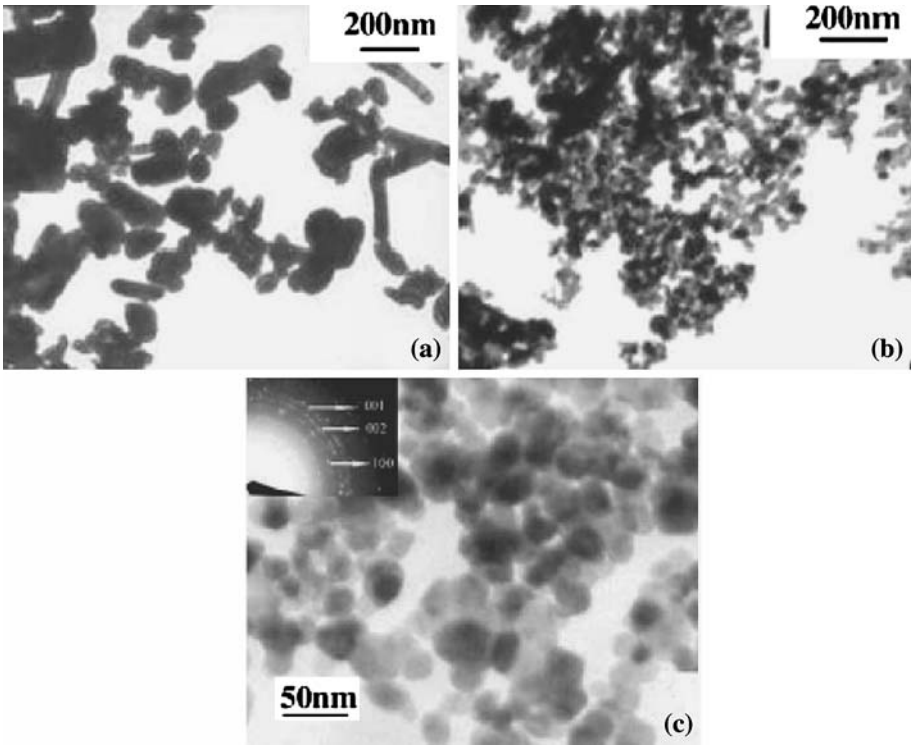


Figure 3. TEM images of the ZnO nano-particles thermally decomposed from (a) $Zn(CH_3COO)_2 \cdot 2H_2O$, (b) $Zn(CH_3COO)_2$ coated by β-CD, (c) The further magnified image of (b).

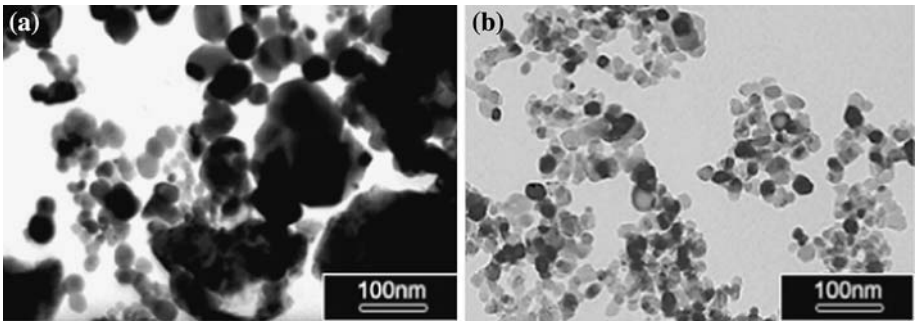


Figure 4. TEM images of NiO nano-particles prepared from thermal decomposition of (a) pure $Ni(CH_3COO)_2 \cdot 4H_2O$; (b) $Ni(CH_3COO)_2 \cdot 4H_2O$ coated on β-CD

improved by the β-CD coating. In order to investigate the mechanism we performe TG-DTA and EI-MS experiments also. There are several strong exothermal peaks in the DTA curve, which implies that the complex reactions are taken place at this stage, such as the decomposition and carbonization of β-CD accompanied with the decomposition of nickel acetate powder. At EI-MS spectrum the most strong signals of $m/z = 1192.7$ correspond to $[\beta\text{-CD} + CH_3COO^-]$ is observed . It is indicated that the inclusion complex between β-CD and acetate ion with molar ratio = 1:1 is formed. Probably ultrafine carbon black powder produced during the thermal decomposition process could prevent the agglomeration of nano-particles, and β-CDs might provide a restricted space for the nucleation of ZnO/NiO due to the inclusion. This method could also be used to prepare other nano-scaled metal oxide from thermal decomposition process.

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