

Intercalation of Functional Organic Molecules with Pharmaceutical, Cosmeceutical and Nutraceutical Functions into Layered Double Hydroxides and Zinc Basic Salts

Sung-Ho Hwang, Yang-Su Han, and Jin-Ho Choy*

National Nanohybrids Materials Laboratory (NNML)

School of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-747, Korea

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Negatively charged functional organic molecules such as retinoic acid, ascorbic acid, indole acetic acid, citric acid, salicylic acid, acidic dye (indigo carmine, Food Blue 1) are intercalatively encapsulated by zinc basic salt (hydrozincite) and layered double hydroxide. Such functional organic-inorganic nanohybrids are realized *via* coprecipitation reaction involving simultaneous formation of layered inorganic lattice and intercalation of anionic species. The heterostructural nature of these nanohybrids, their particle morphology and textural characterizations are mainly discussed on the basis of Powder X-ray Diffraction and Field Emission Scanning Electron Microscopy results.

Keywords : Layered double hydroxide (LDH), Zinc basic salt (ZBS), Functional molecules, Intercalation, Nanohybrid.

Introduction

Intercalation of organic and biomolecules into lamellar inorganic lattices is of great interest due to its scientific and practical importance.¹⁻⁶ Two dimensional crystals consisting of thin crystalline layers with a thickness of molecular scale can be regarded as an ideal nanohybrid matrix since the thin crystalline layers are stacked by van der Waals and/or weak electrostatic interactions, and a variety of foreign chemical species can be inserted as guests into the interlayer spaces to form layered nanohybrids.

A large number of ion exchangeable layered crystals are known; swellable clay minerals, zirconium phosphates, and transition metal oxides/oxy salts such as titanates, uranates, vanadates, and molybdates.⁷ They have exchangeable interlayer cations to balance the negative charge created within the framework. In contrast to a variety of cation exchangeable layered crystals, anion exchangeable ones are very rare. This is probably because anions are used as building units constructing the framework of crystal structures, and strongly bound to cations. Hydrotalcite-type layered double hydroxide (LDH) with a general formula of $[M^{II}_{1-x}M^{III}_x(OH)_2]^{x+}Y^{z-}_{x/z} \cdot nH_2O$ is an example among few anion exchangeable crystals,¹ where the positive layer charge is created by substituting divalent cation with trivalent one in the octahedral hydroxide layers (Figure 1(a)). The charge balancing anions are located between the hydroxide layers, and easily exchanged with various anions. And the other type of anion exchangeable layered solid is zinc basic salt such as $Zn_5(OH)_8Cl_2 \cdot nH_2O$ and $Zn_5(OH)_8(NO_3)_2 \cdot nH_2O$.⁸ The Zn ions stabilized in such basic salt lattices form brucite-type hydroxide layers with some octahedral vacancies, but a part of zinc ions are positioned just above and below the vacant sites outside the

hydroxide layers to form tetrahedral coordination (Figure 1(b)). One quarter of the octahedral sites of the zinc hydroxide layers can be vacant at maximum. Then interlayer anions are weakly bound to the tetrahedral Zn^{2+} ions, completing the tetrahedral coordination, and easily exchanged with most of inorganic anions as well as organic ones.

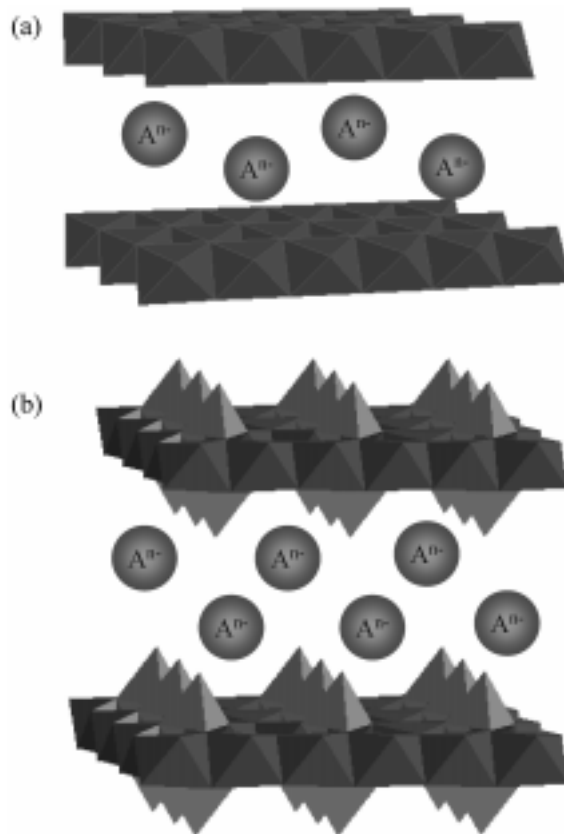


Figure 1. Crystal structures of hydrotalcite-type (a) and zinc basic salt (ZBS)-type (b) layered metal hydroxides.

*Author to whom correspondence should be addressed. E-mail: jhchoy@plaza.snu.ac.kr; Tel: +82-2-880-6658; Fax: +82-2-872-9864

In this study, the anion exchange properties of LDHs and zinc basic salts (ZBS) are further exploited for the encapsulation of negatively charged functional molecules or active organic ones in the interlayer space of hydroxide layers. For instance, vitamin compounds such as retinoic acid (Vitamin A), ascorbic acid (Vitamin C), and tocopherol (Vitamin E) are very sensitive to light, temperature, oxygen, *etc.*, which limit their applications as active ingredients in cosmetics, foods, and drugs. It is, therefore, required to stabilize such unstable molecules by intercalating them into layered inorganic lattices. In addition, some pharmaceutical molecules are especially required to release in a controlled manner to alleviate their toxicity or side effect as well as to increase the durability and stability. With these points of view, the layered metal hydroxides are thought to be ideal candidates as bio-compatible inorganic matrices for encapsulating, stabilizing, transferring and releasing various unstable and toxic molecules with negative charge. In the present study, an attempt has been made to stabilize several organic molecules with cosmeceutical, nutraceutical, and pharmaceutical functions by intercalating them into the hydrotalcite-type layered double hydroxide (LDH) lattice and zinc basic salt-type layer (ZBS) one.

Experimental Section

Materials. Organic and inorganic reagents are of analytical grade and were used without any further purification. The active organic molecules with specific functions for the present study are as follows; The α -hydroxy acid (AHA) molecule of citric acid (2-hydroxy-1,2,3-propanetricarboxylic acid, $C_6H_8O_7$, Duksan, 99%) was selected as an representative antioxidant. Salicylic acid (2-hydroxybenzoic acid, $C_7H_6O_3$, Aldrich, 99%) as an active ingredient and Indole acetic acid ($C_{10}H_9NO_2$, Aldrich, 99%) as a representative anti-wrinkle and anti-aging ingredient in cosmetics, were also used as guest molecules, since the former cures the acne and the latter promotes the proliferation activity of fibroblast in dermis. *L*-Ascorbic acid (Vitamin C, $C_6H_8O_6$, Aldrich, 99.9%) was also selected because of its well known nutrient function for human metabolism and because of active application in cosmetics due to its melanogenesis inhibition, cell regeneration, anti-oxidant and free radical scavenging activities resulting in anti-aging and skin whitening effects. Retinoic acid (Vitamin A acid, $C_{20}H_{28}O_2$, Aldrich, 99%) was also a candidate molecule, since it has been potentially used as anti-acne, anti-aging and anti-wrinkle ingredient for dermatological cure. α -tocopherol acid succinate (Vitamin E succinate, $C_{33}H_{54}O_5$, Sigma, 99%), an anti-oxidant in cosmetics, was also stabilized in LDH. An edible blue dye like Indigo carmine (Food Blue 1 & Acid blue 74, $C_{16}H_8N_2Na_2O_8S_2$) was also used as a guest species. Inorganic starting materials such as $Zn(NO_3)_2 \cdot 6H_2O$ (99%, Aldrich) and $Al(NO_3)_3 \cdot 9H_2O$ (99%, Aldrich) are also of guaranteed reagent grade.

Preparation. The organic derivatives of layered double hydroxide containing aluminum and zinc ions (ZnAl-LDH) were prepared by direct coprecipitation method. Typically, a mixed metal solution of $Zn(NO_3)_2 \cdot 6H_2O$ (4.6 g, 0.015 mol)

and $Al(NO_3)_3 \cdot 9H_2O$ (2.9 g, 0.0075 mol) in 200 mL decarbonated water was added dropwisely over 2 h to an aqueous solution containing organic guest species under nitrogen atmosphere with vigorous stirring. During the titration, the solution pH was adjusted to 7-8 with 0.1 N NaOH solution to induce coprecipitation reaction. Then the precipitate was aged at room temperature for 12 h, filtered, washed with decarbonated water thoroughly, and finally dried under vacuum. Citric acid, tocopherol acid succinate, and indigo carmine, indole acetic acid molecules were encapsulated by this coprecipitation method using ZnAl-LDH inorganic matrix. The mixing ratio between [Organic]/[Al^{3+}] was fixed to 2 in molar equivalent.

The nanohybrids between zinc basic salt-type lamellar solids and organic guests were also prepared by coprecipitation method. In a typical reaction, $Zn(NO_3)_2 \cdot 6H_2O$ (15.5 g, 0.05 mol) was dissolved in decarbonated water (300 mL), and then the aqueous solution was added into an mixed solution of decarbonated water and ethanol containing organic acids such as salicylic acid, ascorbic acid, and retinoic acid. The pH of the reaction solution was also controlled to 6-7 by simultaneous addition of aqueous solution (0.1 N) of NaOH with vigorous stirring under a nitrogen atmosphere. Then the precipitate was also aged at room temperature for 12 h, filtered, washed with decarbonated water thoroughly, and finally dried under vacuum. The mixing ratio between [Organic]/[Zn^{2+}]/[OH] was fixed to 1 : 8 : 4 in molar equivalent.

Characterization. Powder X-ray diffraction patterns (XRD) were recorded with a Philips PW 3710 diffractometer with Ni-filtered Cu-K α radiation ($\lambda = 1.5418 \text{ \AA}$). Field emission-scanning electron microscopic (FE-SEM) observation for the present organic-inorganic nanohybrids was carried out using a Hitachi S-4300. Prior to the observation, the powdered samples were coated with Pt-Pd for 180 s under vacuum.

Results and Discussion

Intercalation of organic molecules with pharmaceutical functions into the gallery spaces between metal hydroxide layers leads to an expansion of basal spacing according to their molecular size and geometrical arrangement in the interlayer space. The powder X-ray diffraction patterns for the present layered nanohybrids are represented in Figure 2. Firstly, the citric acid forms a single phasic layered nanohybrid with $[Zn_2Al(OH)_6]^+$ -brucite type lattice with a basal spacing of 12.1 \AA (Figure 2(a)). Taking into account the layer thickness of brucite (4.8 \AA), the observed gallery height of 7.3 \AA indicates that the interlayer citric acid molecules are arranged in a monolayer. Since the citric acid is a triprotic acid and has isotropic charge distribution, the monolayer stacking inbetween the hydroxide layer would be energetically favorable. Upon intercalation of ascorbic acid into the ZnAl-LDH layers (Figure 2(b)), the gallery height of the intercalate is determined to be 5.7 \AA , suggesting the monolayer arrangement between the hydroxide sheets as in the case of the citrate intercalate. The intercalation of retinoic acid also increases largely the basal spacing of LDH up to

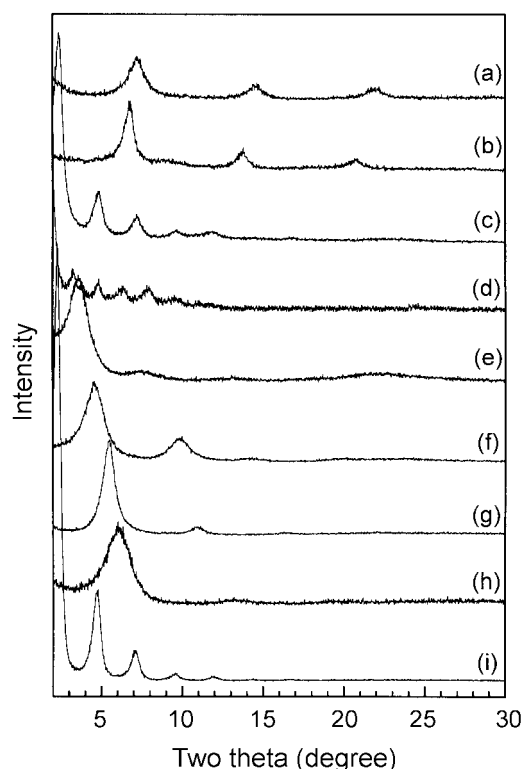


Figure 2. Powder X-ray diffraction patterns; (a) citrate-LDH, (b) ascorbate-LDH, (c) retinoate-LDH, (d) indigo carmin-LDH, (f) indole acetate-LDH, (g) salicylate-ZBS, (h) ascorbate-ZBS, and (i) retinoate-ZBS, respectively.

37.8 Å (Figure 2(c)). The gallery height of 33 Å obtained after subtracting the brucite thickness (4.8 Å) exceeds the molecular length of retinoate. Since the hydroxide layer has its limit in accommodating guest species owing to its anionic

charge density, the voluminous molecule like retinoate adopts a paraffine-like bilayer stacking between the hydroxide layers in order to overcome large steric restriction, resulting in a large interlayer separation. Similarly, the tocopherol acid succinate forms an intercalation compound with a basal spacing of ~54 Å (Figure 2(d)) and the interlayered tocopherol molecules are arranged in a manner of paraffin-like bilayers between the hydroxide sheets. The blue dye molecules can also be encapsulated by ZnAl-LDH hydroxide layers to form a layered nanohybrid where the interlayer guest molecules are arranged parallel to the hydroxide layers in a monolayer fashion with a gallery height of 25.6 Å (Figure 2(e)). The indole acetic acid also forms an LDH intercalation compound (Figure 2(f)) with a similar interlayer structure as in the case of blue dye molecule (indigo carmin).

Not only the layered double hydroxides, but also the zinc basic salt-type lamellar solid can also intercalate negatively charged organic molecules to form layered nanohybrids. Upon incorporation of salicylic acid into zinc hydroxide layers, the intercalative nanohybrid with a basal spacing of 16 Å is resulted (Figure 2(g)). The diffraction peak at 16 Å is assigned as the d_{003} , reflecting that the guest molecules are lying horizontally to the hydroxide layers in a monolayer. From a previous study on intercalation of acetic acid into the mixed NiZn-basic salt,⁸ it is well known that the oxygen atom in carboxylate groups directly bonds to tetrahedral Zn ion to complete tetrahedral coordination. In the case of the ascorbate-ZBS derivative (Figure 2(h)), a similar intercalation phase could be prepared as in the case of LDH derivative (Figure 2(b)). However, the basal spacing is slightly larger than that of LDH one, which might be due to the differences in layer structure and interlayer charge density. As compared in Figure 1, a part of Zn ions are

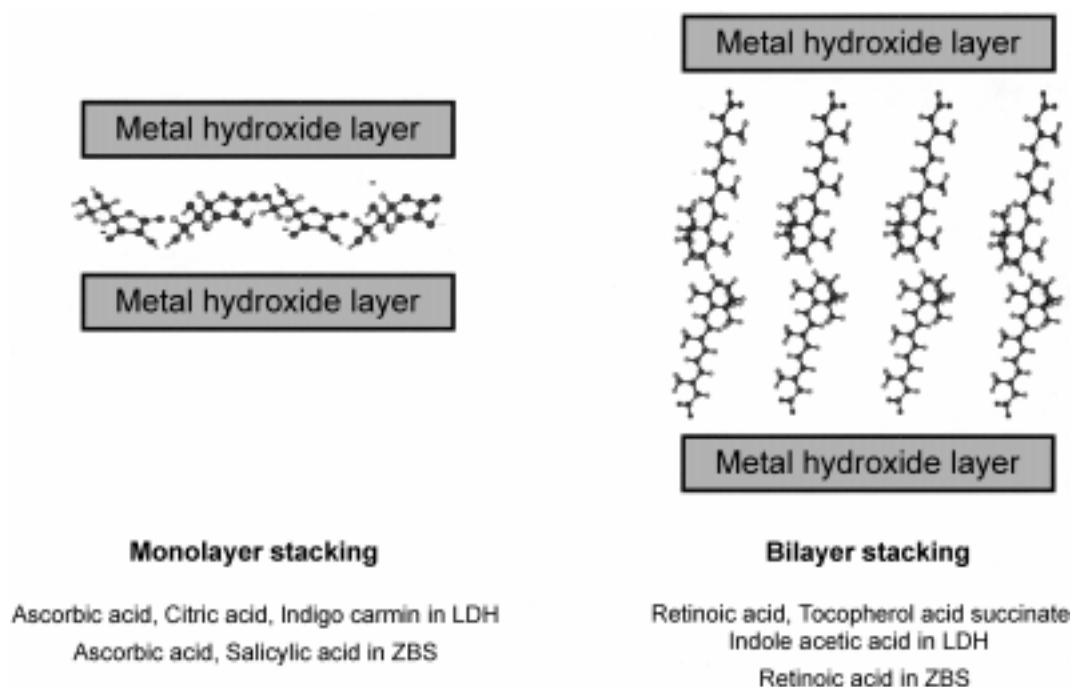


Figure 3. Schematic illustrations of layered nanohybrids.

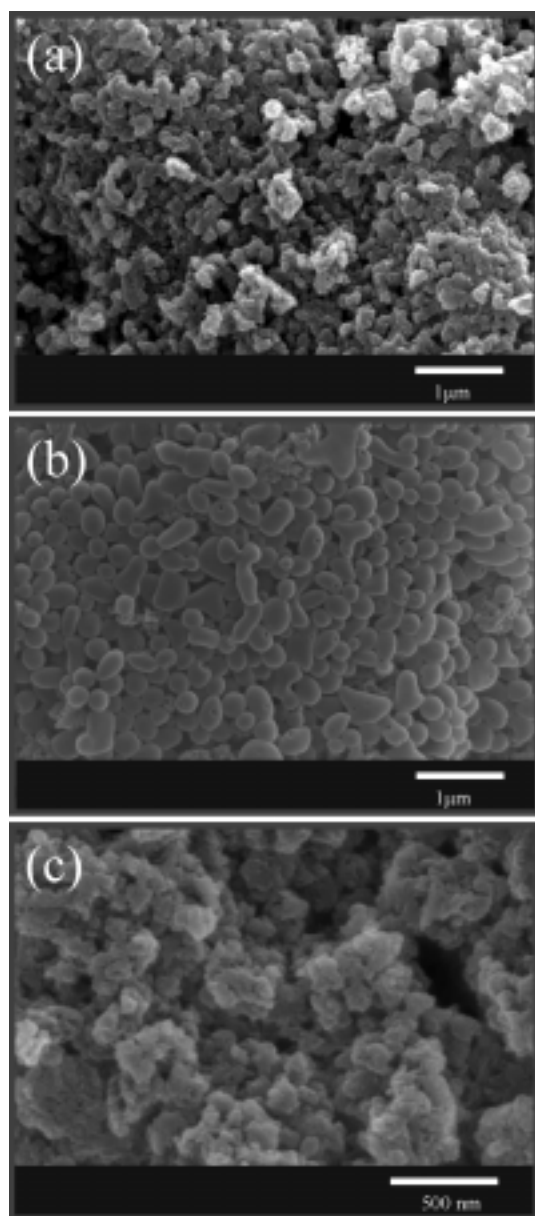


Figure 4. Scanning electron micrographs of the (a) citrate-LDH, (b) ascorbate-ZBS, and (c) indigo carmin-LDH nanohybrids, respectively.

positioned to form the tetrahedral sites above and below the vacant sites outside the hydroxide layers in the ZBS layers. Even though the brucite framework is the same in both layer compounds, the thickness of zinc basic salt-type layers is slightly larger than that of pure brucite layers owing to the outside tetrahedral units to which organic functional groups are directed. Furthermore, the interlayer charge density of ZBS-type layers is higher than that of the LDH-ones; the basal areas for unit charge are *ca.* 16 Å² for Zn₅(OH)₈ and *ca.* 24 Å² for Zn₂Al(OH)₆ layers, respectively. Therefore, a larger number of guest molecules can be included in the ZBS-type layers to compensate the excess positive layer charge, leading to a higher packing density in the unit basal plane. These two reasons are surely responsible for the larger interlayer separation in the zinc basic salt-type layers

for the same guest species. Comparing the basal spacing of the ascorbate-ZBS derivative (Figure 2(h), $d_{003} = 14.5$ Å) with that of the LDH one (Figure 2(b), $d_{003} = 10.5$ Å), it becomes clear that the layer thickness and the layer charge density play important roles in controlling the interlayer packing structure of guest molecules. The hybrid structures based on XRD analyses are proposed as shown in Figure 3.

Figure 4 represents the scanning electron micrographs for some selected layered nanohybrids. The citrate-LDH hybrid (Figure 4(a)) exhibits fine particle aggregates consisting of nanometer sized primary crystallites with an average size of ~100 nm. The ascorbate ZBS intercalate is also composed of very small spherical particles with an average size of 200-300 nm (Figure 4(b)). However, the blue dye-ZnAl-LDH hybrid (Figure 4(c)) is observed to be plate-like particles with the size of ~100 nm. The particle morphology and its size are slightly different according to the guest species, but the particle size for all the samples falls into the range of < 300 nm.

Conclusions

Various functional organic molecules with negative charge can be encapsulated in the zinc basic salt and hydrotalcite-type metal hydroxide layers by the direct coprecipitation route. Intercalation of organic molecules into metal hydroxide layers results in the well ordered layered nanohybrids with different interlayer distances and packing structures depending upon the molecular geometries of guest species and inorganic matrix. The layered nanohybrids are mainly composed of nanometer sized particles, which can be applicable as cosmetic and food ingredients, drug reservoir and carrier, and industrial additives.

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