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Simple Intercalation Reaction of Layered Double Hydroxide with Sodium Valproate under Solid Conditions

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The intercalation of sodium valproate, a hygroscopic antiepileptic drug, was successful for the first time in the interlayer region of nitrate-type LDH simply by mixing both powders in a mortar at room temperature. The addition of a small amount of water accelerated the reaction.

Solid–solid reactions are economical, simple and quick, without limitations of solvent, and may produce different compounds than solid–solution or solid–gas reactions.[1] The formation of inorganic–organic hybrids by solid–solid reactions has previously been reported.[2] For example, various amines were intercalated into montmorillonite through ion exchange or adsorption by solid–solid reactions under dry conditions,[3] and a complex of smectite with a drug was formed identical to the reaction in aqueous solution.[4] However, there have been no cases in which solid–solid reactions were applied to the formation of complexes of organic molecules with layered double hydroxide (LDH). Layered double hydroxide is composed of a cationic layer and an interlayer anion and has anionic-exchange properties.[5] Compared with montmorillonite and smectite, the layer charge density of LDH is large, and the interaction between the LDH layer and the interlayer anion is strong. Consequently, the ion-exchange reaction under solid conditions would be difficult to perform. However, it has been reported that inorganic anions such as Br^- could be exchanged with the interlayer NO_3^- of nitrate-type LDH [LDH(NO_3)] in KBr pellets used for FT-IR measurements.[6] There are three intercalation methods into LDH: ion exchange, reconstruction, and coprecipitation.[7] For all of these methods, the reaction takes place in aqueous solution. Sodium valproate (VPA, Figure 1) is hygroscopic and requires careful treatment and storage. We previously reported that VPA-intercalated LDH was obtained by ion exchange in aqueous solution and could protect VPA from humidity.[8] In this work, we report that a successful solid–solid ion-exchange reaction with LDH and VPA was performed simply by mixing the powders in a mortar. This is the first time that the interlayer anion in LDH has been exchanged under solid conditions with an organic anion that is larger than the inorganic anion.

LDH(NO_3) [$Mg_{0.66}Al_{0.33}(OH)_{2.31}(NO_3)_{0.27}(CO_3)_{0.02}\cdot 0.20H_2O$, Mg/Al = 2.0] was synthesized by the coprecipitation method.[9] The reaction was performed by grinding 0.10 g of LDH(NO_3) and 0.02–0.10 g of VPA powders in an agate mortar for 5 min. The obtained solid was dried under vacuum for 3 h at room temperature and characterized by powder X-ray diffraction (XRD), solid-state NMR spectroscopy, and elemental analysis. All reagents were previously dried under vacuum at room temperature. In order to examine the effect of added water on the reactivity, small amounts of water were added to the mixture. These products were compared with those obtained in aqueous solution according to our previous report.[8]

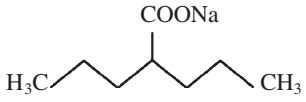

Figure 1. Structure of sodium valproate (VPA).

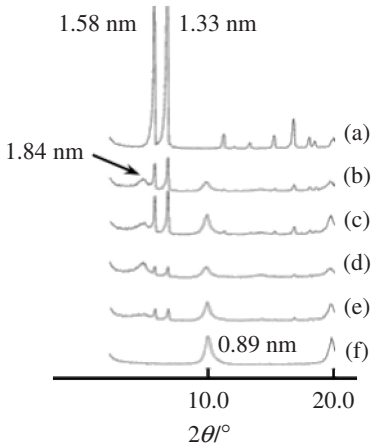

Figure 2. XRD patterns of samples prepared by grinding LDH(NO_3) and various amounts of VPA: (a) VPA only, (b) 0.10, (c) 0.07, (d) 0.05, (e) 0.035 g, (f) LDH(NO_3) only.

The XRD patterns of LDH(NO_3) ground with various amounts of VPA (0.035–0.10 g) in a mortar (Figure 2) exhibited a new peak at 1.84 nm in addition to the peaks of the reactants. The interlayer distance was the same as that of the intercalation compound obtained in aqueous solution,[8] suggesting that intercalation of VPA into the interlayer region of LDH(NO_3) under solid conditions was successful. The peak intensities of LDH(NO_3) decreased with the increase of VPA, but they did not disappear completely. It was found that the amount of added VPA had little influence on the reactivity, because additional VPA did not induce formation of the intercalation compound. Therefore, the effect of added water was examined next.

Figure 3 shows XRD patterns of samples obtained by grinding 0.07 g of VPA and 0.10 g of LDH(NO_3) with various amounts of water. With increasing amounts of water added, the peak at 1.84 nm increased and the peaks of both LDH(NO_3) and VPA disappeared almost completely at 20 μL of added water, suggesting complete intercalation. This result indicates that the addition of water during grinding promotes the reaction effectively. The amount of water required for complete reaction depends on the amount of VPA, e.g., 40 μL for 0.10 g of VPA, 20 μL for 0.07 g of VPA, and 10 μL for 0.035 g of VPA.

In addition, the peaks observed at higher angles ($2\theta = 29.5$ and 31.9°) were not derived from the original peaks of either

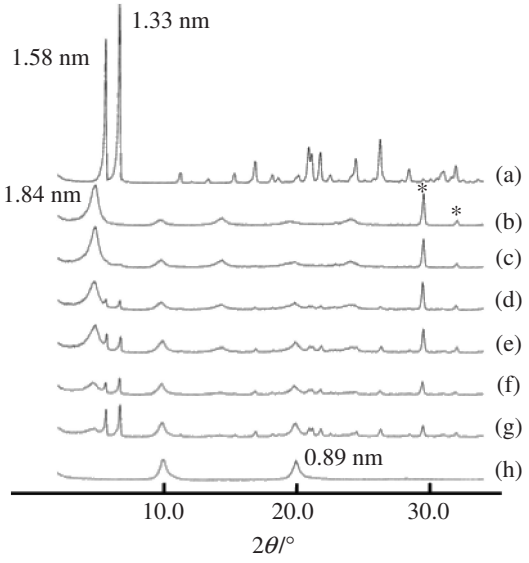

Figure 3. XRD patterns of samples prepared by grinding $LDH(NO_3)$ and VPA with various amounts of water added: (a) VPA only, (b) 20, (c) 15, (d) 10, (e) 6, (f) 3, (g) 0 μL, (h) $LDH(NO_3)$ only. * indicates $NaNO_3$.

$LDH(NO_3)$ or VPA, and their intensity increased with the progress of the reaction. These peaks correspond to sodium nitrate ($NaNO_3$), suggesting that the nitrate ion of $LDH(NO_3)$ and the sodium ion in VPA form $NaNO_3$. This is another indication that the nitrate ion in the interlayer region of $LDH(NO_3)$ exchanged with the anionic VPA. Thus, there is clear evidence that the ion-exchange reaction progressed in the solid state without using aqueous solution. The added water is considered to activate the molecular mobility between particles and in the interlayer region, although a detailed mechanism requires more study.

In order to investigate the VPA molecule in the interlayer region, solid-state ^{13}C NMR spectra were measured for the intercalation compound. The carbons are numbered as follows: $^{1}CH_3{}^{2}CH_2{}^{3}CH_2{}^{4}CH(^{5}COOH)CH_2CH_2CH_3$. Table 1 summarizes the ^{13}C chemical shifts of VPA in solid and solution states. VPA-Na and VPA-H represent the anionic and acidic forms of VPA in solution, and $LDH(NO_3)$–VPA (a) and (b) are intercalation compounds obtained in aqueous solution and by solid–solid reaction, respectively. The chemical shifts of $LDH(NO_3)$–VPA by the solid–solid reaction were nearly the same as those of the intercalation compound obtained in aqueous solution. Additionally, these chemical shifts were close to those of VPA-Na. These results suggest that the VPA molecule in the interlayer region of both intercalation compounds exists in anionic form. Therefore, it was confirmed that the ion-exchange reaction proceeded while manually grinding both original powders in the solid state.

The deintercalation reaction of $LDH(NO_3)$–VPA was examined in sodium carbonate (Na_2CO_3) solution. The interlayer distance of the sample after the deintercalation reaction was 0.78 nm, which is identical to that of carbonate-type LDH [$LDH(CO_3)$]. This result indicates that $LDH(NO_3)$–VPA converted to $LDH(CO_3)$ by exchanging VPA with carbonate ion. This is further evidence that the VPA in $LDH(NO_3)$–VPA by the solid–solid reaction is in the anionic form.

Table 1. ^{13}C chemical shift data of VPA-Na and VPA-H in aqueous solution and VPA-intercalated LDH from (a) aqueous solution and (b) solid–solid reaction

	δ			
	VPA-Na	VPA-H	$LDH(NO_3)$–VPA	
			(a)	(b)
C-1	14.0	11.8	14.9	15.0
C-2	21.0	18.6	21.6	21.6
C-3	35.5	32.6	35.1	35.3
C-4	49.0	43.2	48.7	48.8
C-5	186.6	180.6	186.6	186.1

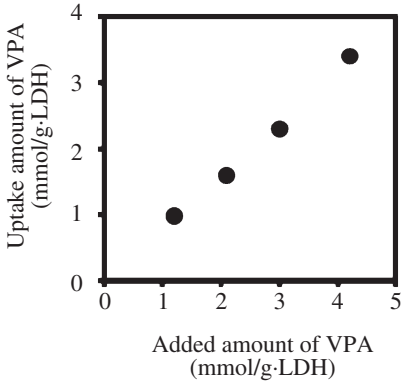

Figure 4. Uptake amount of VPA into $LDH(NO_3)$ by solid–solid reaction.

After washing the sample with 200 μL of water, no peaks from the original VPA were observed in the XRD pattern, and the interlayer distance remained at 1.84 nm. The uptake amount of VPA in the washed sample was obtained by elemental analysis and is shown in Figure 4. The uptake amount of VPA depended on the added amount of VPA, with 80% of added VPA consistently incorporated into LDH. The maximum uptake amount of VPA was 3.4 mmol per gram of $LDH(NO_3)$. This value corresponds to 81% of the theoretical ion-exchange capacity (4.2 mmol g^{-1}) and is close to that of the intercalation compound obtained in aqueous solution (3.8 mmol g^{-1}). In addition, the maximum uptake amount of VPA by the solid–solid reaction was reached by adding 4.2 mmol of VPA per gram of $LDH(NO_3)$ for only 5 min. In contrast, in order to obtain VPA-intercalated LDH with the same exchange rate in aqueous solution, 6.0 mmol of VPA per gram of $LDH(NO_3)$ and a reaction time of 1 day were required. Clearly, the solid–solid reaction proceeds more efficiently than the reaction in aqueous solution.

The ion-exchange scheme of the solid–solid reaction is shown in Figure 5. The VPA molecules in the interlayer region of the intercalation compound are arranged as a bilayer structure with the long axes of the VPA molecules parallel to the hydroxide layer, similar to that obtained in aqueous solution.

In summary, the intercalation reaction occurred simply by manual grinding of both VPA and $LDH(NO_3)$ powders in a mortar, and the intercalation compound was formed by ion exchange under solid conditions. This is the first time that a

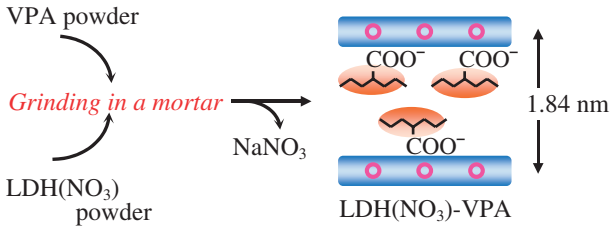

Figure 5. Scheme of ion-exchange reaction under solid conditions.

solid–solid reaction has been applied to the intercalation of an organic anion into LDH. As this reaction does not require the preparation of aqueous solutions, it is easy to perform and can be completed in a short time. Recently, we found that potassium sorbate in food additives was also intercalated into LDH(NO_3) by mixing powders in a mortar. It is expected that drugs can be included into LDH by solid–solid reactions during pharmaceutical processing accompanied by this method. At the same time, this process would decrease the degradation of drugs, due to their hygroscopic nature or by decomposition by light. Therefore, it is a revolutionary method to obtain pharmaceutical materials.

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