

Anionic Clays Containing Anti-Inflammatory Drug Molecules: Comparison of Molecular Dynamics Simulation and Measurements

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Three representative nonsteroidal anti-inflammatory drug molecules, Ibuprofen, Diclofenac, and Indomethacin, have been intercalated within the galleries of an anionic clay, Mg–Al layered double hydroxide (LDH). X-ray diffraction, IR and Raman vibrational spectroscopy and ^{13}C cross-polarization magic-angle spinning NMR have been used to characterize the confined drug molecules, while molecular dynamics (MD) simulations were used to probe the interlayer structure, arrangement, orientation, and geometry of the intercalated species. All three drug molecules are arranged as bilayers in the interlamellar space of the anionic clay. But while the structure of the intercalated Ibuprofen is identical to that of the molecule outside the layers, spectroscopy as well as MD simulation shows that there is a change in the geometry of Diclofenac and Indomethacin upon confinement within the galleries of the LDH. The change in geometry of Diclofenac and Indomethacin upon intercalation is shown to originate from the electrostatic interaction between the electronegative chlorine atoms on the drug molecule and the positively charged metal hydroxide sheets of the anionic clay. It is shown that these changes in the geometry of the intercalated drug molecules allow for the observed interlayer spacing to be realized without the bilayers having to interdigitate, which would otherwise have been necessary if the structure of the drug molecules had remained identical to that outside the layers. Comparisons of experimental measurements with simulation have provided a more detailed understanding of the geometry and organization of flexible drug molecules confined in the anionic clay.

Introduction

Intercalation of organic species into layered inorganic solids provides a useful and convenient route to prepare organic and inorganic hybrids that contain properties of both the inorganic host and organic guest in a single material.¹ The layered double hydroxides (LDHs) or anionic clays are host–guest materials that have found wide applications as catalysts² and catalyst precursors,³ as sorbents and scavengers for halogens⁴ and weak acids,⁵ and more recently for storing and delivering biologically active agents.⁶ The LDHs, $[\text{M}_x^{3+}\text{M}'_{1-x}{}^{2+}(\text{OH})_2]^{x+}[\text{A}^{n-}]_{x/n}$, are host solids whose structure is built by positively charged brucite-like layers and interlamellar exchangeable anions, A^{n-} . The ion-exchange intercalation chemistry of the LDHs is extensive; a variety of inorganic and organic anions may be incorporated between the LDH layers thus imparting new functionality to the LDH. The dimensions and functionality of the guest are critical in determining the interlayer separation of the intercalated compound. The charge on the layer, size, and orientation of the guest as well as the interaction of the negatively charged guest with the positively charged LDH layers are all critical factors.

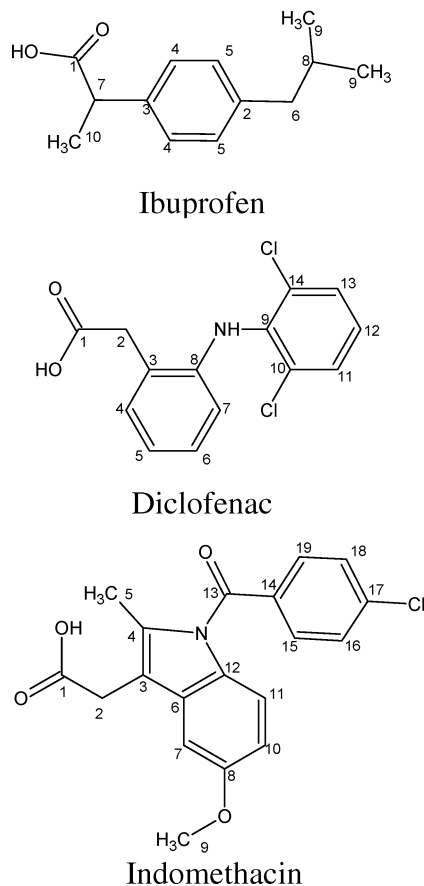
Many commonly prescribed drugs and over-the-counter medicines, especially the nonsteroidal anti-inflammatory drugs (NSAIDs) either are anions or can be conveniently and reversibly converted into an anionic form. It has been recognized that these molecules may be intercalated into a host LDH via a simple ion-exchange process or by the addition of the layered double hydroxides to an aqueous solution of the chosen

pharmaceutically active compound. It has been shown that many common NSAIDs, such as Diclofenac, Ibuprofen, Gemfibrozil, and Naproxen intercalate rapidly, via ion exchange into $[\text{LiAl}_2(\text{OH})_6]\text{Cl}\cdot\text{H}_2\text{O}$ and $[\text{Mg}_2\text{Al}(\text{OH})_6]\text{Cl}\cdot\text{H}_2\text{O}$ layered double hydroxides.^{7–11} The resulting drug–LDH hybrids are more than just a chemical curiosity. Since the LDH sheets dissolve in acidic media, the drug may be quantitatively recovered, from the hybrid, on contact with gastric juices in the stomach. Initial studies suggest that the drug–LDH hybrid could form the basis for a controlled drug-release system.^{8,9,11} Apart from the potential of using these materials for in vivo drug delivery, the host itself provides additional benefits. It may be possible to control the point of release and pharmacokinetic profile by selection of the metals ions in the host layers of the drug–LDH hybrid. Confinement of the drugs between the metal hydroxide layers isolates the molecules from the environment thereby improving long-term stability and storage, especially since many of the NSAIDs are easily hydrolyzed. More importantly, LDHs such as $\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3$ (hydrotalcite) are known to be effective antacids¹² that could counter the gastric irritability associated with most NSAIDs.¹³

As part of an ongoing study of the organization of intercalated guest molecules in layered solids using molecular dynamics (MD) simulation we have looked at the interlamellar arrangement and orientation of representative NSAID molecules confined by intercalation in the anionic clay, hydrotalcite. Hydrotalcites are LDHs with the chemical composition $[\text{Mg}_{1-x}\text{Al}_x(\text{OH})_2]^{x+}[\text{A}^{n-}]_{x/n}\cdot m\text{H}_2\text{O}$ (Mg–Al–LDH) that consists of positively charged layers constructed from edge-sharing $\text{Mg}(\text{OH})_6$ and $\text{Al}(\text{OH})_6$ octahedra.¹⁴ The positive charge of the layers is compensated for by interlayer anions that are usually

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SCHEME 1



hydrated. Computer simulation provides a powerful technique to probe the structural and dynamic properties at a molecular level and offers a direct connection between local structural details and experimental measurements. In particular, simulations are well suited for the study of intercalated guest molecules.¹⁵ MD simulations and energy minimization have been used to study the Mg–Al LDH crystal structure¹⁶ and to predict the interlayer arrangement of intercalated halide ions¹⁷ as well as the influence of layer charge and hydration on the orientation of organic guest molecules.^{18,19} The NSAID molecules chosen for the present study were Ibuprofen (isobutyl phenyl propionic acid), Diclofenac (the sodium salt of *o*-(2,6-dichloroanilino)phenylacetate), and Indomethacin (1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid) (Scheme 1). These are nonsteroidal drugs commonly used for the relief of symptoms of rheumatoid arthritis and osteoarthritis. Our simulations showed that for Diclofenac and Indomethacin, the geometry of the drug molecule confined between the layers of the Mg–Al LDH to be significantly different from that of the molecule in the “free” state outside the layers or in the solid crystalline state. This is rather surprising since in a majority of intercalated compounds the interlayer spacing of the host is adjusted so as to accommodate the guest molecule in the minimum energy geometry, which it possesses outside the layers. The results of the simulation warranted a more detailed experimental investigation of the LDH–drug hybrid. Here we report the characterization of Ibuprofen, Diclofenac, and Indomethacin anions intercalated in hydrotalcite using powder X-ray diffraction, vibrational (Fourier transform infrared (FT-IR) and Raman), and ¹³C NMR spectroscopy. The experimental observations are compared with the results of the simulation to

obtain a more detailed understanding of the geometry and organization of NSAID drug molecules confined in the anionic clay.

Experimental Section

Preparation and Characterization. Mg_{1-x}Al_x(OH)₂(NO₃)_x [Mg–Al LDH–NO₃] was prepared by coprecipitation through the dropwise addition of known volumes of aqueous Mg(NO₃)₂ (0.04 M) and Al(NO₃)₃ (0.02 M) into NaOH at a constant pH of 8, under N₂ atmosphere, following the procedure reported by Meyn et al.²⁰ The resulting white precipitate was aged for 24 h prior to washing with decarbonated water. The Mg/Al ratio in the Mg–Al LDH was determined by inductively coupled plasma spectroscopy (Jobin Yvon JY24). The composition of the starting Mg–Al LDH–NO₃ was Mg_{0.66}Al_{0.33}(OH)₂(NO₃)_{0.33}. Intercalation of drug anions within the Mg–Al LDH was achieved by the ion exchange of NO₃[–] ions in Mg_{0.66}Al_{0.33}(OH)₂(NO₃)_{0.33} with the corresponding anion of the pharmaceutical agent. Ibuprofen, Diclofenac, and Indomethacin were obtained commercially. In a typical preparation, 100 mg of Mg–Al LDH–NO₃ was added to 10 mL of a 5 mM aqueous drug solution at room temperature and stirred for 24 h. Completion of the intercalation of the drug anions was confirmed by the absence of 00*l* reflections with basal spacing of 8.9 Å, due to Mg–Al LDH–NO₃, in the powder X-ray diffraction (Shimadzu XD-D1, Cu Kα) and the appearance of a new set of 00*l* reflections with basal spacings of 23.6, 22.9, and 24.47 Å for Ibuprofen, Diclofenac, and Indomethacin intercalated Mg–Al LDH drug hybrids, respectively. Completion of exchange was also ascertained by the absence of the 1384 cm^{–1} NO₃[–] ion band in the IR spectra of the drug–LDH hybrid. The drug anion stoichiometry in the Mg–Al LDH was established independently from C, H, N elemental analysis.

Measurement Techniques. Powder X-ray diffraction patterns of Mg–Al LDH–NO₃ and the Mg–Al LDH–drug hybrids were recorded on a Shimadzu XD-D1 X-ray diffractometer using Cu Kα radiation with λ = 1.54 Å. The samples were mounted by pressing the powders on a glass plate, and the data was collected at a scan speed of 2° 2θ/min. Thermogravimetric analysis runs were recorded on a Perkin-Elmer-Pyris-Diamond thermogravimetric/differential thermal analyzer (TG/DTA) system in flowing air. FT-IR spectra were recorded as KBr pellets on a Bruker IFS55 spectrometer operating at 4 cm^{–1} resolution. FT-Raman spectra were recorded on a Bruker IFS FT-Raman spectrometer using a Nd YAG (λ = 1064 nm) laser for excitation. Spectra were recorded at a resolution of 4 cm^{–1} with an unpolarized beam using an Al sample holder. Laser power was kept at 150 mW. ¹³C cross-polarization magic-angle spinning (CP-MAS) NMR was recorded on a Bruker DSX-300 solid-state spectrometer at a Larmor frequency of 75.46 MHz with a contact time of 1 ms. The spectra were externally referenced to tetramethylsilane (TMS). CHN analysis was performed on a CHNS (CARLO ERBA) elemental analyzer.

Simulation Methods

Simulations were performed using either the Cerius² or Materials studio software packages²¹ running on SGI machines. The first step in the simulation was the preparation of the positively charged Mg–Al LDH layers. The hydroxide layers were constructed using atomic coordinates from the previously reported crystal structure of hydrotalcite,²² [Mg₄Al₂(OH)₁₂](CO₃)·3H₂O, whose X-ray crystal structure had been refined in a trigonal unit cell with space group *R3m* and lattice parameters *a* = *b* = 3.054 Å and *c* = 22.81 Å. The interlayer carbonate

ions and water were removed from the hydrotalcite structure and a supercell was constructed containing 32 hydrotalcite crystallographic unit cells. The supercell parameters were $a = 12.22 \text{ \AA}$, $b = 12.22 \text{ \AA}$, $c = 60.00 \text{ \AA}$; $\alpha = 90.0^\circ$, $\beta = 90.0^\circ$, $\gamma = 120.0^\circ$ (equivalent to 4×4 hydrotalcite unit cells in the ab -plane and a two layer repeat with an initial interlayer spacing of 30 \AA). The Mg/Al ratio was adjusted to 3 so that each hydroxide layer contains 12 Mg^{2+} and 4 Al^{3+} atoms with the constraint that Al^{3+} ions did not occupy adjacent octahedra. The composition of the Mg–Al LDH supercell is thus $[\text{Mg}_{48}\text{Al}_{16}(\text{OH})_{128}]^{16+}$. Instead of placing full formal charges on the Mg and Al ions, charges were averaged over the atoms of the Mg–Al LDH layer using the charge equilibration method.²³ The partial charges are +0.64 for Mg, +1.3 for Al, -0.605 or -0.59 for O, and +0.19 or +0.17 for H, depending on the environment of the atom. Although there is no X-ray crystallographic evidence for long range ordering of Al^{3+} ions in the hydrotalcite structure, we were forced to assume complete ordering because of the periodic boundary condition imposed on the simulation supercell and the fact that partial occupancy was disallowed. Except for periodic boundary conditions no symmetry constraints were imposed. The structure was treated as triclinic ($P1$), and all lattice parameters were treated as independent variables in the simulation.

An integral number of the appropriate NSAID anions were then introduced between the Mg–Al LDH layers such that overall charge neutrality was maintained. In each case, the drug molecules were placed in the galleries with their longest axis oriented approximately parallel to the normal interlayer in a bilayer-like arrangement. The geometries of the Ibuprofen, Diclofenac, and Indomethacin at the start of the simulation were obtained by molecular mechanics energy minimization using the Dreiding force field.²³ Atomic charges were calculated using the charge equilibration method.²⁴ Simulations were also carried out with the starting geometry, and charges on the drug anion calculated using the MOPAC semiempirical molecular orbital method.²⁵ Although the optimized geometries by the two methods are similar, there are significant differences in the magnitude of the partial charges. The optimized geometries were almost identical to that reported from X-ray crystal structure determination of the respective drug molecule.²⁶

The total nonbonded potential interaction energy of the simulated system consisted of long-range Coulombic interactions between partial atomic charges and van der Waals interactions, computed using the Ewald summation technique. Short-range, repulsive van der Waals interactions were treated with a direct cutoff radius of approximately 8 \AA . The potential energy due to bonded interactions was computed using a modified version of the Dreiding force field. The modification given by Newman et al.²⁷ includes additional parameters for Mg and has been shown to reproduce the experimental structure of the Mg–Al LDH layer during simulations as well as being applicable to the organic moiety.

Molecular dynamics simulations were performed on a constant composition isothermal–isobaric (NPT) ensemble at 300 K .²⁸ A time step of 0.001 ps was used. Temperature was maintained using the Hoover thermostat²⁹ implemented with a relaxation time of 0.1 ps and a cell–mass prefactor of unity.³⁰ The equivalent hydrostatic pressure was set to 0.0001 GPa (approximately 1 atm). Periodic boundary conditions were applied in three dimensions so that the simulation cell is effectively repeated infinitely in each direction.³¹ The total simulation time was 50 ps . The results showed that equilibrium values for the crystallographic parameters and thermodynamic

quantities such as the potential energy were generally reached within the first $15\text{--}20 \text{ ps}$. Equilibrium values of the lattice parameters were judged to have been reached when these quantities fluctuate around an average value that remains constant over time. Equilibrium values of the lattice parameters and thermodynamic quantities were also checked by repeating the simulations with a slightly different starting orientation of the interlamellar drug anion as well as different interlayer spacing. The convergence to similar conformations, interlayer spacing, and properties from different initial values is a good indicator that equilibrium has occurred.

Thermogravimetric measurements of the Mg–Al LDH drug hybrids did not indicate any significant change in weight between 100 and 150°C due to the loss of water (see Supporting Information). Nevertheless, simulations with included interlamellar water molecules were carried out for the Mg–Al LDH Ibuprofen hybrid since earlier reports of simulations of guest molecules in Mg–Al LDH had found significant changes in the computed value of the interlayer spacing on inclusion of water.^{18,19} Simulations were carried out with 32 water molecules, 2 per intercalated Ibuprofen, in the supercell. This would correspond to a 14.8% weight loss in a TGA experiment. It was found that agreement with the experimental interlayer spacing of Mg–Al LDH Ibuprofen was much poorer on inclusion of water in the simulation supercell. Consequently, interlamellar water molecules were not included in the simulation of the Mg–Al LDH drug hybrids. Moreover, as the TGA showed, there was no experimental justification for the inclusion of water.

Results

I. Experimental Measurements. A. X-ray Diffraction. The powder X-ray diffraction patterns of the Mg–Al LDH–drug hybrids are shown in Figure 1. For comparison, the pattern of the parent Mg–Al LDH– NO_3 is also shown. The absence of Mg–Al LDH– NO_3 peaks in the XRD patterns of the drug–LDH hybrid indicates the completeness of the ion-exchange process. Because of the layered nature of the intercalated Mg–Al LDH compounds, the crystallites exhibit a pronounced preferred orientation; consequently, only $00l$ reflections are seen in the XRD patterns. In all materials, the $00l$ reflections could be indexed to a unique interlayer spacing (Table 1). The gallery height on intercalation of the drug may be obtained by subtracting the hydroxide layer thickness of 4.8 \AA . The gallery height in the Mg–Al LDH Ibuprofen hybrid, 18.8 \AA , may be accounted for by a bilayer arrangement with the carboxylate group of the Ibuprofen anion (length $\sim 9.6 \text{ \AA}$) anchored to the hydroxide layer. For the Mg–Al LDH–Diclofenac and Mg–Al LDH–Indomethacin hybrids, if the dimensions of the Diclofenac and Indomethacin molecules and geometry are the same as in their crystalline state, then the observed gallery heights can be realized only if the drug molecules are arranged in partially interdigitated bilayers. Such an arrangement had been proposed in an earlier report on the Mg–Al LDH–Diclofenac and Mg–Al LDH–Indomethacin hybrids.^{8,11}

B. IR, Raman, and ^{13}C NMR Spectroscopy. The vibration and ^{13}C NMR spectra of the drug–LDH hybrids are compared with the respective solid-state spectra of the drug molecule outside the layers.

Mg–Al LDH–Ibuprofen. The IR spectra of the Mg–Al LDH–Ibuprofen hybrid shows most of the characteristic bands of Ibuprofen (see Supporting Information). The absence of the NO_3 ion band at 1384 cm^{-1} and the appearance of new bands at 1588 cm^{-1} (asymmetric stretch of COO^-) and 1398 cm^{-1}

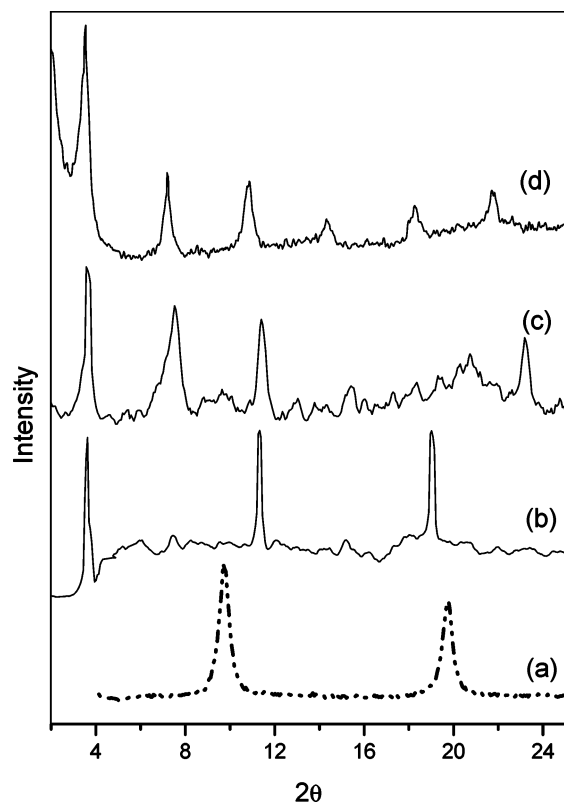


Figure 1. X-ray diffraction pattern of (a) Mg–Al LDH–NO₃, (b) Mg–Al LDH–Ibuprofen, (c) Mg–Al LDH–Diclofenac, and (d) Mg–Al LDH–Indomethacin.

TABLE 1: Interlayer Spacing for the Mg–Al LDH Drug Hybrids from X-ray Diffraction and MD Simulation

	<i>d</i> (Å) (experimental)	<i>d</i> (Å) (simulation)
LDH–Ibuprofen	23.6	24.2 (24.2) ^a
LDH–Diclofenac	23.0	22.7 (25.3)
LDH–Indomethacin	24.47	24.2 (29.2)

^a The values in parentheses are for the simulations in which partial charges on the drug molecules were calculated using MOPAC.

(symmetric stretch of COO[−]) in Mg–Al LDH–Ibuprofen clearly indicate the complete exchange of NO₃[−] ions for Ibuprofen anions within the galleries. The band at 1715 cm^{−1} in the spectra of Ibuprofen, due to the asymmetric stretch of the undissociated –COOH, is absent in the intercalated material (Figure 2a). The methyl symmetric and asymmetric stretching modes at 2954 and 2868 cm^{−1} in the intercalated Mg–Al LDH–Ibuprofen hybrid are well resolved, and their positions show no significant difference from those of pure Ibuprofen (Supporting Information), but the methyl bending mode at 1462 cm^{−1} is shifted to 1466 cm^{−1} upon intercalation (Figure 2a). The characteristic M–OH layer stretching modes at around 427 and 620 cm^{−1} are well defined in the intercalated hybrid, indicating that the inlayer structure of the LDH is unaffected upon intercalation of Ibuprofen.

The Raman spectra of the intercalated Mg–Al LDH–Ibuprofen (Figure 2b) is similar to that of Ibuprofen except that the COOH band at 1651 cm^{−1} present in the latter is absent, instead, a band at 1462 cm^{−1} assignable to the asymmetric stretch of the ionized COO[−] group is present in the hybrid. (The Raman spectra between 100 and 3000 cm^{−1} along with assignments are provided in the Supporting Information.) The positions of the CH₃ asymmetric (2954 cm^{−1}) and symmetric stretching modes (2868 cm^{−1}), the CH₂ asymmetric stretch

(2920 cm^{−1}) and bending mode (1452 cm^{−1}), and the phenyl ring modes (1608 and 1575 cm^{−1}) in the Mg–Al LDH–Ibuprofen are similar to that in the Raman spectra of Ibuprofen in its crystalline state.

In the ¹³C CPMAS NMR spectra of Ibuprofen and Mg–Al LDH–Ibuprofen (Figure 2c), the C₁ resonance in the hybrid is shifted downfield by 3 ppm as compared to neutral Ibuprofen. The resonance positions (see Supporting Information) of the carbon atoms C₃, C₇, and C₁₀, which are in close proximity to the carboxylate group, are also shifted downfield in the intercalated hybrid. These shifts are because the carboxylate group in the intercalated compound is ionized whereas in Ibuprofen it is present in the undissociated form. The resonance positions of the other carbon atoms are unaffected upon intercalation.

The IR, Raman, and ¹³C NMR spectra confirm that the integrity of the Ibuprofen anion is preserved upon intercalation within the Mg–Al LDH galleries with a structure and geometry similar to that of the molecule outside the layers.

Mg–Al LDH–Diclofenac. The IR and Raman spectra of the Diclofenac anion show little change upon intercalation. (The infrared (400–4000 cm^{−1}) and Raman (50–3500 cm^{−1}) spectra along with the assignments are provided as part of the Supporting Information.) The positions of most IR active bands including the phenyl ring vibrations of the intercalated ion are identical to that for the sodium salt of Diclofenac. There is, however, a significant change in the position of the Raman C8–N–C9 bending mode (numbering of carbon atoms as shown in Scheme 1) as well as the Raman N–H stretching mode; the former is blue shifted from 648 to 661 cm^{−1} while the latter is red shifted from 487 to 477 cm^{−1} upon intercalation (Figure 3a). The ¹³C CPMAS NMR spectra of the Mg–Al LDH–Diclofenac hybrid shows small downfield shifts (~1 ppm) in the positions of the C8, C9, and C12 resonances as compared to the NMR spectra of Na–Diclofenac (Figure 3b).

As in the case of the Mg–Al LDH Ibuprofen hybrid, the vibration and ¹³C NMR spectra of the Mg–Al LDH–Diclofenac hybrid indicate that the integrity of the drug ion is preserved upon intercalation but with a small, yet significant, change in positions of the Raman vibrational modes involving the C8–N–C9 set of bonds, which link the two phenyl rings of the Diclofenac molecule.

Mg–Al LDH–Indomethacin. The IR and Raman spectra of Indomethacin anions intercalated in the Mg–Al LDH have been compared with that of solid Indomethacin (see Supporting Information for spectra covering the full spectral range as well as assignments of the IR and Raman bands). The positions of most Indomethacin bands in the vibrational spectra are identical in the two phases. The most notable change in the infrared spectra is that the 1717 cm^{−1} band of the carboxylic acid group of Indomethacin is no longer seen in the Mg–Al LDH–Indomethacin hybrid; instead a band at 1560 cm^{−1} due to the ionized COO[−] group is present (Figure 4a). Similarly in the Raman spectra (Figure 4b), the 1650 cm^{−1} band of the carboxylate group of Indomethacin is replaced by a band at 1591 cm^{−1} upon intercalation. These changes are a straightforward consequence of the fact that Indomethacin anions rather than neutral molecules are the intercalated species in the Mg–Al LDH–Indomethacin hybrid. In addition to these changes, it may also be seen that the infrared band at 1691 cm^{−1} due to the stretching mode of the carbonyl group, which is part of the link between the phenyl and indole rings (see Scheme 1), is shifted to 1676 cm^{−1} upon intercalation. This band is known to be sensitive to the geometry and environment of the Indomethacin

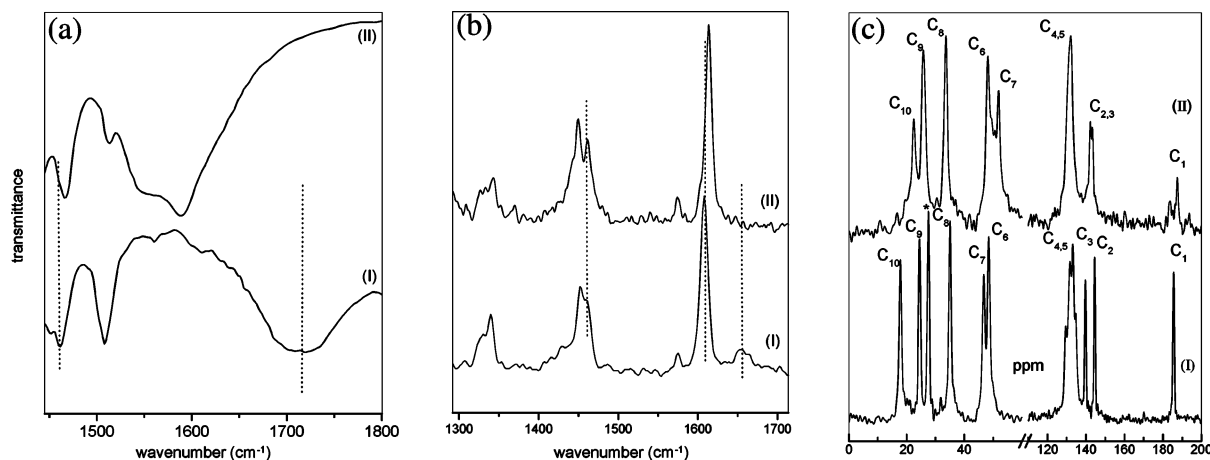


Figure 2. (a) IR spectra and (b) Raman spectra of (I) Ibuprofen and (II) Mg-Al LDH-Ibuprofen (the spectral features that show change upon intercalation are indicated with dashed lines), and (c) the ^{13}C NMR spectra. The numbering of the C atoms in the NMR spectra is as shown in Scheme 1.

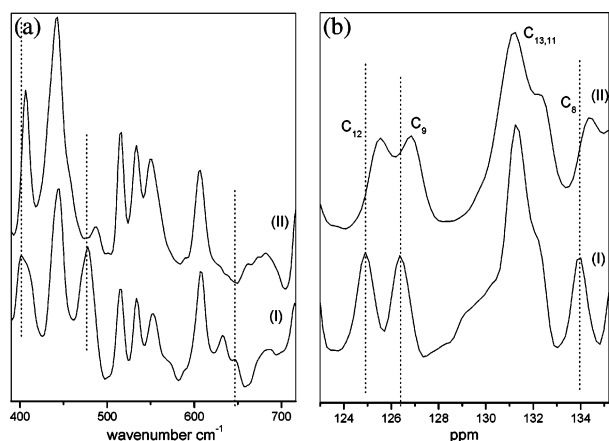


Figure 3. (a) Raman spectra and (b) ^{13}C NMR spectra of (I) Diclofenac and (II) Mg-Al LDH-Diclofenac. The numbering of the C atoms in the NMR spectra is as shown in Scheme 1. (The spectral features that show change upon intercalation are indicated with dashed lines.)

molecule, for example, in the Raman spectra of Indomethacin in the solid state (Figure 4b) they appear as two bands at 1680 and 1689 cm^{-1} that have been interpreted as Indomethacin molecules present in crystalline and amorphous phases, respectively. In the Raman spectra of the Mg-Al LDH-Indomethacin hybrid, this band appears at 1673 cm^{-1} . The C-Cl deformation in the Raman spectra that appears as a medium intensity band at 400 cm^{-1} in Indomethacin appears as a broad band at 410 cm^{-1} in the Mg-Al LDH-Indomethacin hybrid. In addition, there are minor changes in the positions of the methyl and methylene groups of Indomethacin upon intercalation (see Supporting Information).

The ^{13}C CP MAS NMR spectra of the Mg-Al LDH-Indomethacin hybrid and Indomethacin solid are shown in Figure 4c (the positions of the resonances are given as part of the Supporting Information). The resonances of the CH_2 group and the C_3 carbon, attached to the carboxylate group of the Indomethacin, are downfield shifted by ~ 3 ppm upon intercalation, due to anion formation. The 175.5 ppm resonance of the $-\text{COOH}$ group of Indomethacin is absent in the Mg-Al LDH-Indomethacin hybrid. In addition, it may be seen that the resonances of the methylene CH_2 (C_2) and $-\text{OCH}_3$ (C_9) groups are shifted by 1.7 and 3.7 ppm, respectively, upon intercalation.

To summarize, the spectroscopic studies indicate that the integrity of the Indomethacin molecule is preserved upon

intercalation, but the fact that the positions of the structure-sensitive features in the vibrational/ ^{13}C NMR spectra are shifted suggests that the geometry of the intercalated molecule could be quite different from that outside the layers.

2. Computer Simulation. A. Interlayer Structure of the Intercalated Mg-Al LDH Drug Hybrid. Snapshots of the simulation of the Mg-Al LDH drug hybrid are shown in Figure 5 (the simulation cell is indicated in dashed lines). In each case the snapshot is after 50 ps of MD simulation at 300 K, at which time thermal equilibration has adjusted to be reached by the constancy of the potential energy of the system and the interlayer spacing.

Lattice parameters were obtained by averaging over the last 10 ps of the simulation. For all three Mg-Al LDH-drug hybrids, it was found that the inlayer Mg-Al LDH structure showed little change from the starting unit-cell values ($a = 12.32$ Å, $b = 12.35$ Å, and $\gamma = 119.8^\circ$). The average interlayer spacing for the three intercalated drug molecules is in reasonable agreement with the respective X-ray interlayer spacing (Table 1). It was found that the method for calculating atomic charges on the guest drug molecule made a significant difference to the value of the interlayer spacing obtained from MD simulations for the intercalated Diclofenac and Indomethacin molecules but not for Ibuprofen. Charges calculated using the charge equilibration method gave better agreement with the experimentally determined interlayer spacing as compared to simulations in which charges were calculated using the semiempirical MOPAC molecular orbital method. The charge equilibration method places a higher charge on the Cl atoms of the Diclofenac and Indomethacin molecules as compared to MOPAC (see Supporting Information). The interlayer spacing values in Table 1 are those obtained using the charge equilibration method. The corresponding values for which charges were calculated using MOPAC are given in parentheses in Table 1. Simulations initiated with slightly different initial orientations of the guest molecules and interlayer spacing were found to converge to the values given in Table 1.

The snapshots of the drug molecules in the galleries of the Mg-Al LDH show that they are arranged as bilayers with the drug anions, as expected, anchored to the Mg-Al LDH sheets through their carboxylate groups. The bilayers were not interdigitated for any of the intercalated drug molecules, Ibuprofen, Diclofenac, or Indomethacin. It may be recalled that if the observed interlayer spacing for the intercalated Diclofenac and Indomethacin ions had to be rationalized assuming that their

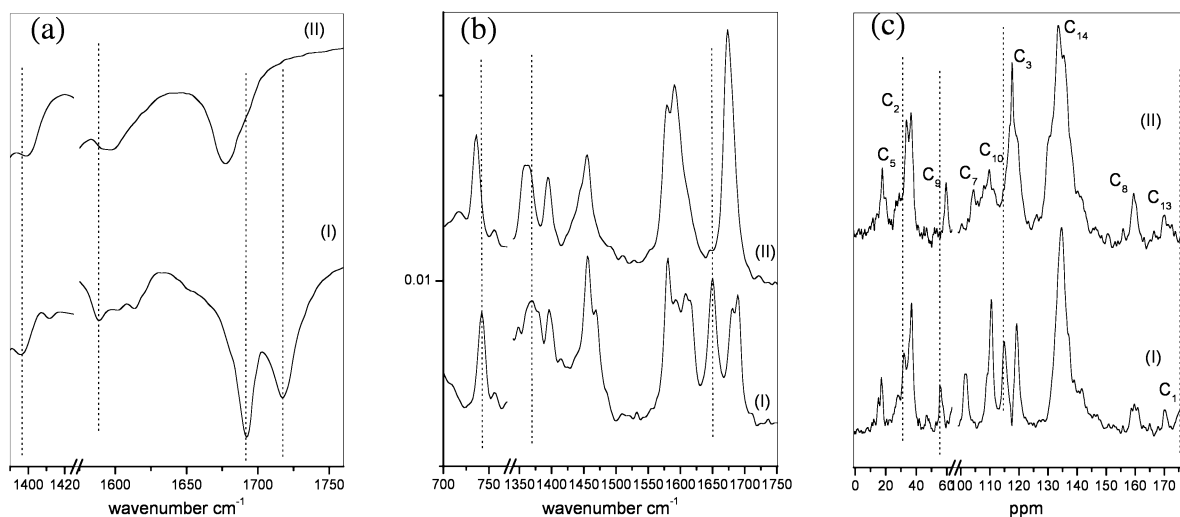


Figure 4. (a) IR spectra (b) Raman spectra, and (c) ^{13}C NMR spectra of (I) Indomethacin and (II) Mg-Al LDH-Indomethacin. The numbering of the C atoms in the ^{13}C NMR spectra is as shown in Scheme 1. (The spectral features that show change upon intercalation are indicated with dashed lines.)

molecular dimensions are identical to that in their crystalline state, then an interdigitated bilayer is required.^{8–10} The snapshots of the simulation show that the bilayers are not interdigitated; instead the drug anions in the galleries adopt a geometry different from that outside the layers.

B. Geometry and Orientation of the Intercalated Drug.

The structures of the confined drug molecule intercalated in the Mg-Al LDH, obtained from simulations, have been compared to the structure of the molecule outside the layers in Figure 6. In Figure 6, the structure in the left of the panel is the optimized minimum energy structure using the Dreiding force field for the drug molecule outside the layers. This is the structure of the drug that was placed in the interlayer space at the start of the simulations. For all three drug molecules, it also happens to be almost identical to the structure of the drug molecule obtained from X-ray crystallographic studies.²⁶

The snapshots of the simulations indicate that the structure of Ibuprofen within the layers is identical to that of those outside. The intercalated Ibuprofen anions in the bilayer are tilted away from the interlayer normal and are oriented such that the carboxylate group is in close contact with the -OH of the Mg-Al LDH sheet. The center-to-center distance between Ibuprofen anions, intercalated between the Mg-Al LDH layers, is ~ 6.4 Å. The intercalated Diclofenac ions, too, are attached to the Mg-Al LDH sheet through their carboxylate group. Although bond lengths remain unchanged upon intercalation, there are changes in the bond angles (see Supporting Information). The most significant change upon intercalation is in the torsional angles C1-C2-C3-C4, which change from -76° to -152° and the C3-C8-N-C9, which change from -38.3° to -55.4° (numbering of carbon atoms are as shown in Scheme 1). As a consequence of these changes, the dihedral angle between the planes passing through the two phenyl rings is altered. In the optimized geometry and also in the crystalline state, this dihedral angle is 65° . Our simulations for the intercalated Diclofenac show this angle varying between 60 and 90° for different snapshots. The value averaged over the last 5 ps of simulation is 58° . These values for the structure of intercalated Diclofenac are from simulations in which charges have been calculated by the charge equilibration method. The deviation from the “free” ion geometry is considerably less when charges are calculated using MOPAC; the interlayer spacing however is larger than that for the experimental value (Table 1).

The interlayer Indomethacin guest molecules are arranged within the galleries in a bilayer mode with an average intermolecular distance of 6.2 Å between the N atoms of adjacent indole rings. The Indomethacin ions are oriented such that in addition to the carboxylate groups being in close proximity to the layer, the oxygen atoms of either the methoxy or carbonyl group also approach the layer (Figure 6c). The arrangement is such that in a layer either all methoxy or all carbonyls would approach the Mg-Al LDH sheet, while in the opposing layer it would be reversed. As a consequence of this orientation, the planes of the benzene rings in opposing layers are almost perpendicular to each other and show an identical inclination with respect to the layers. This orientation of the interlayer Indomethacin was always realized even when the long axis of the Indomethacin axis was tilted away from the interlayer normal at the start of the simulation. The structure of the confined Indomethacin shows considerable difference from that outside. The torsional angles involving the bonds that link the indole and phenyl rings are the most affected. The C12-N-C13-C14 torsional angle changes from 24.3° to 64.1° and the N-C13-C14-C15 angle from 45.9° to 51.8° upon intercalation (see Supporting Information). These changes lead to the dihedral angle between the planes of the indole and phenyl groups changing from the free ion value of 64° to 76° . As in the case of the intercalated Diclofenac ions, the deviation in the geometry of the intercalated Indomethacin from the free ion geometry is less when charges are calculated using MOPAC. The partial charge on the chlorine atom is considerably less when charges are calculated using MOPAC as compared to the charge equilibration method (see Supporting Information).

3. Discussion. The results of the experimental measurements and simulations of the Mg-Al LDH drug hybrids are in reasonable agreement. The Mg-Al LDH Ibuprofen hybrid is the most straightforward to understand. The positions of the features in the IR, Raman, and ^{13}C NMR spectra of the intercalated Ibuprofen ion are identical to that of the Ibuprofen outside the layers except for a feature assignable to the carboxylate group, which exists as the ionized species within the layer. These results suggest that the geometry of the Ibuprofen is unaffected upon intercalation. This conclusion is also supported by the results of the simulation. The snapshot of the simulation shows that the anchored Ibuprofen anions

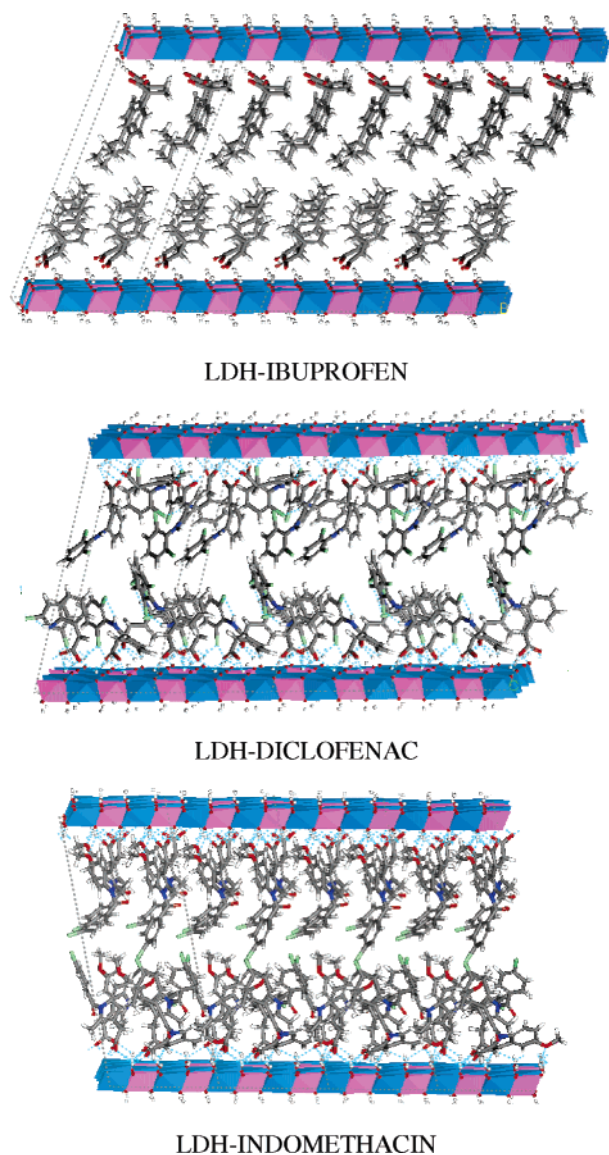


Figure 5. Snapshots of the simulation of the Mg–Al LDH drug hybrid. Dashed lines indicate the initial simulation unit cell. Color codes: blue N, green Cl, red O, gray C, white H, pink Al, and bluish-green Mg.

are arranged in a tilted bilayer, and the interlayer spacing so obtained, in good agreement with the X-ray diffraction spacing.

For the intercalated Diclofenac ion most spectral features appear at the same position as in the spectra of the ion outside the layers except for the Raman vibrational modes involving the C8, N, and C9 set of atoms. These are the atoms that form the bonds that link the two phenyl rings. The simulations, too, indicate that these are the bonds that are affected when Diclofenac anions are intercalated in the Mg–Al LDH. Snapshots of the MD simulations show that the intercalated Diclofenac ions are arranged as bilayers with the torsional angles C1–C2–C3–C4 and C3–C8–N–C9 having values different from that for the molecule outside. This change in geometry explains how the observed interlayer spacing is realized without the interdigitation of the bilayer that had been suggested earlier,¹¹ which is based on the molecular dimensions of the Diclofenac ion in the “free” state outside the layers.

Vibrational spectra and MD simulations indicate a change in geometry of the Indomethacin ion upon intercalation. As in the case of the Diclofenac, it is the vibrational modes and bond angles involving the atoms that act as the hinge between the

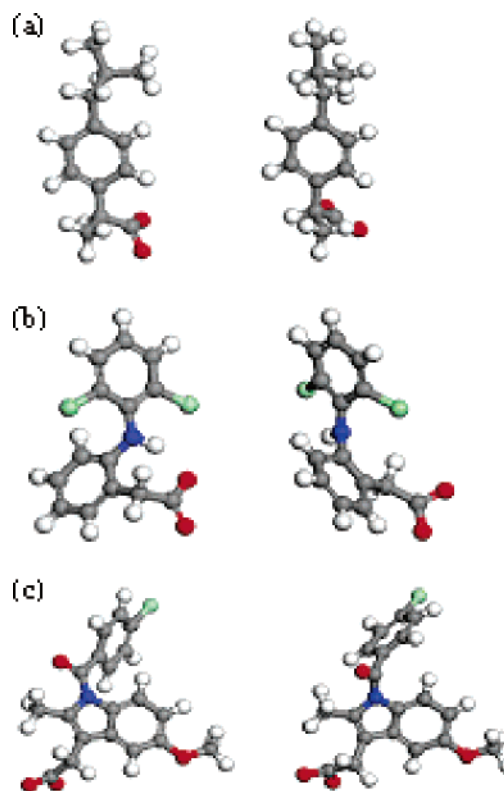


Figure 6. Molecular structure of (a) Ibuprofen, (b) Diclofenac, and (c) Indomethacin. The structure on the left of the panel is the potential energy minimized optimized geometry of the drug. The structure on the right is a snapshot of the same molecule in the Mg–Al LDH–drug hybrid following 50 ps of molecular dimension simulation. Color codes: blue N, green Cl, red O, gray C, and white H.

two rigid moieties, in this case, the indole and phenyl rings that are affected. In the Raman spectra, this change is reflected in the position of the carbonyl-stretching mode while in the simulation in the changed values of the torsional angles C12–N–C13–C14 and N–C13–C14–C15. The value of the interlayer spacing obtained from simulation of the Mg–Al LDH Indomethacin is in good agreement with the X-ray diffraction measurements.

The key to understanding the origin of the change in structure of the Diclofenac and Indomethacin ions upon intercalation is the fact that it depends quite significantly on the method used for calculating partial charges on the atoms of the guest species. As mentioned earlier, the value of the interlayer spacing obtained from simulation is in better agreement with the measured spacings when charges are calculated by the charge equilibration method rather than the semiempirical MOPAC molecular orbital method. The former places a much larger charge on the electronegative Cl atom as compared to the latter (see Supporting Information). The change in structure of the drug on confinement may be rationalized as due to attractive Coulombic interaction between the negatively charged Cl and the positively charged Mg–Al LDH sheets. The phenyl ring bearing the chlorine atom is pulled toward the layer, and as a consequence, the dihedral angle between the planes of the two phenyl rings in the case of Diclofenac or between that of the indole and phenyl rings for Indomethacin is changed. This would explain why the positions of the Raman bands involving the bonds that link the two rigid moieties are shifted upon intercalation. This change in geometry of the intercalated drug leads to a reduction in the dimensions of the molecule in the direction perpendicular to the layers, and as a consequence, the observed interlayer spacings are realized

without the bilayers having to interdigitate. The orientation and arrangement of the intercalated Indomethacin ions in the bilayer of the Mg–Al LDH Indomethacin hybrid allows for electrostatic repulsive interactions between chlorine atoms of opposing bilayers to be minimized while maximizing the positive attraction between the chlorine and the Mg–Al LDH sheets within a bilayer. The fact that the MD structure and vibrational spectra of Ibuprofen is unaffected upon intercalation underlines the importance of electrostatic interactions involving the chlorine atoms of the confined drug and the positively charged metal hydroxide sheet.

4. Conclusion. Three representative NSAID molecules, Ibuprofen, Diclofenac, and Indomethacin, have been included within the galleries of the anionic clay, Mg–Al layered double hydroxide by ion-exchange intercalation. These hybrid materials have been identified as potential candidates for pH-triggered drug release as well as drug storage.⁷ In the present study, powder X-ray diffraction, IR and Raman vibrational spectroscopy, and ¹³C CPMAS NMR have been used to characterize the confined drug molecules in the Mg–Al LDH drug hybrids. Molecular dynamics simulations have been used to probe the interlayer structure, arrangement, orientation, and geometry of the intercalated species.

Spectroscopic measurements indicate that the structure of the intercalated Ibuprofen is identical to that outside the layers. This conclusion is also supported by MD simulations which also show how a bilayer arrangement of the intercalated drug gives rise to the observed interlayer spacing. In the case of the intercalated Diclofenac and Indomethacin molecules, the presence of the electronegative chlorine atom gives rise to additional electrostatic interactions between the chlorine atoms and the positively charged Mg–Al LDH sheets. As a consequence, the bonds linking the chlorine-substituted phenyl ring with rest of the molecule are affected and the geometry of the intercalated drug differs from what it has outside. This observation is supported by spectroscopic measurements as well as by the simulations. The simulations also show how as a consequence of the change in geometry the experimentally observed interlayer spacing can be realized by a simple bilayer arrangement of the drug molecules without any interdigitation.

One of the long standing paradigms in the host–guest chemistry of layered host lattices is that the interlayer spacing of the host is always adjusted so as to accommodate guest molecules without any change from the minimum energy geometry that they possess outside the layers. While the orientation and arrangement of the intercalated guest molecules in the galleries of different hosts could differ, depending on a number of factors including the charge on the layer and the extent of hydration, the geometries are usually the same and identical to that outside the layers. The Mg–Al LDH drug provides an exception to this rule; the geometry of the intercalated drug molecule is different. This is a consequence of electrostatic interactions between the electronegative atoms on the drug molecule and the charge on the layer. In conclusion, we have shown how spectroscopic measurements and MD simulations complement each other in providing a better insight into the orientation and geometry of flexible guest molecules in layered host lattices.

Supporting Information Available: (1) Thermogravimetric data for Mg–Al LDH–Ibuprofen and Mg–Al LDH–NO₃. (2) ¹³C NMR, IR, and Raman spectra of Ibuprofen, Mg–Al LDH–

Ibuprofen, Diclofenac, Mg–Al LDH–Diclofenac and Indomethacin, and Mg–Al LDH–Indomethacin along with tables of band positions and assignments. (3) Partial charges on the drug molecules calculated using the charge equilibration method and the semiempirical MOPAC molecular orbital method. (4) Bond and torsional angles of the drug molecules before and after 50 ps of MD simulation.

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