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Supporting Information

INTERCALACIÓN DE CIPROFLOXACINA EN ESMECTITAS: CÁLCULOS DE PRIMEROS PRINCIPIOS Y DE DINÁMICA MOLECULAR

INTERCALATION OF CIPROFLOXACIN IN SMECTITE: FIRST PRINCIPLES AND MOLECULAR DYNAMICS CALCULATIONS

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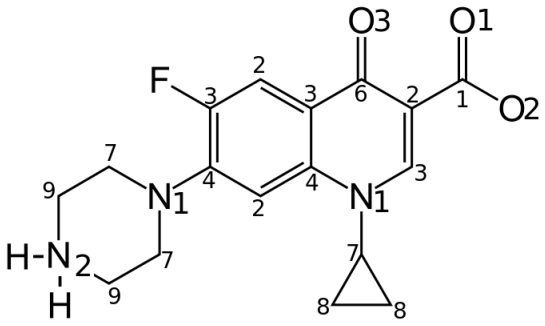

Figure SI1. Representation of the zwitterionic form of ciprofloxacin molecule. The atomic representation is the used in Table S1, S2 and S3.

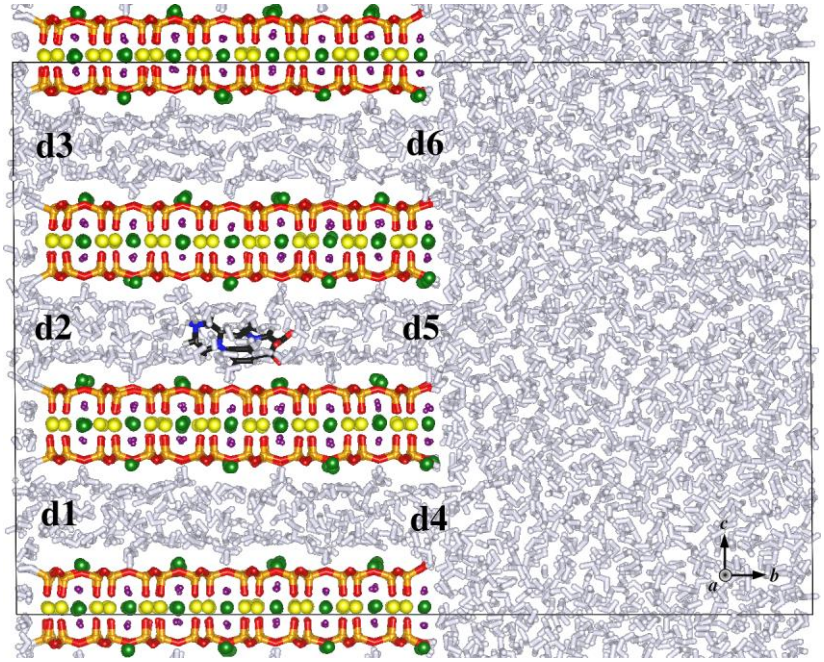

Figure SI2. Starting geometry of the *LiFh-cipro-in* system. Orange, red, green, yellow, violet, black, white, and blue balls correspond to Si, O, Li, Mg, F, C, H and N atoms, respectively. The simulation box is delimited by the black rectangle.

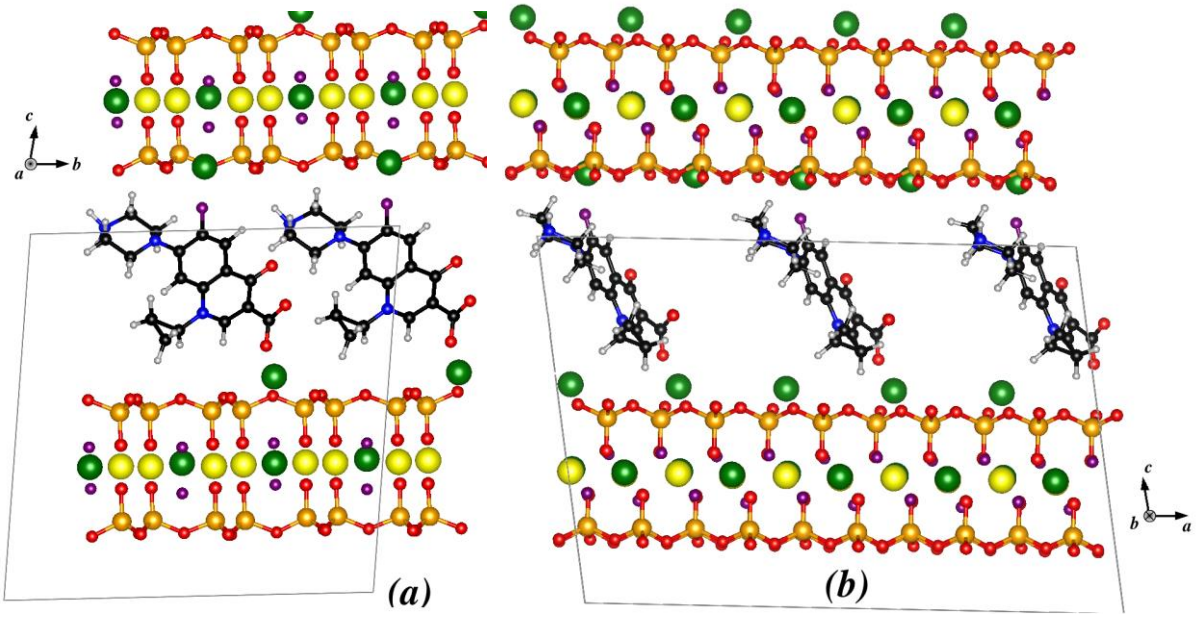

Figure SI3 Starting geometry of the *LiFh-6cipro* system. (a) View along *a* direction (b) View along *b* direction. Orange, red, green, yellow, violet, black, white, and blue balls correspond to Si, O, Li, Mg, F, C, H and N atoms, respectively. The simulation box is delimited by the black parallelogram.

Potentials and parameters used in the simulations

The interactions of the clay atoms were treated with the CLAYFF force field (Cygan et al 2004) adapted by Marry et al (Marry et al 2011). The parameters of Li^+ compensating cation were taken from Koneshan et. al., (Koneshan et. al., 1998). The charge of the Li^+ was +1, the same charge was assumed for the octahedral Li. While the charge of the octahedral F was set to -1. A small change in the charges of the oxygen labeled as O(os) and the octahedral Mg was done in order to ensure the neutrality of the system. They were set to -1.365 and 1.5975, respectively.

Additionally, the bond of the OH group used to compensate the edge of tetrahedral atoms was described by an harmonic potential with the form:

$$V_{ij} = k_1\left(r_{ij} - r_0\right)^2 , \qquad (1)$$

with k_1= 1109.86 kcal/mol and r_0= 1.0 Å.

The charges and atomic parameters for van der Waals interactions of the clay atoms are given in Table S1.

UFF (Universal Force Field) potential (Rappé et al 1992) was employed to model the cipro molecule represented in Figure 1. The drug atomic charges were determined from DFT/PBE0 calculation of an isolated zwitterionic cipro molecule. Averaged charges were used for those atoms of the same element with very similar atomic charges, i.e. for some C, N and H. They are shown in Table S1.

In UFF, bond potentials is described by a harmonic potential given by the equation 1, while angle potential was determined as:

$$U(\theta) = A\left[1 + \cos\left(m\theta - \delta\right)\right]. \qquad (2)$$

All the parameters, k_1, r_0, A, m and δ, presented in equations (1) and (2) are presented in Tables S2 and S3.

Water molecules were described with SPC potential (Berendsen *et. al.* 1981). In this scheme the Lennard-Jones (LJ) parameters do not include terms for H atoms (HW). However, was necessary to

introduce van der Waals interactions of HW with the atoms of the cipro molecule with negative charge: O, F and H. In those cases, UFF LJ parameters of the H atom was applied to the HW.

The intermolecular interactions, *i.e.*, the van der Waals and electrostatic interactions, between the atoms of the clay, cipro and water molecules, have been treated with the parameters proposed by the different force fields and are presented in Table S1.

UFF and ClayFF force fields describe van der Waals interactions using the analytical form,

$$V_{ij} = D_{0ij}\left[\left(\frac{R_{ij}}{r_{ij}}\right)^{12} - 2\left(\frac{R_{ij}}{r_{ij}}\right)^{6}\right]. \qquad (3)$$

While, in our simulations van der Waals interactions were described by Lennard Jones potentials with the analytical form:

$$V_{ij} = 4\varepsilon_{0ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right], \qquad (4)$$

where $\varepsilon_{0ij} = D_{0ij}$, and $\sigma_{ij} = 2^{-1/6} R_{ij}$.

The R_{ij} values were obtained using standard arithmetic combination rule, while D_{ij} using standard geometric combination rule, as in CLAYFF force field. It is important to note that UFF uses geometric rule for both R_{ij} and D_{ij} determinations. However, there is no significant difference in the R_{ij} determination calculated by both combination rules (the deviations were lesser than 1%).

Table SI1. Charges and atomic parameters for van der Waals interactions.

Clay	symbol	charge (*e*)	ε_{0i} (kJ/mol)	σ_i (Å)
	Si[a]	2.1000	7.7007 x10^{-6}	3.3020
	Mg	1.5975	3.7781 x10^{-6}	5.2643
	Li	1.0000	3.7781 x10^{-6}	5.2643
	Li+[b]	1.0000	0.6700	2.3370
	F	-1.0000	0.7532	3.1170
	O[a]	-1.0500	0.6502	3.1655
	Oi[a]	-1.3650		
	Oo	-1.2825		
Cipro	symbol	charge (*e*)	ε_{0i} (kJ/mol)	σ_i (Å)
		average DFT calculations	UFF	
	F_	-0.1620	0.2092	2.9970
	N1	-0.5502*	0.2887	3.2607
	N2	-0.5000*		
	O1	-0.6740*	0.2510	3.1181
	O2	-0.4596*		
	O3	-0.5330*		
	C1	0.5340*	0.4393	3.4309
	C2	-0.1800*		
	C3	0.0000*		
	C4	0.2925*		
	C6	0.4500*		
	C7	-0.0800*		
	C8	-0.3000*		
	C9	-0.1800*		
	H	0.1800*	0.1841	2.5711
	H1	0.3600*		
water SPC	HW**	0.4100		
	OW	-0.8200	0.6498	3.1655

[a] Cygan et al (Cygan et al, 2004).
[b] Koneshan et. al., (Koneshan et. al., 1998)
**HW parameters for LJ interaction with the O, F and H atoms of the cipro molecule.

Table SI2. UFF bond term parameters, equation 1.

species *i*	species *j*	k_1 (kJ/mol Å^2)	r_0 (Å)
O1	C1	5950.53	1.271060
O2	C1	6573.76	1.229550
O3	C6		
C1	C2	3871.50	1.379256
C2	C3		
C2	C4		
C2	C6		
C3	C4		
C3	C6		
C7	C8	2927.09	1.514000
C7	C9		
C8	C8		
N1	C3	5374.38	1.359893
N1	C4		
N1	C7	4404.27	1.453192
N2	C9	4395.21	1.454190
F_	C3	3508.08	1.379914
H	C2	2988.42	1.081700
H	C3		
H	C7	2767.98	1.109700
H	C8		
H	C9		
H1	N2	4369.92	1.048200

Table SI3. UFF parameters for angle interactions, equation 2.

species *i*	species *j*	species *k*	*A* (kJ/mol Å^2)	δ (º)	*m*
C3	C2	C3	931.317	180.00	3.00
C4	C3	C2			
C2	C6	C3			
C3	C4	C2			
C4	C2	C4			
C3	C2	C6			
C6	C3	C4			
C6	C3	C2			
C2	C6	O3	1318.800	180.00	3.00
C2	C1	O2			
O3	C6	C3			
C3	C4	N1	1265.530	180.00	3.00
N1	C4	C2			
C2	C3	N1			
C2	C3	H	479.194	180.00	3.00
C3	C2	H			
C4	C2	H			
O1	C1	C2	1093.950	180.00	3.00
C3	N1	C4	971.650	180.00	3.00
C2	C3	F_	844.499	180.00	3.00
F_	C3	C4			
C4	N1	C7	876.883	180.00	3.00
C7	N1	C7	796.257	180.00	3.00
N1	C7	C9	1266.330	99.38	2.55
C7	C9	N2	1265.070	99.38	2.55
C9	N2	C9	1084.450	82.02	2.45
H1	N2	H1	401.518	82.02	2.45

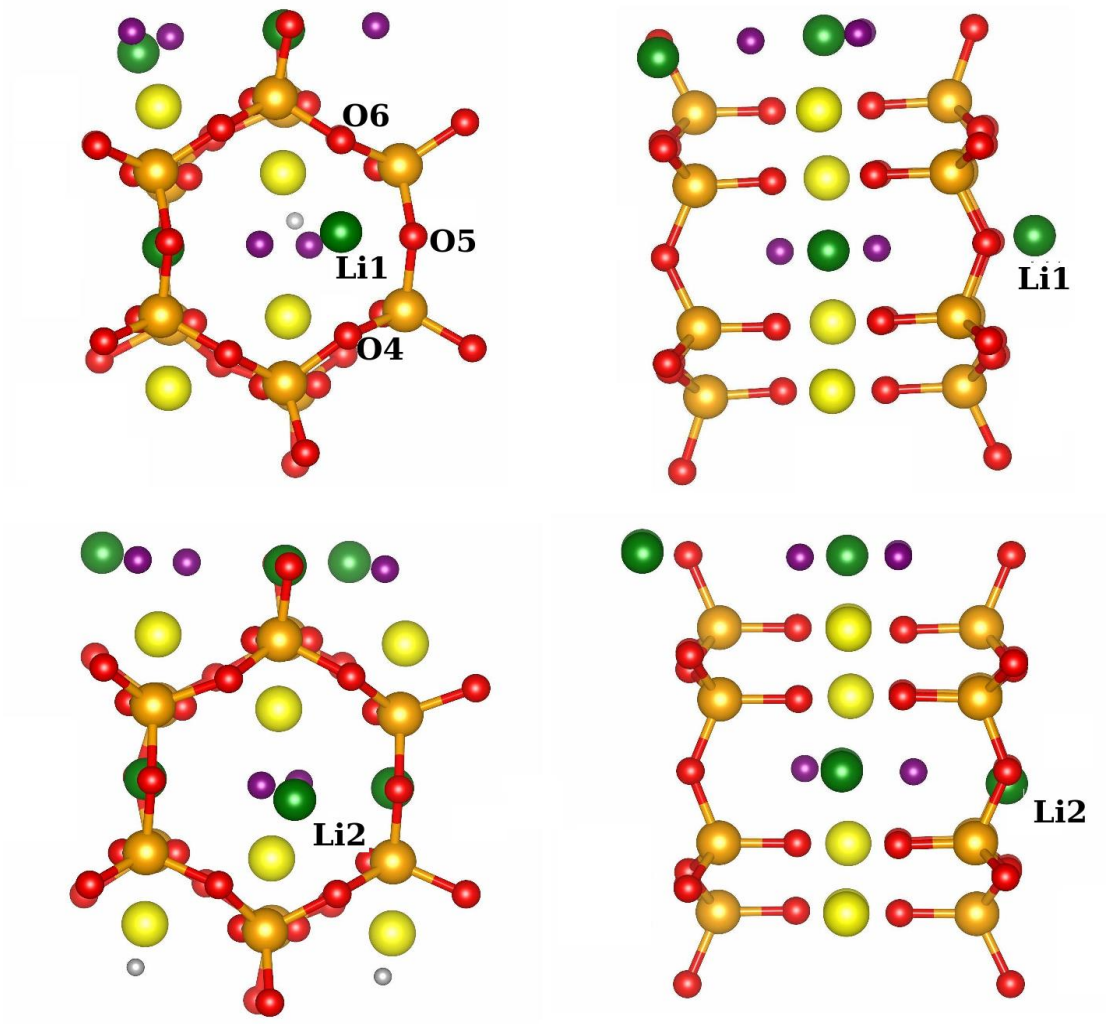

Figure SI4. Position of Li^+ compensating cations related to hexagonal cage of clay model. Orange, red, green, yellow, violet, black, white, and blue balls correspond to Si, O, Li, Mg, F, C, H and N atoms, respectively.

Table SI4. Distances, Hydrogens bonds and energy values reported by PBE0 and PBE0-D2 calculations. The atoms labeled are shown in Figure 2 of the manuscript.

Distance (Å)	PBE0	PBE0-D2
Li1-O1	1.75	1.74
Li1-O4	2.39	2.15
Li1-O5	2.07	2.24
Li1-O6	2.22	2.14
Li2-F2	1.95	1.95
Li2-F1	2.03	2.02
Li1-O7	2.16	2.33
Li1-O8	2.22	2.25
Li1-O9	2.39	2.27
Li1-O10	-	2.50
Li1-O2	3.56	3.58
Li2-O3	6.27	6.51
Number Hydrogen Bonds		
Type 1 (clay-drug)	7	9
Type 2 (drug-drug intermolecular)	2	2
Type 3 (drug intramolecular)	15	15
Energy ($x10^6$ kcal/mol)	-3,88858976	-3,88876886

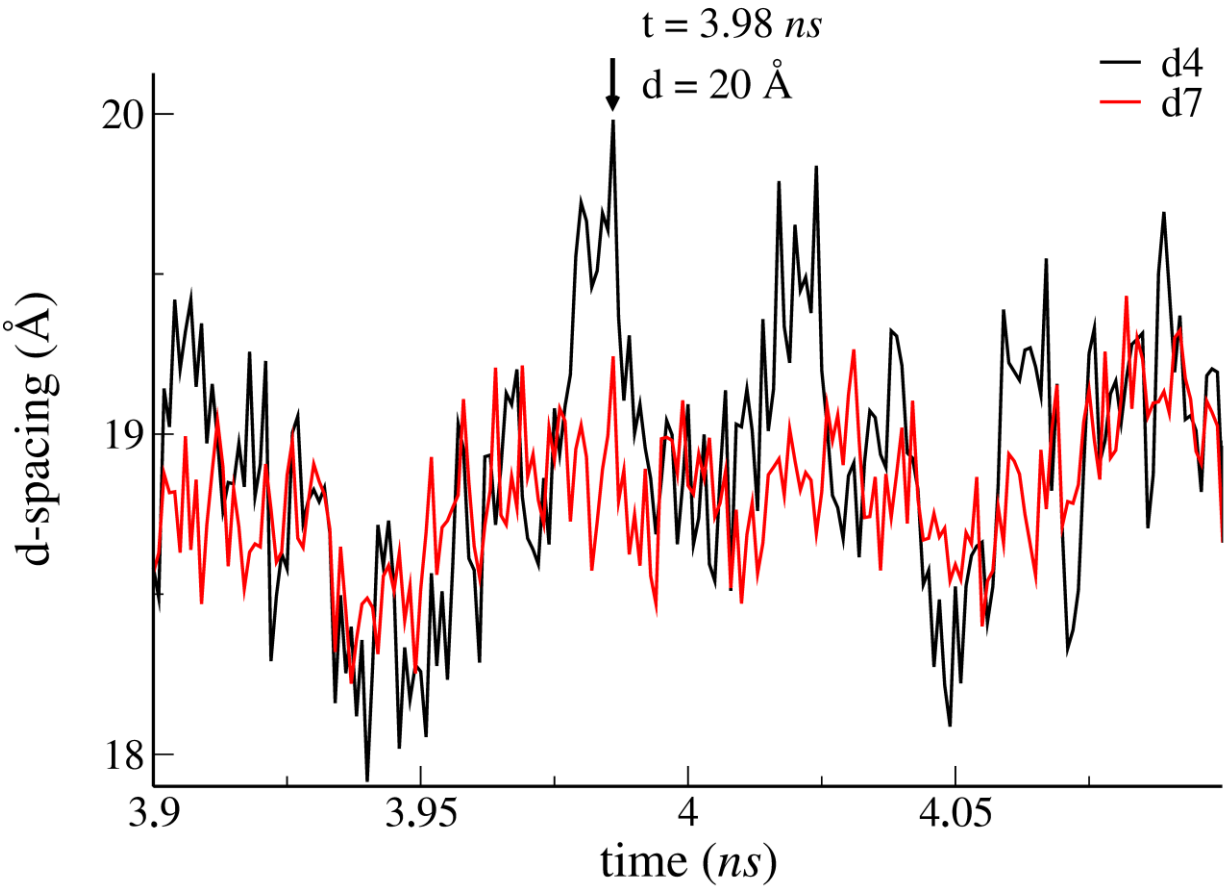

Figure SI5. *d*-spacing of d4 and d7 (the interlayer distance at the center of the layer) between 3.9 and 4.1 ns in the *LiFh-cipro-out* system.

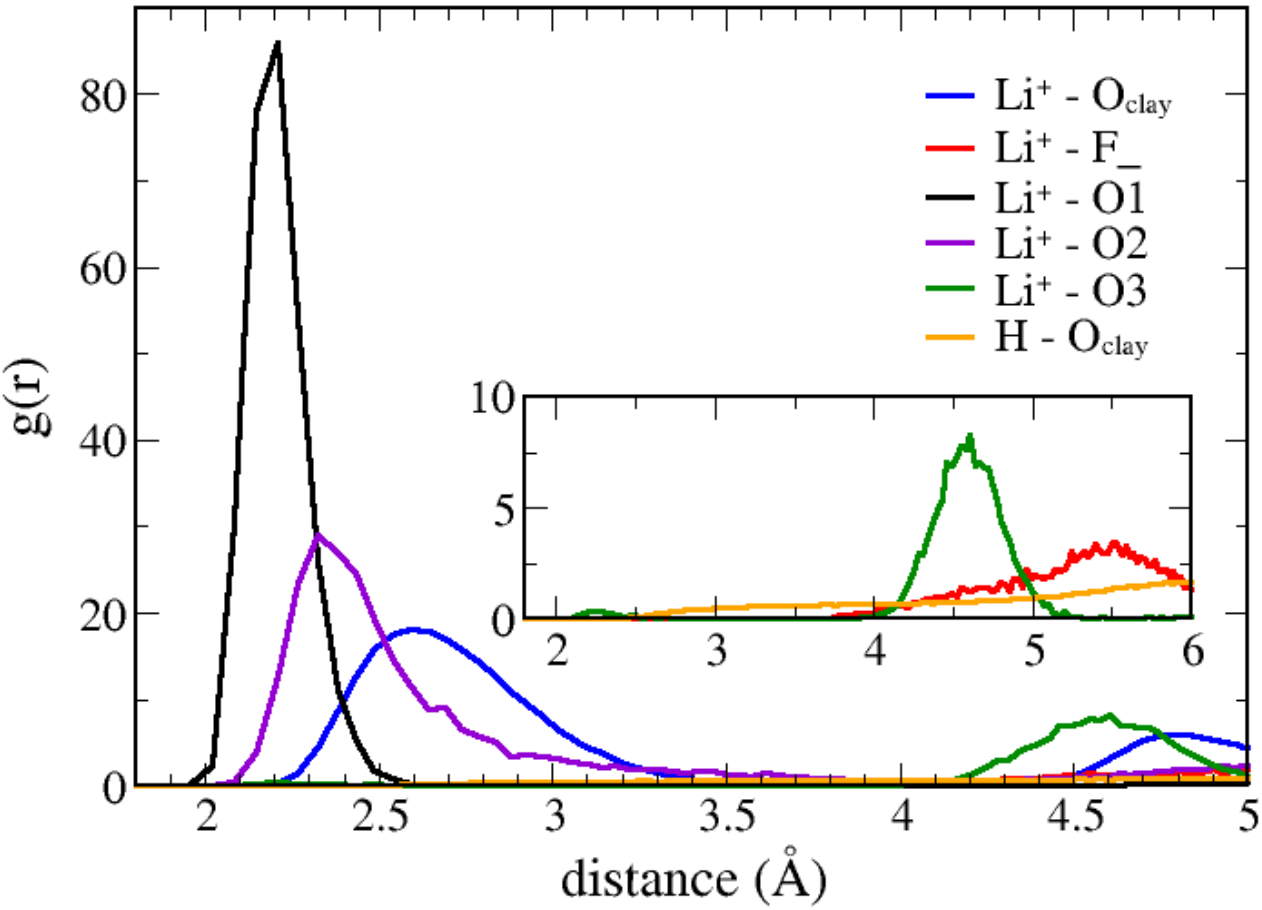

Figure SI6. Radial distribution function of the clay Li^+ cations and the oxygen atoms of clay and the cipro molecules (except H1) and the oxygens of the clay and the oxygens and fluorine of the cipro molecules in the *LiFh-cipro-in* system.

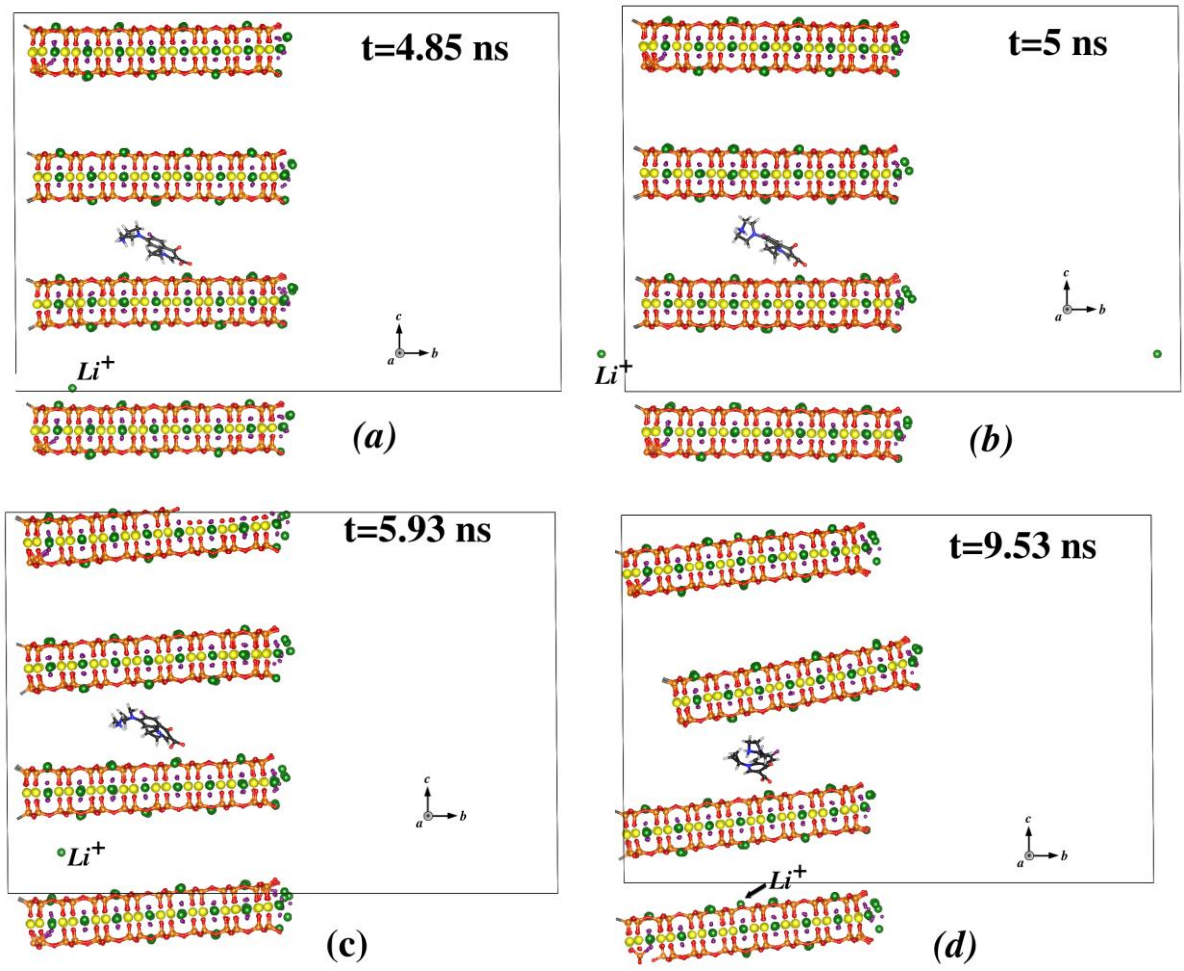

Figure SI7. Different snapshots of the movement of one Li^+ during the simulation of the *LiFh-cipro-in* system. In Figure b, the Li^+ appears twice considering periodic boundary conditions. Orange, red, green, yellow, violet, black, white, and blue balls correspond to Si, O, Li, Mg, F, C, H and N atoms, respectively.

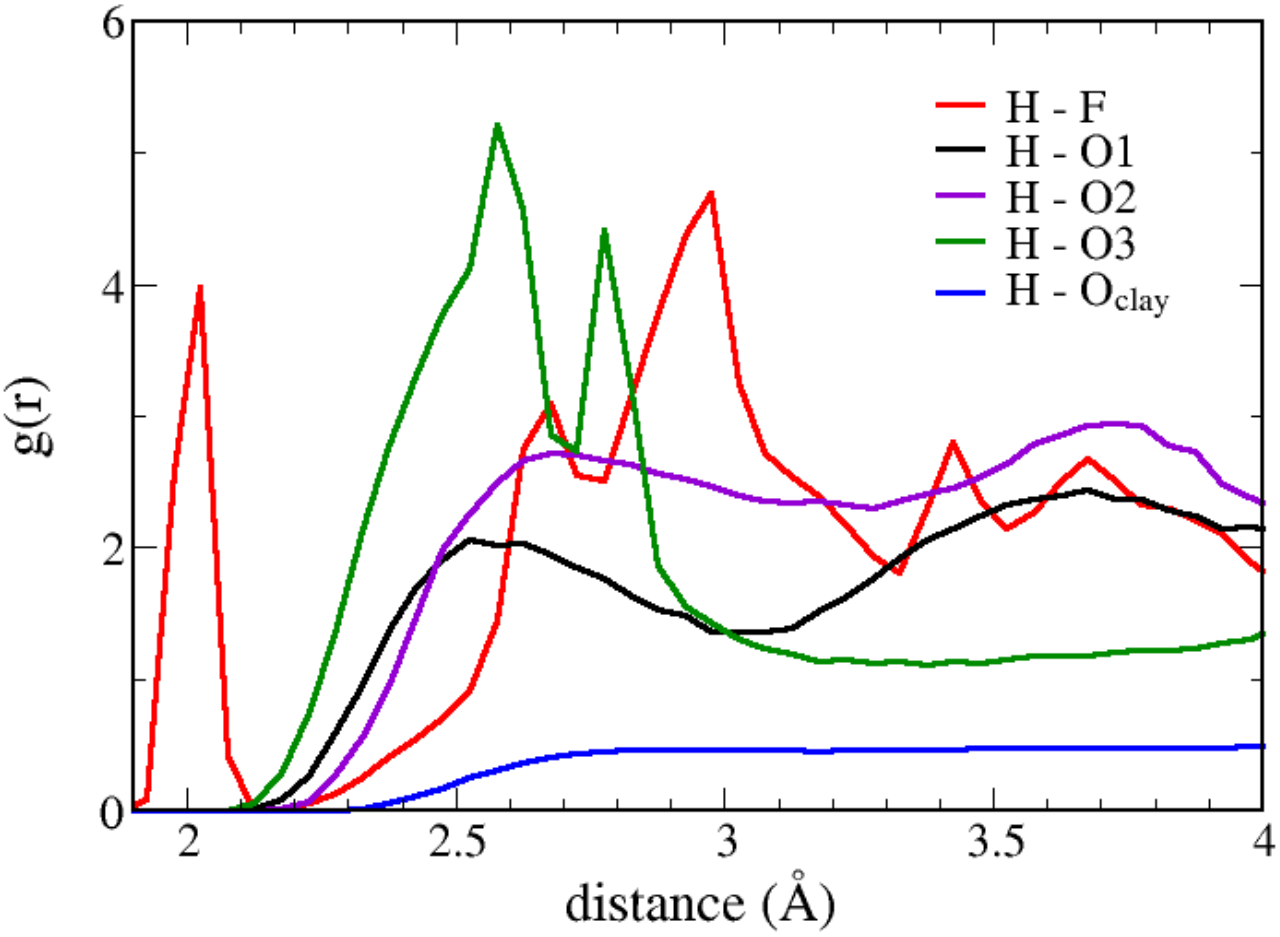

Figure SI8. Radial distribution function of the Hydrogens of the cipro molecules (except H1) and the oxygens of the clay and the oxygens and fluorine of the cipro molecules in the *LiFh-6cipro* system.

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