

Supplementary Information

Diversity of Methyl Groups Dynamics in Felodipine: a DFT Supported NMR and QENS Study

Aleksandra Pajzderska^{1,*}, Kacper Druźbicki^{1,2}, Miguel Angel Gonzalez³, Jacek Jencyk⁴,
Jadwiga Mielcarek⁵, Jan Wąsicki^{1,4}

¹*Department of Radiospectroscopy, Faculty of Physics, Adam Mickiewicz University, Umultowska 85, 61-614, Poznan, Poland;*

²*Frank Laboratory of Neutron Physics, Joint Institute for Nuclear Research, 141980, Dubna, Russian Federation;*

³*Institut Laue Langevin, B.P. 156x, 38042 Grenoble Cedex 9, France;*

⁴*The NanoBioMedical Centre, A. Mickiewicz University, Umultowska 85, 61-614, Poznan, Poland;*

⁵*Department of Inorganic and Analytical Chemistry, Poznan University of Medical Science, Grunwaldzka 6, 60-780 Poznan, Poland.*

*Corresponding author. E-mail: apajzder@amu.edu.pl

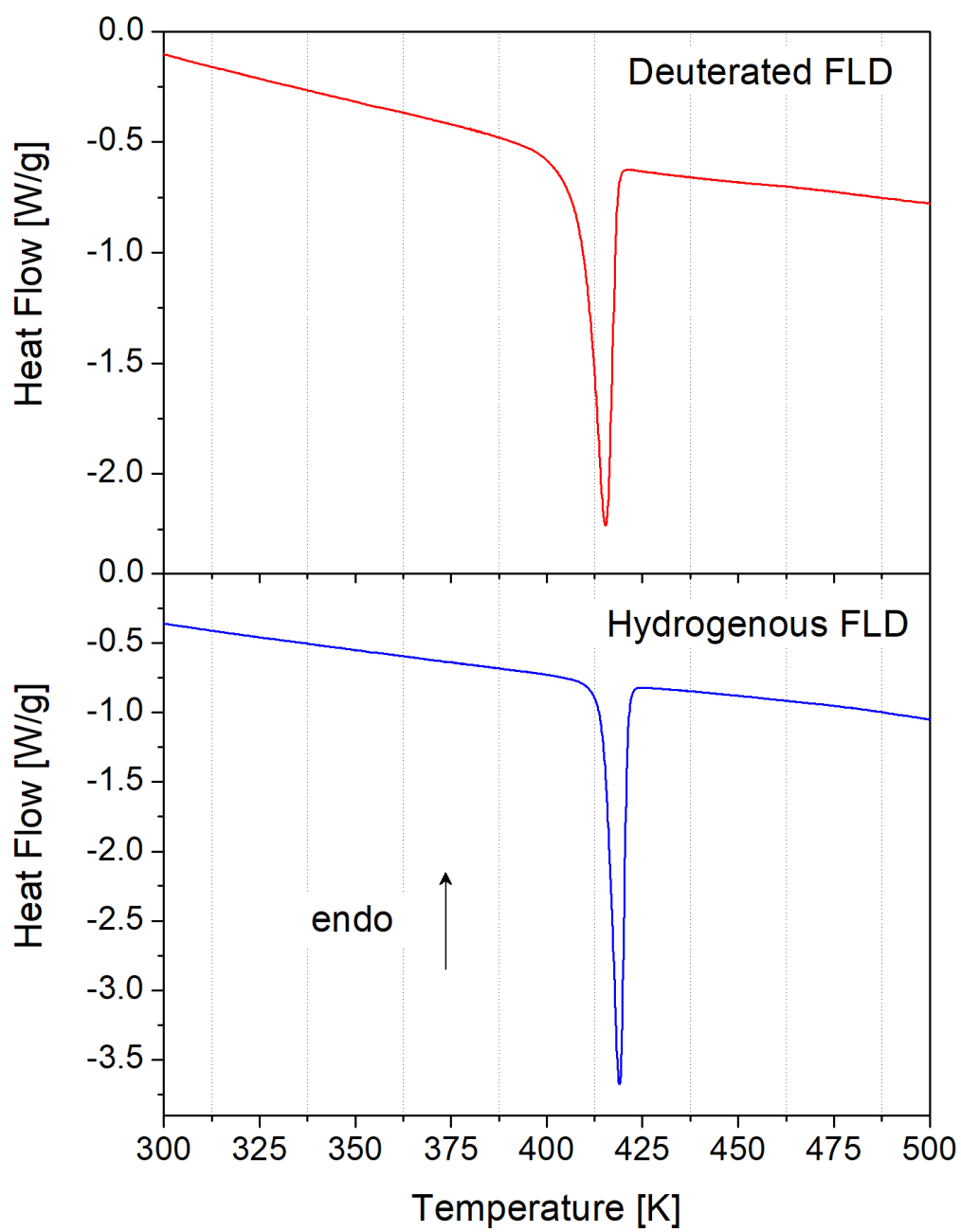


Fig. S1. Differential scanning calorimetry analysis of hydrogenous (blue line) and partially deuterated (red line) FLD form I.

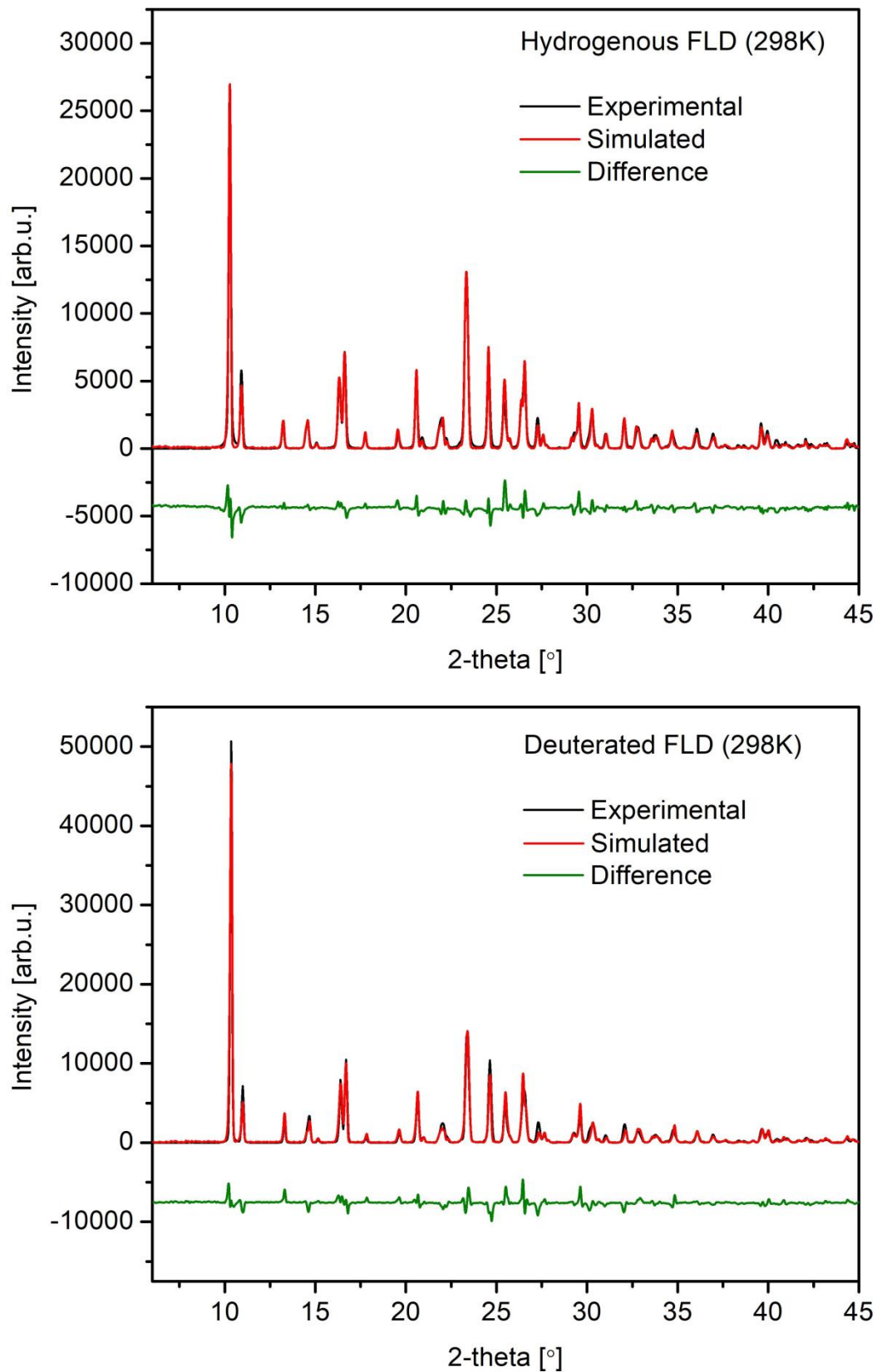


Fig. S2. Powder diffraction patterns of the fully hydrogenous (top) and partially deuterated (bottom) samples of FLD form I. The experimental curves are compared to the results of Rietveld refinement (see the simulated and the difference curves).

Table S1. Summary report for the Rietveld refinement of the $P2_1/c$ structure of FLD form I. [1]

	Hydrogenous	Deuterated	PBE-TS	PBE-MBD
Final R_{wp} :	13.62%	13.23%	-	-
Final R_p :	24.86%	21.10%	-	-
a	12.18249 ± 0.02189	12.22616 ± 0.00000	11.85262	11.97895
b	12.24474 ± 0.02204	12.26193 ± 0.00145	12.03877	11.93122
c	13.52193 ± 0.02426	13.53897 ± 0.00158	13.34191	13.32404
α	90.00000	90.00000	90.00000	90.00000
β	116.04935 ± 0.00809	116.05856 ± 0.00000	115.42820	115.11151
γ	90.00000	90.00000	90.00000	90.00000

Table S2. CE-B3LYP estimates of energy components (E_{ele} , E_{pol} , E_{dis} , E_{rep}) and total energies (E_{tot}) for the closest intermolecular interactions (defined by the symmetry operations, $Symop$) in FLD form I, based on the PBE-MBD equilibrium geometry. The energy components were rescaled according to Mackenzie *et al.* [2-3] N refers to the number of molecules with an R molecular centroid-to-centroid distance (Å). Energies are in [kJ/mol]. The interactions with $E_{tot} < 5$ kJ/mol were excluded from the analysis.

N	Symop	R	E_{ele}	E_{pol}	E_{dis}	E_{rep}	E_{tot}	Main Interaction
1	-x, -y, -z	6.15	-5.5	-3.0	-81.5	36.3	-53.6	[DHP...DHP] Anti-Parallel Stacking
1	-x, -y, -z	6.59	-14.7	-1.9	-58.0	27.7	-46.9	[PhCl ₂ ... PhCl ₂] Anti-Parallel Stacking
2	-x, y + 1/2, -z + 1/2	10.56	-41.4	-7.5	-21.6	33.1	-37.4	[NH...O] H-Bonding
2	x, -y + 1/2, z + 1/2	8.89	-19.6	-3.8	-27.7	18.0	-33.1	[C ₂ H ₅ OC=O...DHP] Attraction [CH ₂ CH ₃ ...H(PhCl ₂)] Attraction
2	-x, y + 1/2, -z + 1/2	7.88	-2.6	-0.9	-27.8	11.0	-20.3	[PhCl ₂ ... PhCl ₂] T-Shaped Stacking
1	-x, -y, -z	9.91	-4.1	-0.5	-14.2	5.1	-13.8	[CH ₂ CH ₃ ...Cl(PhCl ₂)] Attraction
2	x, -y+1/2, z+1/2	8.99	-1.1	-0.5	-13.4	7.8	-7.1	[OCH ₃ ... CH ₂ CH ₃] Attraction

Table S3. CE-B3LYP estimates of energy components (E_{ele} , E_{pol} , E_{dis} , E_{rep}) and total energies (E_{tot}) for the closest intermolecular interactions (defined by the symmetry operations, $Symop$) in FLD form I, based on the SXRD geometry.[4] The energy components were rescaled according to Mackenzie *et al.* [2-3] N refers to the number of molecules with an R molecular centroid-to-centroid distance (Å). Energies are in [kJ/mol]. The interactions with $E_{tot} < 5$ kJ/mol were excluded from the analysis.

N	Symop	R	E_{ele}	E_{pol}	E_{dis}	E_{rep}	E_{tot}	Main Interaction
1	-x, -y, -z	6.22	-4.4	-2.8	-79.1	31.6	-54.8	[DHP...DHP] Anti-Parallel Stacking
1	-x, -y, -z	6.80	-11.6	-1.8	-47.5	18.8	-42.0	[PhCl ₂ ... PhCl ₂] Anti-Parallel Stacking
2	-x, y + 1/2, -z + 1/2	10.74	-25.6	-4.7	-18.8	18.4	-30.8	[NH...O] H-Bonding
2	x, -y + 1/2, z + 1/2	9.00	-13.0	-3.0	-24.8	11.4	-29.4	[C ₂ H ₅ OC=O...DHP] Attraction [CH ₂ CH ₃ ...H(PhCl ₂)] Attraction
2	-x, y + 1/2, -z + 1/2	7.81	-3.5	-1.0	-28.6	11.1	-22.0	[PhCl ₂ ... PhCl ₂] T-Shaped Stacking
1	-x, -y, -z	9.65	-5.8	-0.7	-17.2	8.0	-15.7	[CH ₂ CH ₃ ...Cl(PhCl ₂)] Attraction
2	x, -y+1/2, z+1/2	9.06	-0.2	-0.4	-12.5	6.2	-7.0	[OCH ₃ ... CH ₂ CH ₃] Attraction

Table S4. Activation barriers for methyl groups (I–IV) reorientations as calculated for the isolated molecule of FLD and for the crystalline form I. The results come from relaxed solid-state DFT scans with several exchange–correlation functionals (vdW-corrected GGA, GGA+D and vdW-corrected global hybrid, HYBRID+D), performed with CASTEP and Gaussian09 (G09) codes.

ISOLATED MOLECULE [kJ/mol]						
DFT	CODE/Basis Set	XC	I	II	III	IV
GGA+D	CASTEP NCPP/1050 eV	PBE-MBD	1.65	1.50	3.26	11.93
GGA+D	CASTEP NCPP/1050 eV	PBE-TS	1.60	1.52	3.00	11.96
GGA+D	CASTEP NCPP/1050 eV	PBE-D2	2.11	1.83	4.02	12.25
GGA+D	G09/ DEF2-TZVP	PBE-D2	2.01	1.79	3.93	12.55
GGA+D	G09/ DEF2-TZVP	PBE-D3	1.84	1.82	3.40	12.50
GGA+D	G09/ DEF2-TZVP	PBE-D3(BJ)	1.53	1.38	3.17	12.67
HYBRID+D	G09/ DEF2-TZVP	PBE0-D3	1.88	1.76	4.10	13.08
HYBRID+D	G09/ DEF2-TZVP	PBE0-D3(BJ)	1.57	1.42	3.76	12.96
CRYSTAL FORM I [kJ/mol]						
GGA+D	CASTEP NCPP/1050 eV	PBE-MBD	3.41	3.36	2.77	10.85
GGA+D	CASTEP NCPP/1050 eV	PBE-TS	6.00	3.66	4.28	16.39
GGA+D	CASTEP NCPP/1050 eV	PBE-D2	6.15	4.62	5.14	16.63

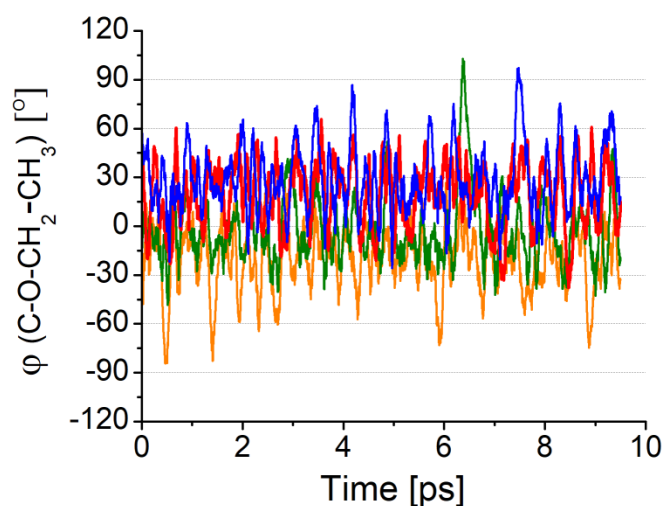


Fig. S3. Evolution of the torsional angle, describing the ethyl group libration in FLD form I, according to a 10 ps production run from the AIMD (PBE-TS) simulations (NVT at 300 K). Each line corresponds to a different FLD molecule from the unit cell.

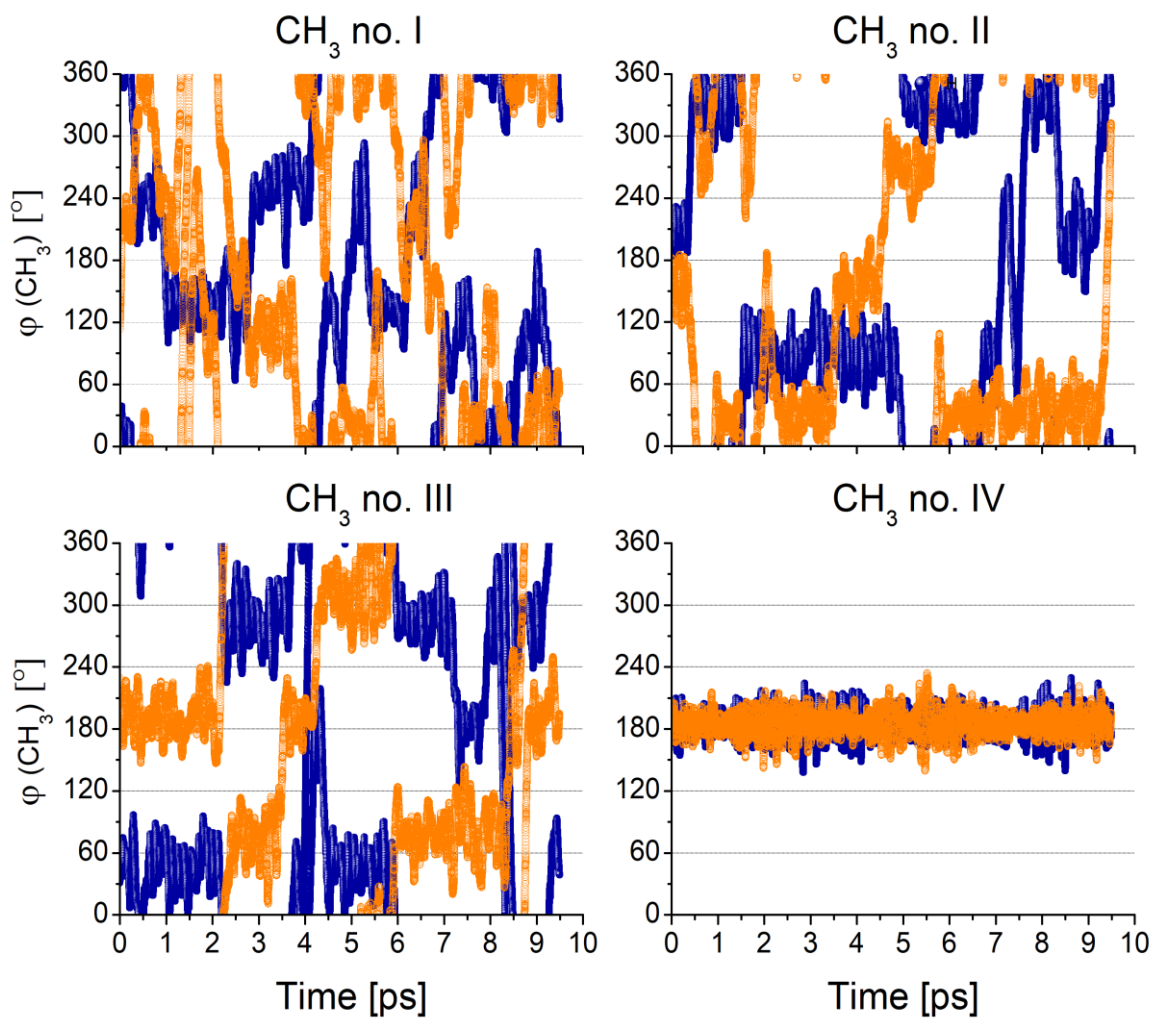


Fig. S4. Evolution of the torsional angles describing the orientation of the methyl groups (no. I – IV) in FLD form I according to a 10 ps production run from the AIMD (PBE-TS) simulations (NVT at 300 K). For the clarity, the results are presented for two selected molecules from the unit cell.

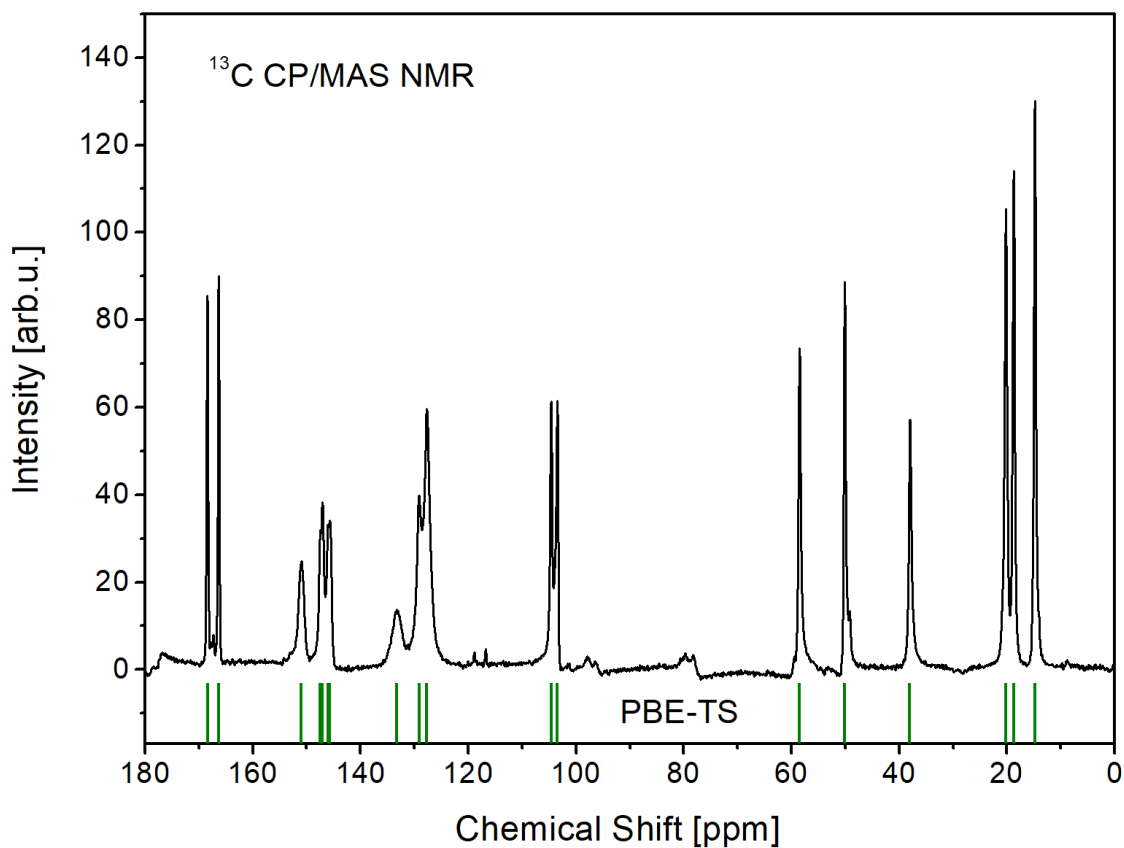


Fig. S5. The experimental solid-state ^{13}C CP/MAS NMR spectrum of FLD form I, recorded at room temperature, compared to the results of theoretical predictions (GIPAW/PBE-TS).

Table S5. Collection of experimental (^{13}C CP/MAS NMR at 298 K) and theoretical (DFT at 0 K) chemical shifts (δ [ppm]) for FLD form I along with their assignment. The theoretical data come from PW-DFT/GIPAW (PBE-TS) calculations. The atom numbering is given in Fig. S6.

δ [ppm]			Assignment
^{13}C CP/MAS NMR	GIPAW		Atom No.
	PBE-TS	MBD	
168.4	168.8	168.9	C(18)
166.3	166.3	165.6	C(15)
151.0	152.9	152.2	C(7)
147.5	149.1	149.5	C(6)
147.1	146.4	146.8	C(2)
146.0	137.2	136.9	C(12)
145.7	137.0	136.2	C(11)
133.3	131.4	130.8	C(8)
129.1	129.7	129.1	C(10)
127.7	128.3	127.1	C(9)
104.6	106.4	105.7	C(3)
103.5	103.8	103.0	C(5)
58.5	57.5	56.8	C(16)
50.1	50.5	50.5	C(19)
38.0	39.0	37.9	C(4)
20.2	21.2	21.7	C(14)
18.7	17.1	17.9	C(13)
14.8	12.9	12.6	C(17)

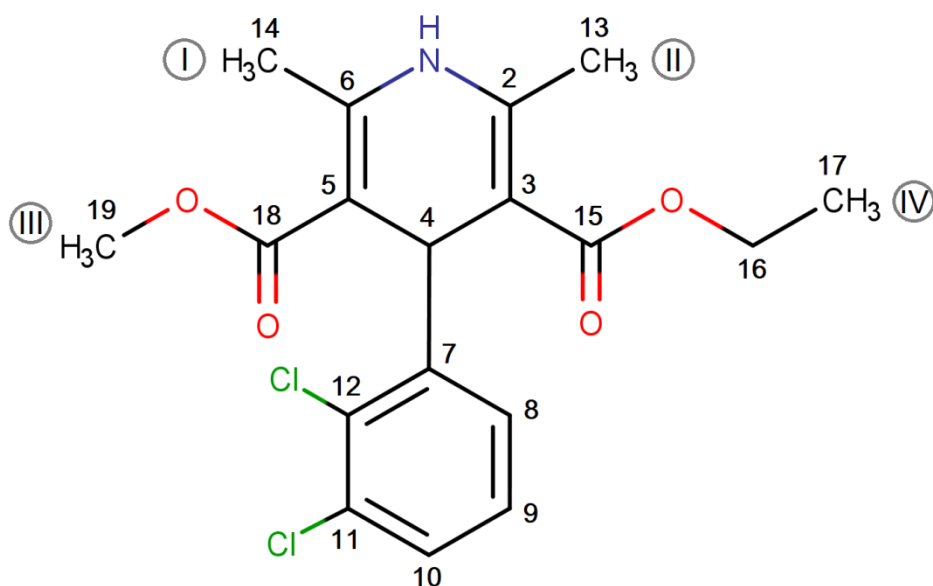


Fig. S6. Carbon atom numbering in FLD adopted in NMR analysis

References

1. REFLEX Plus, Materials Studio, version 6.1; Accelrys Inc.: San Diego, 2013.
2. M. J. Turner, S. P. Thomas, M. W. Shi, D. Jayatilaka and M. A. Spackman, *Chemical Communications*, 2015, **51**, 3735–3738.
3. C. F. Mackenzie, P. R. Spackman, D. Jayatilaka and M. A. Spackman, *IUCrJ*, 2017, **4**, 575–587.
4. R. Fosshem, *Journal of Medicinal Chemistry*, 1986, **29**, 305–307.