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Process of complexation of lovastatin with transition metal ions (cobalt, gadolinium) explored by high resolution NMR spectroscopy and molecular dynamics

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The initial sample of the study was a solution of lovastatin in deuterated acetone (C_3D_6O). This solvent was chosen because lovastatin is insoluble in water[S1]. Lovastatin from «Sigma-AldrichRus» company was used without additional purification. The structural formula of lovastatin is shown in Figure S1.

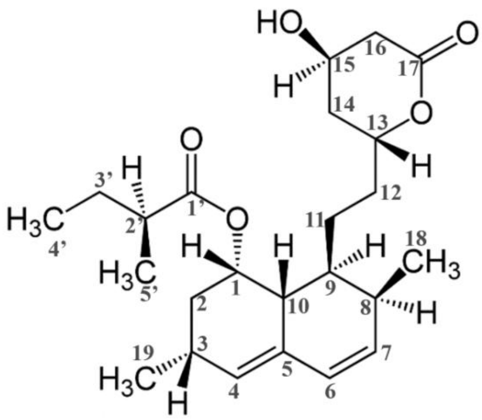

Figure S1. Chemical structure of lovastatin.

The $CoCl_2$ and $Gd(NO_3)_3$ salts were used to prepare solutions of lovastatin to study the complex of lovastatine with Co^{2+}, Gd^{3+} ions. The initial salt was initially dissolved in C_3D_6O and then added to the lovastatin-C_3D_6O sample by titration with calculation of the concentration of Co^{2+}, Gd^{3+} ions in an ampoule.

All samples were prepared in standard 5-mm NMR tubes. Concentrations of the substances dissolved in C_3D_6O were 22.0 mM (lovastatin), 2.2 and 4.4 mM ($CoCl_2$), 0.29 and 0.44 mM ($Gd(NO_3)_3$). The solution volume for all samples were 0.5 ml.

Registration of 1D, 2D NMR spectra of lovastatin in C_3D_6O at a temperature of 308 K with and without addition of Co^{2+}, Gd^{3+} ions were carried out using pulsed NMR spectrometer Bruker Avance III-700 NMR (700 MHz (^{1}H), 175 MHz (^{13}C)). The spectrometers are equipped with a ^{2}H lock system to stabilization of magnetic field. ^{1}H NMR spectra were recorded using 90° pulses, the delay between pulses was 2 s, the spectral width was 10 ppm and a minimum of 16 scans. ^{13}C NMR spectra were recorded using 90° pulses, the delay between pulses was 2 s, the spectral width was 200 ppm and a minimum of 100 scans. Chemical shifts were determined relative to TMS (tetramethylsilane). The TOPSPIN 3.0 software was used to obtain and process the spectra. The assignment of spectral lines in NMR spectra was performed by using high resolution NMR spectroscopy methods of 1D, 2D experiments[S2].

GROMACS software was employed for molecular dynamics simulations investigating interactions between lovastatin and Co^{2+}/Gd^{3+} ions in acetone solution using CHARMM36 force field. The initial configuration underwent energy minimization using the steepest descent algorithm with an energy convergence threshold of <1000 kJ/mol·nm. Then, each optimized molecular system was equilibrated in the NVT ensemble (300 K, 200 ps) using the Berendsen thermostat (coupling constant τ = 0.1 ps). Subsequently, the molecular system was equilibrated in the NPT ensemble (300 K, 1 bar, 300 ps) using Berendsen thermostat (τ = 0.1 ps) and Parrinello-Rahman barostat (τ = 3 ps, compressibility = 4.5×10^{-6} bar). Production simulations were subsequently performed in the NPT ensemble (300 K, 1 bar). Periodic boundary conditions were used in the MD simulations. Electrostatic interactions were handled using the Particle Mesh Ewald (PME). The various simulations were run for at least 500 ns, and snapshots of the trajectories were taken every 2 ns[S3-S5]. The model system consisted of 20 molecules of lovastatin with the addition of Co^{2+} or Gd^{3+} ions (ratios of 5/1, 10/1 for Co^{2+} and 50/1, 75/1 for Gd^{3+} corresponding to the NMR experimentally studied solutions). Then the system was placed in a periodic cubic cell of 10x10x10 nm with 32284 aceton-d_6 molecules (this ratio was also chosen based on the experimentally studied concentration of the solutions). The CHARMM36 force field was used for parameterization.

All T_1-relaxation times were measured on a Bruker Avance III-700 NMR spectrometer. T_1-relaxation measurements were performed using the inversion-recovery method. The following parameters were used to record T_1-relaxation: 90° pulse duration was 8.0 μs, 180° pulse duration was 16.0 μs, the number of scans was 16, the delay before applying the pulse sequence was 120 s, the interval between 180° and 90° pulses was from 0.05 to 30 s. Decays were monoexponential over 2 orders of magnitude.

The electron formula of the cobalt atom: $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^6\ 4s^2\ 3d^7$ (the 3d orbital contains three unpaired electrons). The cobalt ion has an unfilled d-shell, which allows it to effectively participate in coordination interactions with donor atoms (O, N), forming d-π or d-σ bonds. Localization: preferentially in sites rich in hard donors (carboxyl groups, hydroxyl, carbonyl oxygens), where directional coordination is possible.

The electron formula of the gadolinium atom: $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^6\ 4s^2\ 3d^{10}\ 4p^6\ 5s^2\ 4d^{10}\ 5p^6\ 6s^2\ 4f^7\ 5d^1$ (the 4f orbital has seven unpaired electrons and the 5d orbital has one unpaired electron). Localization: preferentially near negatively charged or highly polar groups (e.g., carboxylates, phosphates), where electrostatic stabilization is important rather than directional covalent bonding.

Supplementary files:

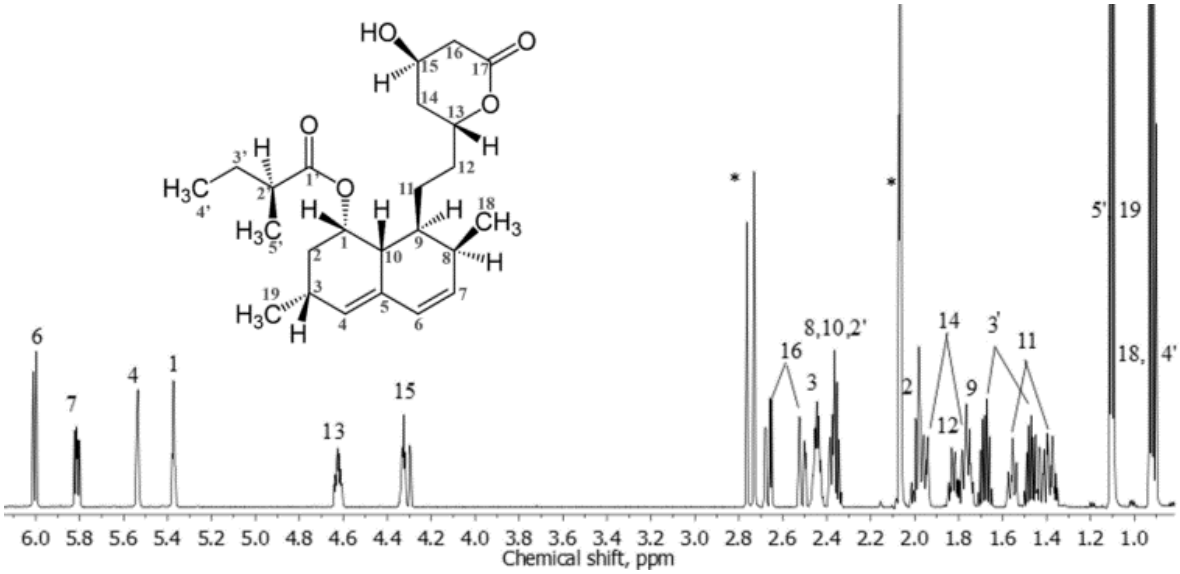

Figure S2. ^{1}H NMR spectrum of lovastatin in acetone-d_6 at 308 K, * - solvent signals.

Table S1 Chemical shifts and changes in the chemical shifts of C<u>H</u>$_2$-16, C<u>H</u>-3, C<u>H</u>-8, C<u>H</u>-10, C<u>H</u>-2’ protons in the ^{1}H NMR spectrum of lovastatin with Co^{2+} ions at statin/ion ratios 1/0 (a), 10/1 (b), 5/1 (c) in acetone-d_6.

Signal / ppm		a	b	c
C<u>H</u>$_2$-16	1	2.68	2.67 {-0.01}	2.66 {-0.02}
	2	2.51	2.50 {-0.01}	2.49 {-0.02}
C<u>H</u>-3		2.44	2.44	2.45 {+0.01}
C<u>H</u>-8		2.38	2.39 {+0.01}	2.40 {+0.02}
C<u>H</u>-10		2.36	2.36	2.37 {+0.01}
C<u>H</u>-2’		2.35	2.35	2.36 {+0.01}

Table S2 Chemical shifts and changes in the chemical shifts of C<u>H</u>$_2$-16, C<u>H</u>-3, C<u>H</u>-8, C<u>H</u>-10, C<u>H</u>-2' protons in the ^{1}H NMR spectrum of lovastatin with Gd^{3+} ions at statin/ion ratios 1/0 (a), 75/1 (b), 50/1 (c) in acetone-d_6.

Signal / ppm		a	b	c
C<u>H</u>$_2$-16	1	2.67	2.67	2.67
	2	2.51	2.51	2.51
C<u>H</u>-3		2.44	2.44	2.44
C<u>H</u>-8		2.38	2.38	2.38
C<u>H</u>-10		2.36	2.36	2.36
C<u>H</u>-2'		2.35	2.35	2.35

Table S3 T_1 relaxation times of different groups of lovastatin in acetone at different statin/cobalt ion ratios at 300 K.

Statin/ion ratio	T_1, s CH-6	T_1, s CH-7	T_1, s CH-4	T_1, s CH-1	T_1, s CH-13	T_1, s CH-15	T_1, s CH_2-16^1	T_1, s CH_2-16^2
no ion	2.38	2.16	2.24	1.20	2.03	2.53	1.6	1.8
20/1	2.21	1.96	2.07	1.07	1.62	1.75	1.46	1.54
10/1	2.07	1.85	2.00	1.03	1.61	1.49	1.19	1.27
5/1	1.84	1.65	1.81	0.90	1.44	1.26	0.97	1.02
1/1	1.09	0.91	0.84	0.45	0.14	0.78	0.74	0.74

Table S4 T_1 relaxation times of different groups of lovastatin in acetone at different statin/gadolinium ion ratios at 300 K.

Statin/ion ratio	T_1, s CH-6	T_1, s CH-7	T_1, s CH-4	T_1, s CH-1	T_1, s CH-13	T_1, s CH-15	T_1, s CH_2-16^1	T_1, s CH_2-16^2
no ion	2.38	2.16	2.24	1.20	2.03	2.53	1.63	1.84
100/1	1.49	1.32	1.43	0.45	0.69	0.49	0.44	0.56
50/1	1.07	1.00	0.96	0.25	0.35	0.18	-*	0.20

* - The 50/1 statin/ion ratio of CH_2-16^1 group is not presented because of target signal has been closed by signal of H_2O from the salt.

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