ELECTRONIC SUPPLEMENTARY INFORMATION

Solvation of diclofenac in water from atomistic molecular dynamics simulations – interplay between solute-solute and solute-solvent interactions

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1 Water under ambient conditions using Car–Parrinello MD

Water seems to be among the simplest, cheapest and easily accessible solvents, but its correct theoretical description, especially for the usage in ambient conditions, is not so simple. After the decades of an extensive search of the correct way for the theoretical treatment of water as a solvent in *ab initio* molecular dynamics (AIMD) simulations, it is still under investigation. There are a lot of approximated models of water used in classical MD simulations, which are successfull in the simulations of proteins, peptides, membranes etc., but more accurate and reasonable ways for the theoretical description of water in ambient conditions in AIMD are under development.

In most cases, the usage of *explicit* water as a solvent is connected with the size of the system studied of ca. hundreds of atoms, therefore, the density functional theory (DFT) approach, is often used in MD simulations. It uses specially designed functionals to describe the properties of the system originated from its electronic structure. Unfortunately, the usage of the Generalized Gradient Approximation (GGA) density functionals is connected with overstructuring of liquid water, an underestimating heat capacity and self-diffusion constant[1,2]. It is caused because of "the presence of self-interaction error and the neglect of non-local electron correlation effect"[3], therefore, the dispersion is not properly described. The lack of dispersion influences the structure of water, H-bond strength and pattern, nuclear quantum effects, stretching vibrations, binding and sublimation energies[2]. To overcome this problem, additional dispersion corrections to DFT functionals should be used[2–8]. It was found the melting temperature of water without including dispersion is 411±4 K (BLYP) and 417±3 K (PBE)[9], while with dispersion correction it decreases on ca. 50 K[7,10]. Among the most common used ways of including dispersion in AIMD simulations of water are Grimme dispersion corrections[2,4,5,11] and dispersion-corrected atom-centered pseudopotentials (DCACPs)[8,12,13]. Both ways give comparable results[14].

DFT description of water in ambient conditions is not influenced only by dispersion, but also by polarizability, which impact the structure of water and, therefore, the radial distribution function (RDF). Polarizability is overestimated in DFT/GGA, so the liquid is supercooled[15]. It can not be fully solved with the addition of the dispersion correction, but with the usage of higher temperature of the simulation that enables solvent to be a liquid-like. As a result, AIMD of water using DFT is performed at elevated temperatures[16]. Temperature of the simulation depends on the used DFT functional. For the most widely used functionals for AIMD simulations of water, i.e. BLYP[5,7,9,11–14] and PBE[2–4,9,11,17–19], the temperature in the range of 330–400 K is used. To obtain the proper temperature of the simulation, RDF of the simulated water should be analyzed[1,2,5] and compared with neutron and x-ray diffraction data[2]. Taking into account the light mass of the hydrogen atom and the quantum mechanical nature in nuclear degrees of freedom, RDF of the oxygen–oxygen distances in water is the best way to check if the computational setup used describes water correctly[2]. Moreover, the height of the first peak on the RDF plot is the most important here[1,6,8].

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In the present research PBE functional was used and the temperature of 390 K was tested as an adequate one to mimic the liquid-like structure of water obtained experimentally[20,21]. Pham et al.[19] have shown that MD simulations using this temperature value are in a good agreement with the experimental data. The radial pair distribution function of the O···O distances of water in the present research is shown in Fig. 1.

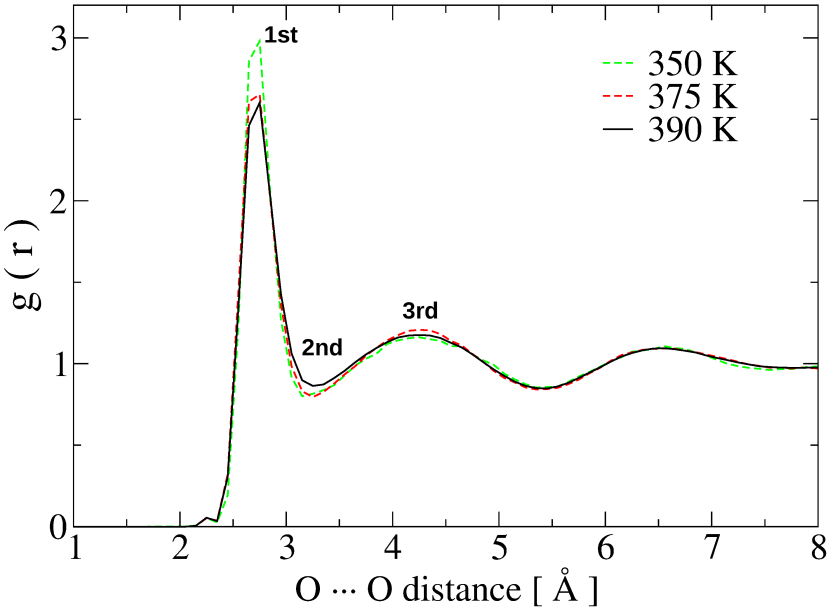

Fig. 1 The oxygen–oxygen radial pair distribution function (RDF) of water at different temperatures from Car–Parrinello molecular dynamics simulations using PBE functional and Grimme D2-dispersion correction.

It is clearly seen that increasing the temperature of AIMD simulations changes the distribution of the O···O distances and makes the system more similar to fluid. The values of the position (r) and intensity ($g(r)$) for three peaks are listed in Table 1. It should be noted that among the mentioned descriptors of each peak (extremum), the value of the intensity $g(r)$ (especially of the 1st one) is the most important and should be carefully checked. The position of the peaks is not temperature-dependent[19].

Table 1 Temperature control of the O–O peak intacts of the radial pair distribution function of water used to dissolve diclofenac molecules in the Car–Parrinello MD simulations. Each peak (extremum) is described with the position r, and intensity $g(r)$. Values marked in blue and red correspond to the production run of the monomer of DCL in water and the dimer of DCL in water, respectively.

T [K]	t [ps]	1st peak			2nd peak			3rd peak		
		r_1 [Å]	$g_1(r_1)$	$\Delta g_1(r_1)^a$	r_2 [Å]	$g_2(r_2)$	$\Delta g_2(r_2)^a$	r_3 [Å]	$g_3(r_3)$	$\Delta g_3(r_3)^a$
350	1	2.75	3.06	0.49	3.15	0.69	-0.15	4.35	1.18	0.06
375	20	2.76	2.64	0.07	3.23	0.78	-0.06	4.24	1.19	0.07
390	5	2.75	2.59	0.02	3.25	0.85	0.01	4.35	1.16	0.04
390	25	2.76	2.60	0.03	3.28	0.84	0.00	4.29	1.20	0.08
390	100	2.76	2.59	0.02	3.24	0.86	0.02	4.28	1.17	0.05
390	100	2.76	2.56	-0.01	3.26	0.79	-0.05	4.28	1.20	0.08
298	Ref.[20]	2.76	2.62	–	3.42	0.82	–	4.43	1.14	–
298	**Ref.[21]**	**2.80**	**2.57**	–	**3.45**	**0.84**	–	**4.50**	**1.12**	–

[a] Compared with data presented in Ref.[21]

The mentioned RDF analysis of water, together with the computational setup used in the previously reported AIMD simulations of water, helped us to select the temperature value of 390 K as an appropriate one for the Car–Parrinello MD simulations in the present research.

2 Conformational space of the diclofenac molecule

In order to check the accuracy of the classical molecular dynamics simulations in reproduction the correct structural parameters of the diclofenac (DCL) molecule, the analysis of the conformational space of the drug molecule was performed. The quantum chemistry approach, using density functional approach with B97-D3/6-311++G(d,p), was used to estimate local minima structures of DCL in the gas phase and to calculate energy barriers for the rotation about the CCNC dihedral angle between two phenyl rings of DCL. The CCNC dihedral angle is among the most important structural parameters of the drug, causing its high biological activity, and it is the best parameter to be verified in different levels of theory. The CCNC dihedral angle of DCL was shown in Fig. 1 in the main text of the publication.

After the geometry optimization, followed by the vibrational analysis, 19 conformers of DCL were selected as different local minima. Coordinates of all estimated local minima structures of diclofenac are attached in Section 5 of the present ESI. In Table 2 the corresponding absolute and relative energies of all conformers are listed. The relative energy was estimated as the difference between the absolute energy of the corresponding local minimum and the absolute energy of the global minimum structure. The global minimum structure is characterized with the lowest absolute energy value (0.00 kcal/mol in Table 2), therefore, positive values of the relative energy denote less stable DCL conformers. All DCL local minima structures are shown in Fig. 2.

Table 2 Conformational space of the diclofenac molecule. All local minima structures obtained using B97D3/6-311++G(d,p) followed by vibrational analysis

Label	$\mathbf{E}_{abs}$ [Hartree]	$\mathbf{E}_{rel}$ [kcal/mol]
a	-1665.5492	0.00
b	-1665.5478	0.87
c	-1665.5451	2.60
d	-1665.5442	3.13
e	-1665.5442	3.14
f	-1665.5440	3.26
g	-1665.5434	3.68
h	-1665.5424	4.32
i	-1665.5419	4.59
j	-1665.5414	4.90
k	-1665.5412	5.07
l	-1665.5411	5.10
m	-1665.5408	5.30
n	-1665.5407	5.39
o	-1665.5403	5.64
p	-1665.5401	5.71
q	-1665.5400	5.82
r	-1665.5397	6.00
s	-1665.5327	10.40

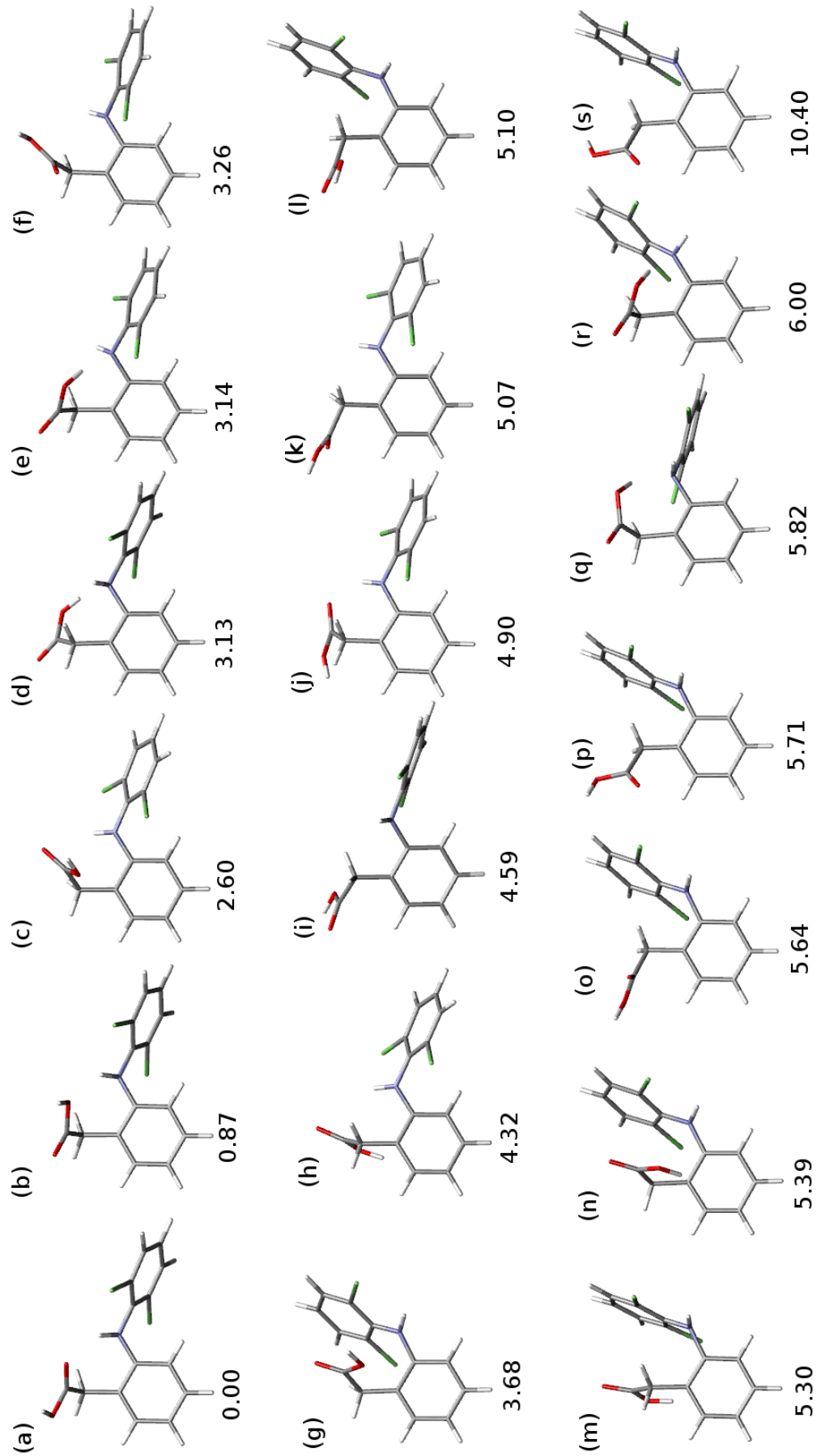

Fig. 2 Local minima structures of the protonated diclofenac molecule obtained using B97D3/6-311++G(d,p). The corresponding values of the relative energy is given for each calculated structure.

The calculations of the energy barrier for the rotation about the CCNC dihedral angle (see Fig. 3) were made every 10° with the full relaxation of the remaining part of the DCL molecule within B97-D3/6-311++G(d,p) approach. From

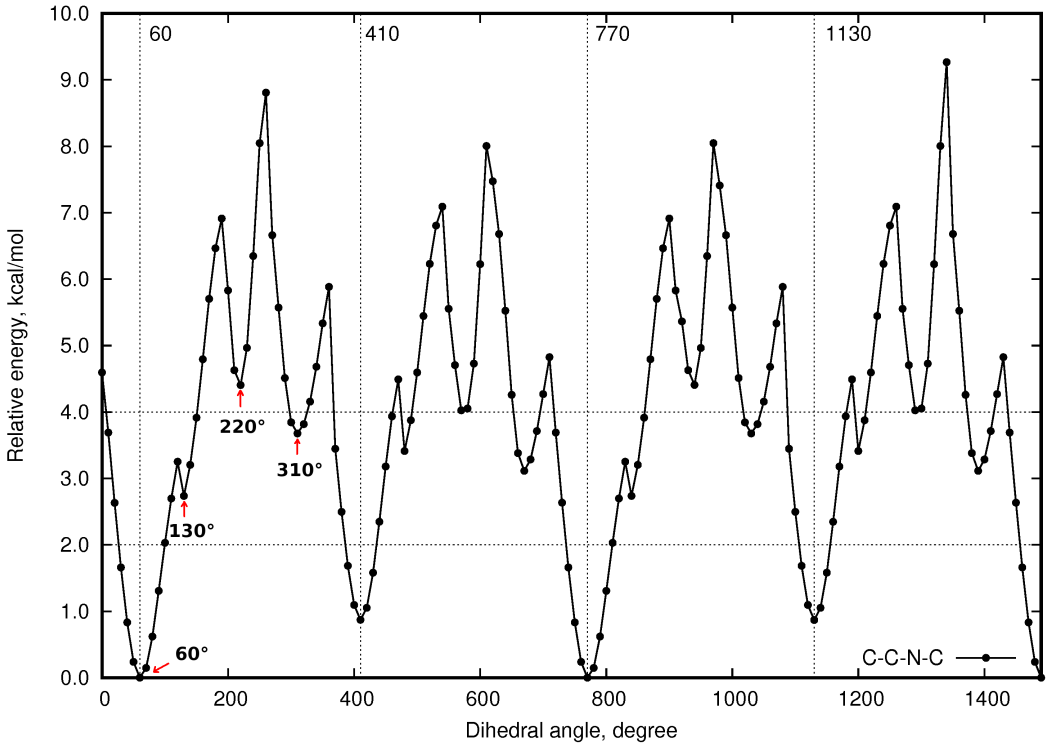

Fig. 3 Energy barrier for the rotation about the CCNC dihedral angle of the diclofenac molecule. The dihedral angle is marked with green circles in Fig. 1 in the main text of the manuscript. The scan was made every 10° (each filled black dot indicates the change by 10°).

Fig. 3 it can be seen that the CCNC dihedral angle is reproduced every two cycles of rotation (every 720°), whereas 4 local minima of DCL molecule exist during the rotation upon 360°. These DCL local minima correspond to the value of CCNC dihedral angle of: 60° (0.00 kcal/mol), 130° (2.74 kcal/mol), 220° (4.41 kcal/mol) and 310° (3.68 kcal/mol). The DCL molecule with the angle of 60° is the global minimum structure. This estimation is in agreement with the previously reported global minimum structure of DCL[22] and the crystal structure of the drug, where the CCNC angle was of 58.55° and 62.56°, respectively.

3 Diclofenac in classical MD simulations: parameters verification

3.1 Monomer of diclofenac

In the present research the combination of different levels of theory was used. The main part of the research focuses on the classical molecular dynamics simulations of the diclofenac molecules in water under ambient conditions. Therefore, the adequate parametrization of the system studied was needed. Taking into account that water models, used in classical MD, are widely known and were tested before, we were interested in parametrization of the solute molecule, i.e. diclofenac. The force field parameters and the topology of the diclofenac molecule were generated using the CHARMM General Force Field (CGenFF)[23,24] (version 1.0.0), which is used to provide parameters for small organic molecules. To estimate the accuracy of the generated parameters several tests were made.

Firstly, the classical MD simulations of one diclofenac molecule in the gas phase were made and checked with the previously published data concerning the gas-phase Car–Parrinello MD simulations of DCL at 300 K[22]. Time evolution of the selected structural parameters of the diclofenac molecule using both levels of theory is shown in Fig. 4. The CP–MD simulation was 30 ps long and no significant changes in the CCNC dihedral angle have been observed. In the classical MD simulation, which was 1 ns long, transition between DCL conformers was seen. This transition corresponds to the change between DCL global minimum structure and the first local minimum (see Fig. 3). Comparing to *ab initio* results, the values of the CCNC dihedral angle of the same conformers in classical MD are ca. 75° and 105–125° instead of 60° and 110–130°.

The superposition of the DCL structure taken from classical MD and Car–Parrinello MD has proven the similarity of both DCL conformers obtained using different level of theory. Additionally, the same transition was estimated in the longer CP–MD simulations (100 ps) of dimer of DCL (see the main text of the manuscript). Altogether, it was established that both DCL conformers are possible to be present, therefore, the topology of DCL was estimated as a correct one.

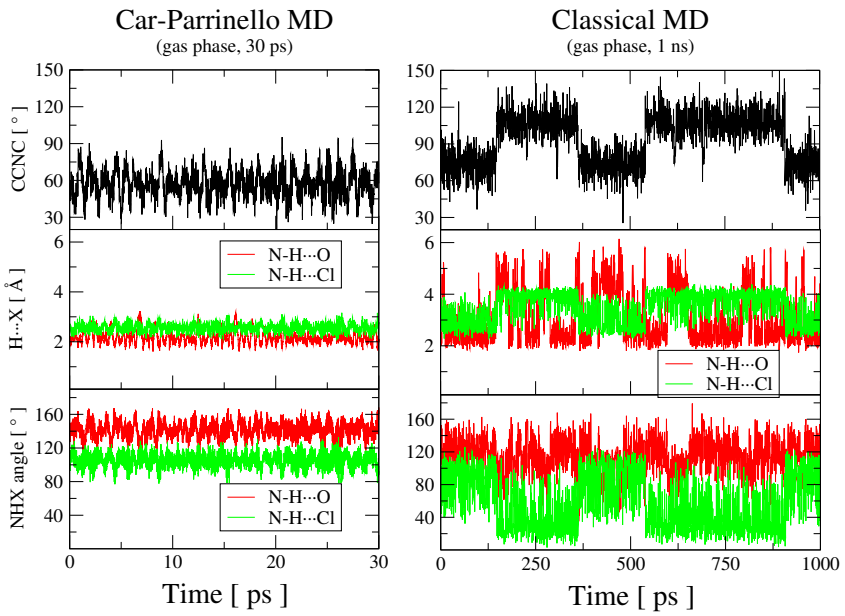

Fig. 4 Time evolution of the selected structural parameters of the diclofenac molecule in the gas phase: CCNC dihedral angle, H···X distance and NHX valence angle of intramolecular N-H···O and N-H···Cl hydrogen bonds, in Car–Parrinello and classical MD simulations at 300 K.

As it was mentioned in the literature[22], the specific structure of the diclofenac molecule is caused also by its intramolecular N-H···O and N-H···Cl hydrogen bonds. Classical MD approach has been known to suffer from the poor description of weak interactions in the system, therefore, the changes of these hydrogen bonds were also analyzed in the present work. From Fig. 4 it could be seen that *dynamics* of both H-bonds is similar in the MD runs of different levels of theory. Due to longer timescale and conformational changes of the DCL molecule in the classical MD simulations, the H···X distance and NHX valence angle are more variable, but, in general, they are reproduced quite well with CP–MD results.

In the next step, the comparison between CP–MD and classical MD simulations was made concerning the diclofenac molecule in water. The time evolution of the same structural parameters of the diclofenac molecule is shown in Fig. 5. From the correlation between quantum and classical MD results, the adequacy of the classical description can be concluded. The production run in CP–MD simulations is definitely too short to see the most important transitions between DCL conformers. The time of 100 ps, which was used for the CP–MD simulation of diclofenac in water, is depicted with orange line on the plots made for the results from classical MD. Therefore, using CP–MD we were able to simulate only short period of time of one of the DCL conformer. The same transitions between DCL local minima, as it was seen in the gas phase, were obtained also in MD simulations in water. Additionally, the transition to the remaining two conformers was established. It means that in longer simulation time DCL changes between four local minima structures, similar to the ones obtained during the analysis of barrier rotation upon the CCNC dihedral angle. Additionally, intramolecular N-H···O and N-H···Cl hydrogen bonds were also analyzed and were found to be properly described with classical MD approach.

During the CP–MD simulation of the DCL monomer, the deprotonation of the drug molecule in water was observed (at 56 ps). It started from the formation of strong intermolecular O-H···O hydrogen bond between the OH group of the diclofenac molecule and O atom of the neighbor water molecule. Due to the fact that the water molecule is, relatively, small and its structure can easily adjust to the DCL molecule and interact via strong O-H···O H-bond, the proton transfer takes place and H atom moves to water with the formation of temporary hydronium cation (the lifetime of the hydronium cation was ca. 150 fs). Since then the hoping of H atom between water molecules has been seen. This fact confirms the transformation between the protonated and deprotonated DCL in water, what strongly depends on the pH of the solution.

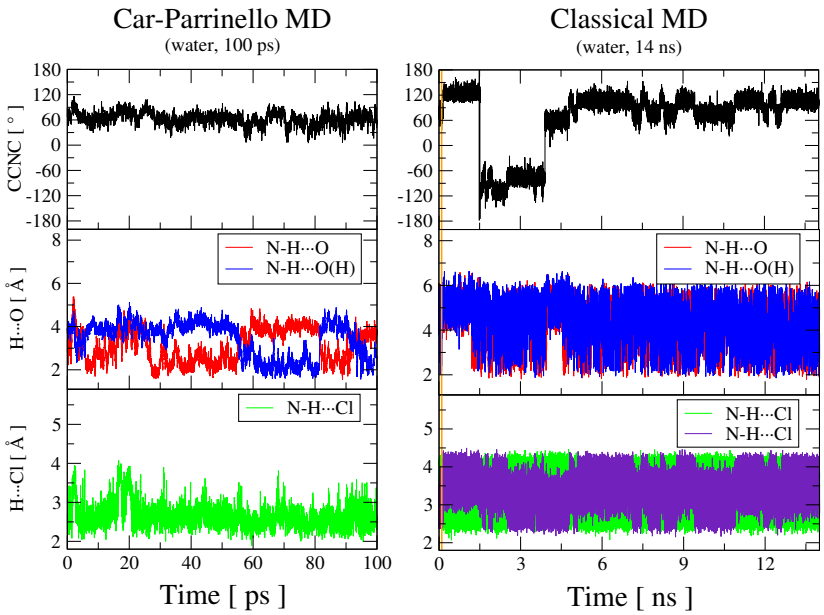

Fig. 5 Time evolution of the selected structural parameters of the diclofenac molecule in water: CCNC dihedral angle, H···O and H···Cl distances of intramolecular N-H···O and N-H···Cl hydrogen bonds, in Car–Parrinello and classical MD simulations at 300 K. The production run of CP–MD and classical MD simulations was of 100 ps and 100 ns, respectively.

3.2 Dimer of diclofenac

The time evolution of the intermolecular interactions between two diclofenac molecules in the DCL dimer in water are depicted in Fig. 6. The dissociation of one DCL molecule in water during CP–MD run is shown with the black dashed line

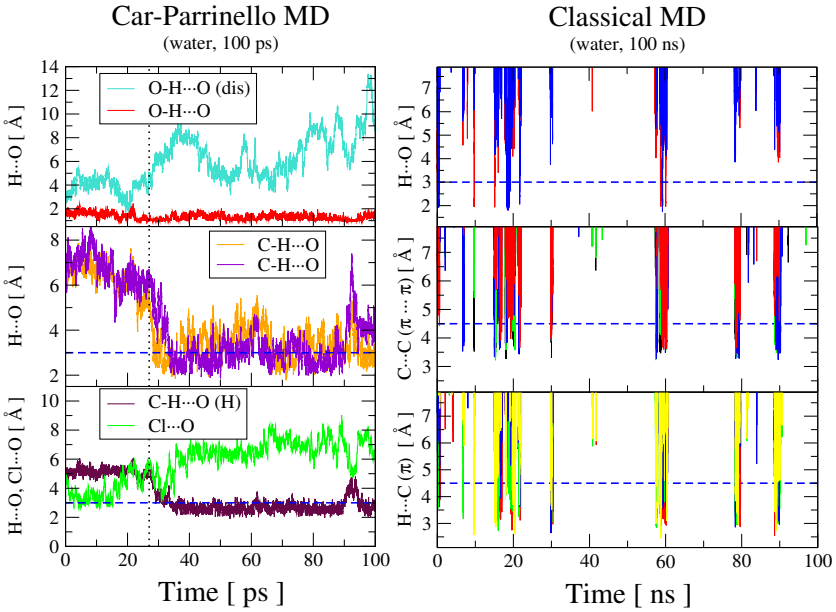

Fig. 6 Time evolution of intermolecular solute–solute interactions between DCL molecules in the DCL dimer during Car–Parrinello and classical MD simulations at 300 K. In the CP–MD run (left panel), the change of the H···O distance of intermolecular O-H···O and C-H···O hydrogen bonds was measured, while in classical MD the H···O distance of intermolecular O-H···O (upper chart), C···C and H···C distances, corresponding to $\pi - \pi$ and C-H···π interactions are plotted.

on the left panel of the figure. It is seen that as the dissociation occurs, the possible interaction via weak O-H···O H-bond in the DCL dimer starts to be excluded. The dissociated hydrogen transfers to water environment and is hopping from water to water. At the same time, the DCL molecules in DCL dimer change the mutual orientation, enabling the formation

of weak intermolecular C-H···O H-bonds: both to the etheric and hydroxylic (marked with H) oxygen atoms. It should be noted that during the existence of the DCL dimer the specific interaction between the chlorine atom from the phenyl ring of one DCL and the etheric oxygen from the second DCL, similar to halogen bonding C-Cl···O-C, was taking place. The time evolution of the distance between Cl and O atoms are given with green curve in Fig. 6. Due to the short lifetime of such interaction, it is neglected in the present analysis.

On the longer timescale, available in the classical MD approach, it is seen that such short weak intermolecular interactions, as obtained in the CP–MD run, are not visible. Instead, the dimer formation of the diclofenac molecules is possible due to $\pi-\pi$ and C-H···π intermolecular interactions. These interactions were measured as the distance between C···C and H···C atoms from different phenyl rings of two DCL molecules. On the plots, obtained using classical MD (right panel), the value of 4.5 Å was used as the cutoff for π-based intermolecular interactions taking into account the possible $\pi-\pi$ interactions between benzene molecules in its dimeric structure.

The CP–MD run of 100 ps has shown the high stability of one of intermolecular O-H···O H-bond between the DCL molecules in the DCL dimer (see Fig. 6). This H-bond remains stable until the end of the MD simulation due to the reversible proton transfer between H-bond donor and acceptor and very good linearity of such interactions (close to 175°). At the same time, classical MD simulations confirmed that such O-H···O based DCL dimer structure, as in its crystal structure, is stable only for the initial 700 ps and participates in the aggregate formation only for the short lifetimes. In the nanoscale time only π-stabilized DCL structures are possible. O-H···O H-bonds are possible only for short contacts between the protonated DCL molecules (the upper chart of the right panel).

3.3 Deprotonated vs. protonated DCL

The comparison of the time evolution of the selected structural parameters of deprotonated (left panel) and protonated (right panel) diclofenac in classical MD simulations is depicted in Fig. 7. The higher stability of the CCNC dihedral angle,

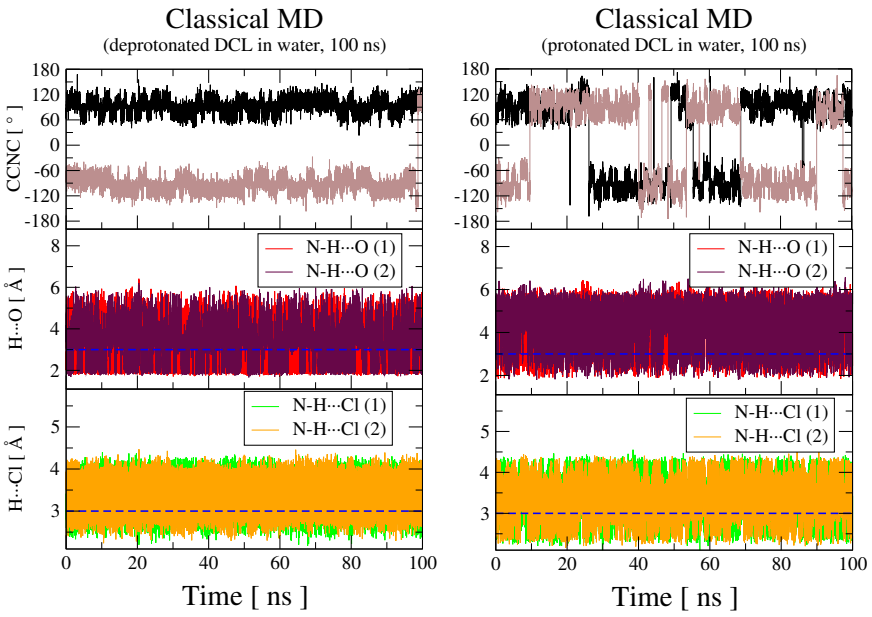

Fig. 7 Time evolution of the selected structural parameters of two deprotonated (left panel) and two protonated (right panel) diclofenac molecules in the DCL dimer from classical MD simulations at 300 K. Among structural parameters are: CCNC dihedral angles between phenyl rings and intramolecular N-H···O and N-H···Cl hydrogen bonds. The changes of both dihedral angles belonging to different DCL are in black and brown, while intramolecular H-bonds are labelled with (1) or (2) of the corresponding DCL molecule. Production run of each classical MD run was 100 ns long. The maximum distance of hydrogen bond of 3.0 Å is marked with the dashed blue line.

in case of deprotonated DCL, is observed (see black and brown curves in the left panel of Fig. 7). Only changes between two local minima, which are energetically the closest ones, are possible in the case of deprotonated DCL. No changes between all four conformers, as for protonated DCL (right panel) is seen. These can be also observed in Fig. 8, where the probability density distribution of the CCNC dihedral angle of two DCL isomers from protonated (red) and deprotonated (blue) DCL dimers in classical approach are plotted together with the CCNC values obtained in CP-MD. The reason of

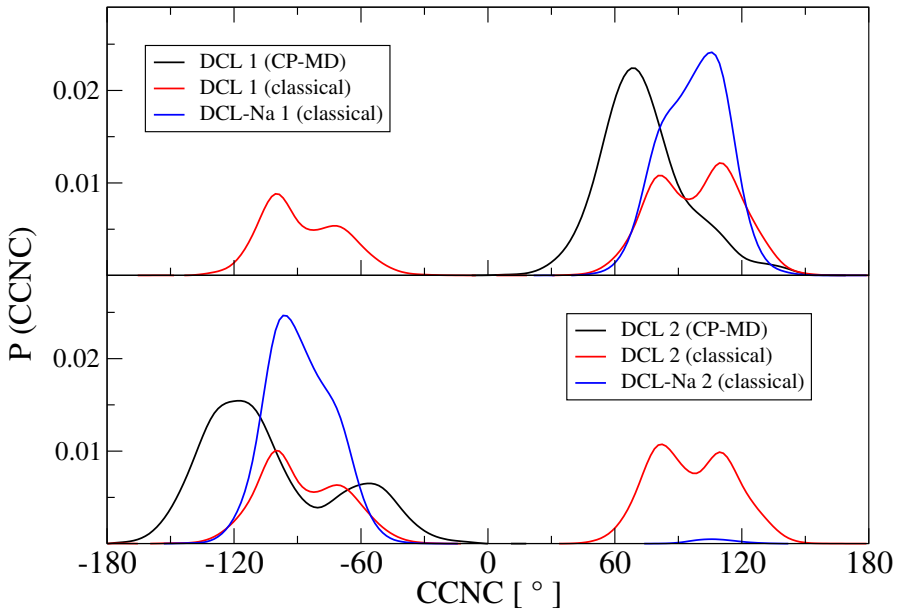

Fig. 8 Probability density distribution of the CCNC dihedral angle of two DCL isomers from DCL dimer using CP-MD and classical approach. DCL1 and DCL2 mean two separate drug molecules from the DCL dimer. DCL and DCL-Na correspond to protonated and deprotonated molecules of diclofenac.

such structural stability of deprotonated DCL is the lack of one hydrogen atom, leading to the lack of hydrogen–hydrogen repulsion between the carboxylic and amino groups. Instead of the repulsion, two very stable hydrogen bonds from the same H-bond donor (NH group) is taking place.

Relatively strong intramolecular N-H$\cdots$O H-bonds stabilize the DCL structure, preventing the significant changes of the CCNC dihedral angle, which is the characteristic feature of the protonated DCL. The difference in the time evolution of the CCNC dihedral angle between two drug forms has strong influence on the further dimer formation and self-aggregation properties of the drug. At the same time, the similar range of the values of the CCNC dihedral angle for protonated and deprotonated DCL in water (see Fig. 8) confirms the comparable accuracy of the force field used in reproducing the structural parameters of two ionic forms of diclofenac.

4 Aggregates of diclofenac in water

In order to perform classical MD simulations in the present research, different systems with solvated diclofenac molecules in water were considered. Different amount of diclofenac molecules and different concentration of the drug in water were used. Technical parameters for all systems used are given in Table 3, where systems with protonated and deprotonated DCL are marked as DCL and DCL-Na, respectively, and the mixture of both forms is marked as mixed.

Table 3 Parameters of the PBC conditions in the systems studied using classical MD simulations

System	N_{DCL}	N_{atoms}	c_{DCL}	Box dimensions
DCL	2	13758	0.025 M	50.472 Å · 47.023 Å · 55.685 Å
DCL-Na	2	15504	0.022 M	48.826 Å · 53.947 Å · 56.819 Å
DCL	4	16749	0.041 M	55.086 Å · 50.378 Å · 57.940 Å
mixed	4	17130	0.040 M	54.740 Å · 54.104 Å · 55.757 Å
DCL-Na	4	18966	0.036 M	54.948 Å · 57.000 Å · 58.560 Å
DCL	4	42387	0.016 M	74.875 Å · 70.139 Å · 77.747 Å
mixed	4	43092	0.016 M	74.513 Å · 73.874 Å · 75.536 Å
DCL-Na	4	46371	0.015 M	74.648 Å · 76.709 Å · 78276 Å

4.1 Calculation of the aggregate formation

During the analysis of the production runs obtained by the classical MD approach, different aggregates of diclofenac were detected. To enable the quantitative analysis of the DCL structures, a home-made algorithm was used. The algorithm was tested by comparison with the visual analysis of the MD trajectory.

The best way to estimate the amount of the specific DCL aggregates is to calculate the distances between the DCL molecules during the MD run. The distance between the nitrogen atoms of the DCL molecules was estimated as the most efficient criterium. Therefore, the amount of DCL dimers in the MD run of protonated and deprotonated DCL in water was computed as the amount of snapshots, where the N–N distance is less than 9 Å (this cutoff was estimated during the analysis of the MD run when the DCL dimer was formed). After the analysis of the N–N distance in both production runs (100 ns, in total 20 000 steps), the amount of snapshots, where the DCL dimer was formed, was determined as 1784 and 596 corresponding to 8.92% and 2.98% for protonated and deprotonated DCL, respectively. The distribution of the N–N distance in the mentioned MD runs is given in Fig. 10.

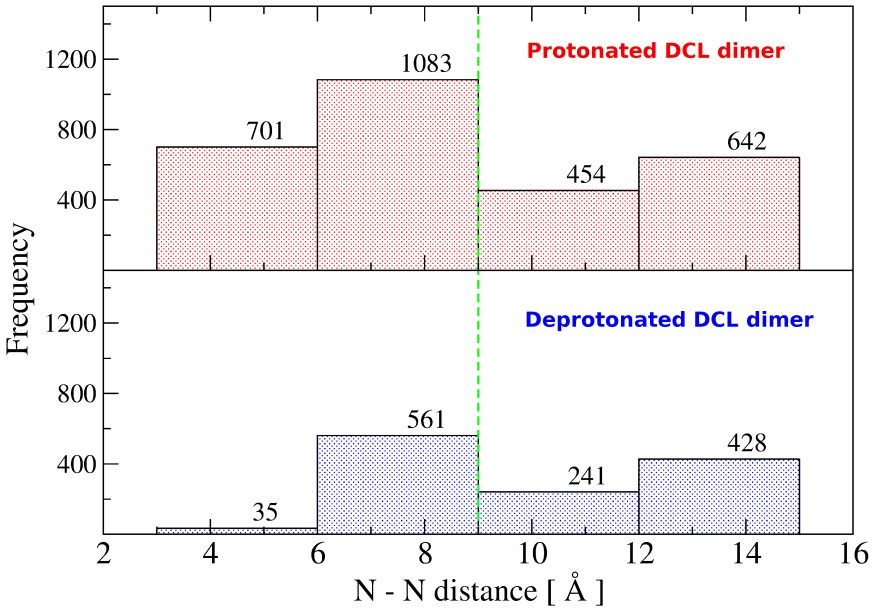

Fig. 9 The distribution of the N–N distance between the DCL molecules in the classical MD simulations of protonated and deprotonated dimer of diclofenac in water. The distance cutoff for dimer formation of 9 Å is marked with the green dashed line. Amount of MD steps when the N–N distances are lower than 9 Å corresponds to the dimer formation. The distribution only in the range of 3–15 Å is given.

During the analysis of four DCL molecules in water, more complex algorithm was used. With four DCL molecules in the system, six different N–N distances are possible: N1N2, N1N3, N1N4, N2N3, N2N4 and N3N4, where the index of N denotes the DCL molecule: first, second etc. It was observed that tetramers are formed when all N–N distances are lower than 13 Å, therefore, the amount of tetramers (step *(1)*) was estimated as the number of snapshots where the sum of all six distances is lower than 78 Å ($6 \cdot 13$).

At the same time, four different trimers can be formed, which are described with the following N–N distances:

- N1N2 + N2N3 + N1N3
- N2N3 + N3N4 + N2N4
- N3N4 + N1N3 + N1N4
- N1N4 + N2N4 + N1N2.

The trimer of DCL is also formed when N–N distances are lower than 13 Å. Therefore, if the trimer is formed the sum of N–N distances is less than 39 Å. Only one trimer can be formed at the same step of the simulation. Thus, the sums of the N–N distances corresponding to four possible trimers were plotted together and the snapshots, where one of four N–N sums was lower than 39 Å, were calculated. In such way (step *(2)*) the total amount of either trimers or tetramers was

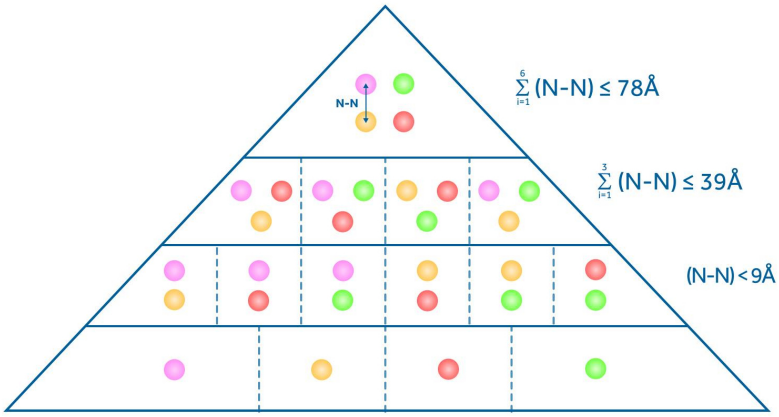

Fig. 10 The schematic representation of the algorithm used to calculate the amount of tetramers, trimers, dimers and monomers of protonated DCL, deprotonated DCL and the mixture of protonated and deprotonated dimers of diclofenac. The description of the algorithm is given in the text.

estimated, because every trimer can be a tetramer. The amount of trimers was calculated as the difference between step *(2)* and step *(1)*.

To estimate the occurence of the dimeric structures of DCL, all six possible N–N distances between each DCL molecule were plotted together and the snapshots, where the value of the N–N distance was lower than 9 Å, were summed (step *(3)*). In such procedure, the sum of dimers, trimers and tetramers was estimated, because in every trimer and tetramer there is a possibility for the dimer formation. The exact amount of dimers was estimated as a difference between step *(3)* and step *(2)*. Amount of monomers was calculated as the difference between all snapshots of the MD simulation and the value estimated in the step *(3)*. All values obtained in such calculations are given in the main text of the manuscript. It should be noted that the usage of the PBC conditions was connected with the hopping of the solute molecules from one PBC cell to another, therefore, all N–N distances were measured after the procedure of recentering of all molecules with respect to each DCL molecule. In such a way all N–N distances were error-free concerning the PBC conditions.

4.2 Solute–solute interactions

In addition to the NCI index analysis of the aggregates of diclofenac presented in the main text of the manuscript, other possible self-associated structures of DCL are shown in Fig. 11 and Fig. 12. In Fig. 11 trimers and tetramers of protonated DCL are depicted, whereas in Fig. 12 only trimers of the deprotonated DCL are shown. Tetramers of deprotonated DCL are less possible to be formed in water (less than 1%). The description of the NCI surfaces and NCI plots is given in the main text of the manuscript.

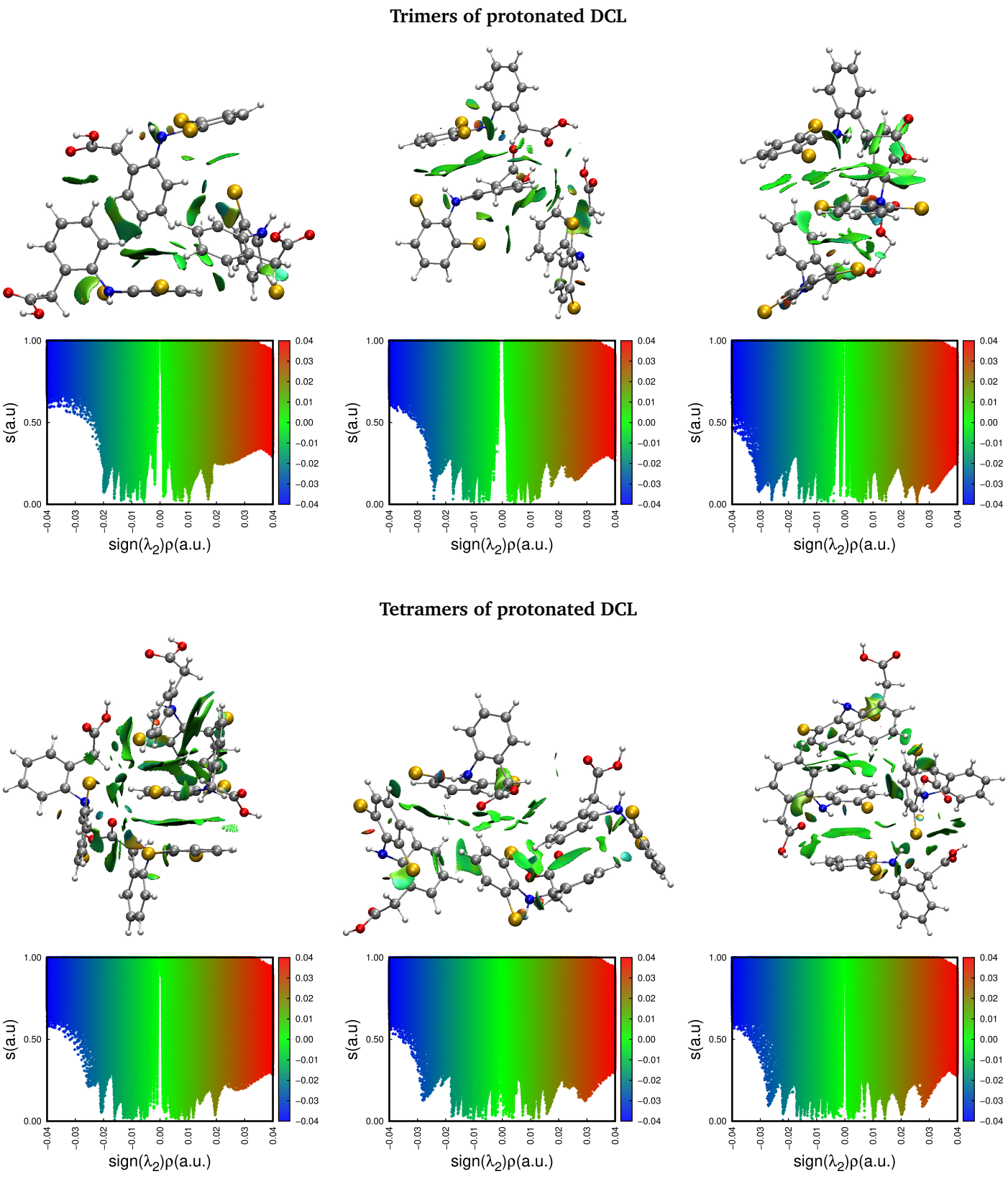

Fig. 11 Examplary trimeric and tetrameric aggregates of **protonated** diclofenac molecules in water at 300 K from classical MD simulations with visualized noncovalent interactions. The NCI surfaces (depicted with gradient green color) correspond to s = 0.3 a.u., a color scale of -0.04 $< \rho <$ 0.04 a.u. and isovalue of 0.3 a.u. Carbon, oxygen, chlorine, nitrogen and hydrogen atoms are silver, red, orange, blue and white, respectively.

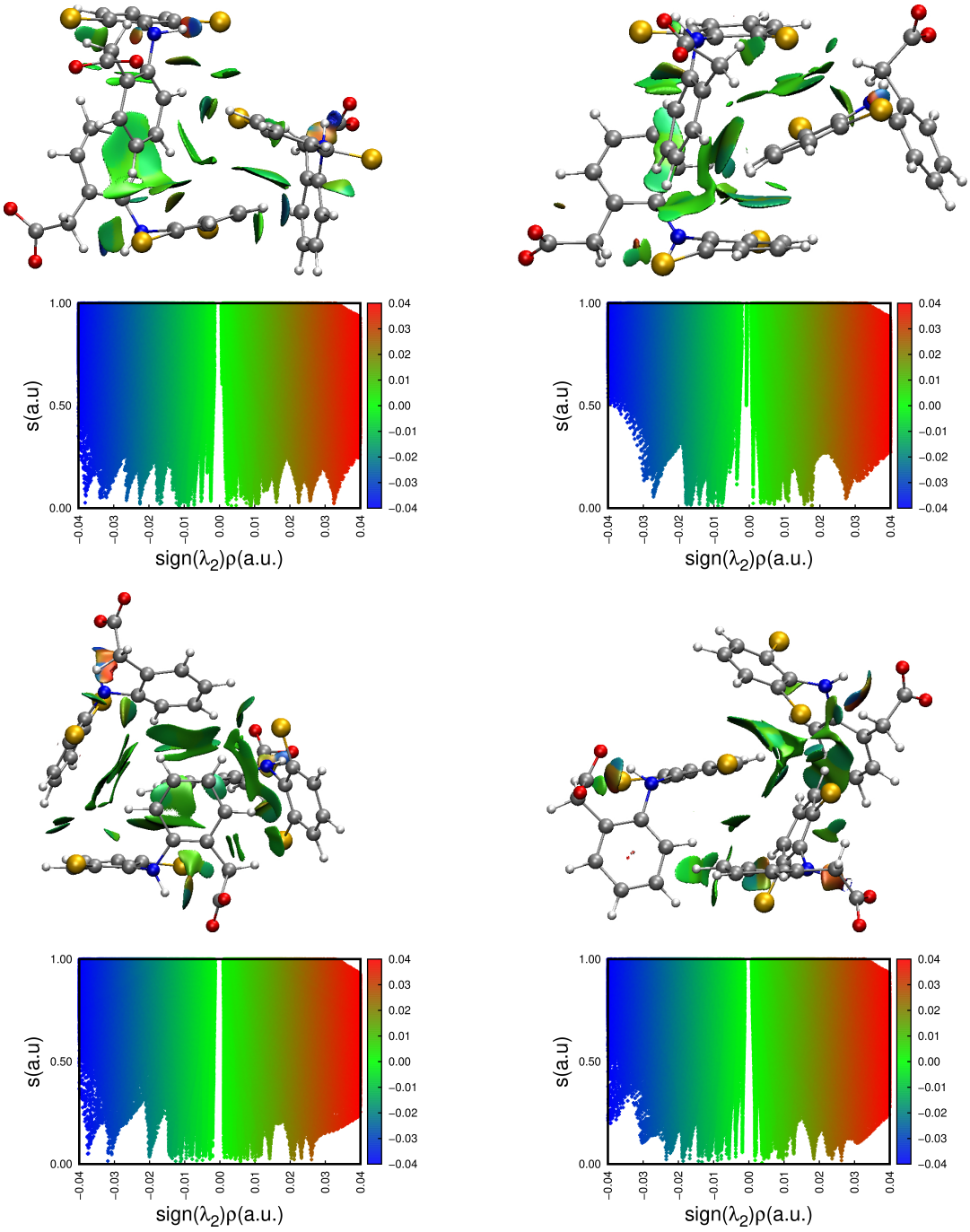

Fig. 12 Examplary trimeric aggregates of **deprotonated** diclofenac molecules in water at 300 K from classical MD simulations with visualized noncovalent interactions. The NCI surfaces (depicted with gradient green color) correspond to s = 0.3 a.u., a color scale of -0.04 $< \rho <$ 0.04 a.u. and isovalue of 0.3 a.u. Carbon, oxygen, chlorine, nitrogen and hydrogen atoms are silver, red, orange, blue and white, respectively.

5 Coordinates of the diclofenac local minima

- **(a): 0.00 kJ/mol**

C 1.4402130 0.1979930 -0.1720320
C 2.1446320 -0.9298700 -0.6599510
C 3.5328000 -1.0323760 -0.5702000
C 4.2722970 0.0186840 -0.0224970
C 3.6226980 1.1670340 0.4345000
C 2.2314920 1.2399060 0.3674010
Cl 1.2661210 -2.2240330 -1.4523630
H 4.0240050 -1.9214800 -0.9543180
H 5.3553720 -0.0531960 0.0373920
H 4.1802900 1.9971430 0.8577830
Cl 1.4306680 2.6795560 0.9785900
N 0.0533640 0.3065560 -0.2720670
C -0.8321420 -0.6147110 0.3331240
C -2.1724510 -0.6691840 -0.1126090
C -3.0602760 -1.5600730 0.5022990
C -2.6376340 -2.4167500 1.5225810
C -1.3040070 -2.3735750 1.9431340
C -0.4108040 -1.4753640 1.3597580
C -2.6375380 0.2080390 -1.2604690
H -4.0929600 -1.5933920 0.1579400
H -3.3388590 -3.1120740 1.9782190
H -0.9584770 -3.0319990 2.7377630
H 0.6207510 -1.4286910 1.7000230
C -2.8870480 1.6259340 -0.7843300
H -1.8494860 0.2543820 -2.0234680
H -3.5488980 -0.1999260 -1.7043910
O -4.2101530 1.9331510 -0.7257450
O -2.0207430 2.4153650 -0.4536570
H -4.2685150 2.8383110 -0.3717710
H -0.3084040 1.2588740 -0.3056260

- **(b): 0.87 kJ/mol**

C 1.4491380 0.1875820 -0.1746420
C 2.1434590 -0.9539870 -0.6455200
C 3.5304650 -1.0670600 -0.5515420
C 4.2799270 -0.0157610 -0.0179570
C 3.6409690 1.1455280 0.4211620
C 2.2511040 1.2282630 0.3501490
Cl 1.2543820 -2.2490150 -1.4221270
H 4.0137840 -1.9661620 -0.9221640
H 5.3620770 -0.0971970 0.0445280
H 4.2056970 1.9767310 0.8325510
Cl 1.4641880 2.6899290 0.9394880
N 0.0646120 0.3115860 -0.2811950
C -0.8365820 -0.5983590 0.3273600
C -2.1711960 -0.6504050 -0.1326430
C -3.0697620 -1.5269860 0.4899550
C -2.6615590 -2.3682490 1.5278780
C -1.3320750 -2.3265060 1.9619480
C -0.4290460 -1.4423620 1.3725800
C -2.6342950 0.2147080 -1.2902210
H -4.0999440 -1.5572160 0.1386400
H -3.3715680 -3.0513770 1.9883760
H -0.9982020 -2.9742250 2.7701660
H 0.5997300 -1.3950720 1.7213350
C -3.1183760 1.5689320 -0.8045140
H -1.8067460 0.3575630 -1.9961390
H -3.4733860 -0.2605690 -1.8039540
O -2.0617460 2.3866120 -0.4735620
O -4.2685230 1.9188110 -0.6779800
H -2.4383150 3.2053680 -0.1085140
H -0.2719910 1.2700950 -0.2832330

- **(c): 2.60 kJ/mol**

C 1.3369390 0.0441940 -0.0037040
C 1.6232110 -0.9984250 0.9099720
C 2.9260890 -1.4441360 1.1347530
C 3.9950090 -0.8262750 0.4814700
C 3.7615730 0.2351700 -0.3954550
C 2.4510860 0.6455750 -0.6343380
Cl 0.3219320 -1.7227290 1.8311130
H 3.0939930 -2.2523540 1.8403340
H 5.0116750 -1.1643580 0.6652220
H 4.5803220 0.7338920 -0.9052140
Cl 2.1721280 1.9676530 -1.7632190
N 0.0397280 0.5092240 -0.2233530
C -1.0103100 -0.2857590 -0.7371790
C -2.3264360 0.2243040 -0.6729850
C -3.3763040 -0.5583600 -1.1648180
C -3.1480280 -1.8288950 -1.7029190
C -1.8413220 -2.3225370 -1.7610180
C -0.7764110 -1.5528000 -1.2905820
C -2.5837540 1.5930970 -0.0828050
H -4.3916070 -0.1679840 -1.1091760
H -3.9807400 -2.4247900 -2.0692510
H -1.6446790 -3.3066150 -2.1818340
H 0.2414400 -1.9294420 -1.3503520
C -2.0804890 1.7790050 1.3448400
H -2.1254900 2.3933170 -0.6781760
H -3.6646640 1.7833810 -0.0738860
O -2.5055440 0.7768850 2.1603250
O -1.4171780 2.7154960 1.7366980
H -2.1244450 0.9572200 3.0366020
H 0.0037440 1.4854710 -0.4925730

- **(d): 3.13 kJ/mol**

C -1.4125330 -0.1115660 -0.1964960
C -1.7360550 1.2247270 -0.5194160
C -3.0584850 1.6701940 -0.5499070
C -4.0982810 0.7765420 -0.2840320
C -3.8207240 -0.5582860 0.0165240
C -2.4923450 -0.9799330 0.0681630
Cl -0.4585740 2.3481110 -0.9175600
H -3.2617340 2.7071970 -0.7992670
H -5.1290890 1.1198820 -0.3184840
H -4.6173820 -1.2665190 0.2221590
Cl -2.1525180 -2.6599140 0.4734990
N -0.0773900 -0.5729500 -0.1960510
C 0.8518940 -0.1156840 0.8097570
C 2.2077030 -0.4737630 0.6579990
C 3.1248970 -0.0080120 1.6100890
C 2.7216150 0.7972810 2.6790480
C 1.3727510 1.1341420 2.8176590
C 0.4380700 0.6709990 1.8886380
C 2.6915420 -1.3300690 -0.4954080
H 4.1737460 -0.2774490 1.4987050
H 3.4553050 1.1538020 3.3983210
H 1.0415540 1.7519660 3.6495350
H -0.6135960 0.9226270 1.9972490
C 2.8632680 -0.5686800 -1.8264750
H 3.6692200 -1.7536210 -0.2555640
H 2.0121160 -2.1761400 -0.6782760
O 1.7480550 0.0107090 -2.3277380
O 3.9203510 -0.5031800 -2.4081590
H 0.9948370 -0.1086620 -1.7016730
H -0.0618290 -1.5893770 -0.2609860

- **(e): 3.14 kJ/mol**

C -1.4126920 0.1089200 -0.1982250
C -1.7365710 -1.2314530 -0.5032570
C -3.0591160 -1.6769790 -0.5277830
C -4.0987120 -0.7796340 -0.2738510
C -3.8208150 0.5590130 0.0088790
C -2.4923340 0.9809610 0.0548230
Cl -0.4593680 -2.3603660 -0.8864910
H -3.2625660 -2.7171900 -0.7632470
H -5.1295940 -1.1231670 -0.3037110
H -4.6173010 1.2701500 0.2049530
Cl -2.1520470 2.6661660 0.4375290
N -0.0774840 0.5700640 -0.2039150
C 0.8515940 0.1265410 0.8082030
C 2.2074590 0.4824630 0.6517150
C 3.1245450 0.0296150 1.6100770
C 2.7210640 -0.7610250 2.6898450
C 1.3721360 -1.0956850 2.8330450
C 0.4375250 -0.6450990 1.8977880
C 2.6913280 1.3231120 -0.5131120
H 4.1734120 0.2974510 1.4950660
H 3.4546560 -1.1079390 3.4138920
H 1.0408720 -1.7018260 3.6734420
H -0.6142290 -0.8946620 2.0101180
C 2.8646590 0.5435410 -1.8334480
H 2.0112360 2.1657810 -0.7084970
H 3.6684230 1.7509870 -0.2785090
O 1.7501260 -0.0439270 -2.3268840
O 3.9219270 0.4709540 -2.4138720
H 0.9964600 0.0839170 -1.7031060
H -0.0617700 1.5854740 -0.2827830

- **(f): 3.26 kJ/mol**

C -1.3381030 -0.0492950 -0.0014810
C -1.6304720 0.8918410 1.0154610
C -2.9375630 1.3020820 1.2818030
C -4.0018210 0.7476960 0.5666630
C -3.7608990 -0.2159890 -0.4149450
C -2.4469130 -0.5899690 -0.6922300
Cl -0.3346510 1.5196840 2.0060850
H -3.1116820 2.0321560 2.0666790
H -5.0209330 1.0584200 0.7826000
H -4.5757670 -0.6647140 -0.9749590
Cl -2.1572590 -1.7893770 -1.9505880
N -0.0353460 -0.4780440 -0.2645240
C 0.9982920 0.3838240 -0.7071870
C 2.3220850 -0.1080590 -0.6993150
C 3.3562600 0.7326570 -1.1223510
C 3.1031930 2.0431620 -1.5401350
C 1.7886460 2.5184260 -1.5449310
C 0.7392450 1.6914210 -1.1403560
C 2.6022110 -1.5162990 -0.2286310
H 4.3780460 0.3563330 -1.1066190
H 3.9235950 2.6844870 -1.8536910
H 1.5735700 3.5337130 -1.8721730
H -0.2846460 2.0557620 -1.1586160
C 2.2269840 -1.7361600 1.2338680
H 2.0967550 -2.2689340 -0.8477040
H 3.6781220 -1.7173890 -0.3065320
O 1.5297870 -2.9029270 1.4028490
O 2.5295380 -1.0130970 2.1534060
H 1.3489310 -2.9740660 2.3562650
H 0.0024140 -1.4085280 -0.6644840

- **(g): 3.68 kJ/mol**

C -0.9612370 0.4963120 0.5761020
C -0.9905010 1.7224870 -0.1334230
C -2.1485660 2.1888230 -0.7575460
C -3.3409120 1.4720730 -0.6508930
C -3.3733670 0.2890280 0.0910660
C -2.2045920 -0.1787490 0.6797780
Cl 0.4440470 2.7347440 -0.2050050
H -2.1076350 3.1272490 -1.3027750
H -4.2427460 1.8378190 -1.1342210
H -4.2894630 -0.2839790 0.1962970
Cl -2.2692330 -1.6842390 1.5989440
N 0.1675820 -0.0147830 1.1948320
C 1.5060230 -0.0169000 0.7140830
C 1.8397600 -0.2822640 -0.6327320
C 3.1966840 -0.2777760 -0.9882730
C 4.2070990 -0.0629260 -0.0487530
C 3.8648480 0.1561770 1.2891720
C 2.5211920 0.1890590 1.6605200
C 0.8045870 -0.5914550 -1.6870670
H 3.4627190 -0.4723750 -2.0264440
H 5.2500360 -0.0749350 -0.3575820
H 4.6376780 0.3205120 2.0372080
H 2.2353360 0.3998400 2.6890340
C -0.0813010 -1.8084230 -1.4564830
H 0.1239140 0.2455740 -1.8731430
H 1.3154960 -0.7807340 -2.6412290
O 0.4890700 -2.7347210 -0.6350980
O -1.1623020 -1.9732960 -1.9783530
H -0.1540980 -3.4614950 -0.5663730
H -0.0286020 -0.7212360 1.8927260

- **(h): 4.32 kJ/mol**

C 1.4199850 0.1969860 0.1851140
C 2.2722840 -0.8627020 0.5702540
C 3.6461870 -0.8257930 0.3267430
C 4.2123880 0.2996870 -0.2762680
C 3.4103830 1.3841040 -0.6384610
C 2.0349380 1.3177570 -0.4179670
Cl 1.6066580 -2.2445800 1.4139940
H 4.2621660 -1.6653820 0.6345060
H 5.2841740 0.3359930 -0.4547010
H 3.8364410 2.2688740 -1.1016540
Cl 1.0272380 2.6735730 -0.8983590
N 0.0425300 0.1756640 0.4423550
C -0.8463400 -0.7321290 -0.1663420
C -2.2037230 -0.7316350 0.2439020
C -3.0921000 -1.6356360 -0.3570930
C -2.6669860 -2.5374350 -1.3375360
C -1.3252700 -2.5293650 -1.7309160
C -0.4231150 -1.6326790 -1.1572080
C -2.6801740 0.2512500 1.2835500
H -4.1330070 -1.6348800 -0.0348330
H -3.3709620 -3.2366380 -1.7819900
H -0.9755870 -3.2181690 -2.4972360
H 0.6129150 -1.6204190 -1.4838100
C -2.8393280 1.6986650 0.7793240
H -3.6681280 -0.0489390 1.6572840
H -2.0084360 0.2889590 2.1482500
O -3.1340990 1.8303380 -0.5448980
O -2.7385120 2.6691400 1.4895950
H -3.1062530 0.9473190 -0.9575890
H -0.3411530 1.0984740 0.6093320

- **(i): 4.59 kJ/mol**

C 1.6510720 0.1278200 -0.2632230
C 1.9040070 -1.2405420 -0.5262690
C 3.2008820 -1.7488320 -0.5994070
C 4.2951610 -0.8925820 -0.4525550
C 4.0914370 0.4712500 -0.2326650
C 2.7889590 0.9567840 -0.1300070
Cl 0.5620330 -2.3258590 -0.8212700
H 3.3424540 -2.8072760 -0.7968820
H 5.3059580 -1.2863720 -0.5212050
H 4.9280100 1.1548070 -0.1237820
Cl 2.5499330 2.6778580 0.1718860
N 0.3560040 0.6449040 -0.2072240
C -0.6093420 0.1785810 0.7339230
C -1.9775160 0.3941840 0.4671890
C -2.9200120 -0.0282160 1.4145400
C -2.5287210 -0.6863350 2.5834200
C -1.1707960 -0.9172280 2.8256760
C -0.2156150 -0.4739460 1.9112150
C -2.3955090 1.0754430 -0.8264710
H -3.9770810 0.1491960 1.2262780
H -3.2797760 -1.0177660 3.2969970
H -0.8521770 -1.4276020 3.7322910
H 0.8436770 -0.6292060 2.1018810
C -3.7458930 0.6011370 -1.3221190
H -2.4634820 2.1626510 -0.6923640
H -1.6404660 0.8653940 -1.5926590
O -3.6480110 -0.6027330 -1.9576340
O -4.8008480 1.1821010 -1.1782300
H -4.5529240 -0.8521900 -2.2129390
H 0.3325400 1.6499990 -0.3400840

- **(j): 4.90 kJ/mol**

C -1.4387090 0.1866200 -0.1738080
C -2.1554620 -0.9454310 -0.6307180
C -3.5410660 -1.0451440 -0.5033960
C -4.2630270 0.0131680 0.0535110
C -3.6004100 1.1644210 0.4835230
C -2.2110040 1.2352490 0.3787930
Cl -1.2975530 -2.2511090 -1.4263750
H -4.0441450 -1.9369460 -0.8651270
H -5.3443280 -0.0559850 0.1424600
H -4.1458140 1.9987350 0.9142870
Cl -1.3905780 2.6750430 0.9558610
N -0.0526530 0.2916160 -0.3126070
C 0.8466420 -0.6038150 0.3004830
C 2.1879960 -0.6489900 -0.1490560
C 3.0833100 -1.5349440 0.4623940
C 2.6754040 -2.3889440 1.4905500
C 1.3445180 -2.3493310 1.9199260
C 0.4406460 -1.4631480 1.3354450
C 2.6367710 0.2399160 -1.2920500
H 4.1122290 -1.5761870 0.1044630
H 3.3831860 -3.0796840 1.9425510
H 1.0083840 -3.0045670 2.7210600
H -0.5888480 -1.4239100 1.6821370
C 2.8336580 1.6749410 -0.8022290
H 3.5580940 -0.1584980 -1.7348970
H 1.8626240 0.2665910 -2.0681510
O 4.0959580 2.0229100 -0.4193490
O 1.9334910 2.4780090 -0.6965360
H 4.6907050 1.2677180 -0.5365680
H 0.3035310 1.2397730 -0.4283500

- **(k): 5.07 kJ/mol**

C -1.6822990 0.2127670 -0.2351230
C -2.1210040 -1.0379370 -0.7332300
C -3.4753740 -1.3605370 -0.8217430
C -4.4414630 -0.4212930 -0.4523540
C -4.0532480 0.8396670 0.0051610
C -2.6954750 1.1334360 0.1186540
Cl -0.9444830 -2.1996520 -1.3068680
H -3.7617490 -2.3356360 -1.2044980
H -5.4970470 -0.6679960 -0.5324730
H -4.7887060 1.5865860 0.2884560
Cl -2.2215040 2.7219570 0.7196400
N -0.3294320 0.5498140 -0.1631000
C 0.6028080 -0.1760600 0.6289220
C 1.9808000 0.0066800 0.3783130
C 2.9026170 -0.6936630 1.1646820
C 2.4817270 -1.5769460 2.1637470
C 1.1154390 -1.7579250 2.3952400
C 0.1800010 -1.0516980 1.6383560
C 2.3957850 0.9472630 -0.7412800
H 3.9674150 -0.5638920 0.9850500
H 3.2174820 -2.1203130 2.7522110
H 0.7744260 -2.4392730 3.1720130
H -0.8841590 -1.1739870 1.8246030
C 3.8507000 0.8142380 -1.1403360
H 1.7903770 0.7233930 -1.6279010
H 2.2033440 1.9912120 -0.4555780
O 4.6386830 1.7254180 -0.4905530
O 4.2974010 0.0103710 -1.9278120
H 5.5489620 1.5655220 -0.7953550
H -0.1772970 1.5522320 -0.1490910

- **(l): 5.10 kJ/mol**

C 1.4130660 -0.4817780 0.3006640
C 1.4820080 -1.0812650 -0.9821210
C 2.5147880 -0.7953860 -1.8761920
C 3.5504490 0.0633590 -1.5045320
C 3.5521920 0.6341540 -0.2290640
C 2.4986300 0.3669160 0.6394010
Cl 0.2792000 -2.2622620 -1.4720330
H 2.5097040 -1.2736610 -2.8513110
H 4.3584570 0.2767920 -2.1990830
H 4.3512550 1.2966640 0.0898940
Cl 2.5015420 1.1293460 2.2304170
N 0.3947110 -0.7194390 1.2099130
C -0.9968460 -0.8217470 0.9278130
C -1.6554330 0.0330100 0.0172210
C -3.0238460 -0.1746960 -0.2160890
C -3.7431160 -1.1536030 0.4717350
C -3.0923610 -1.9572510 1.4140370
C -1.7240890 -1.7989630 1.6257330
C -0.9148890 1.1529600 -0.6971720
H -3.5362980 0.4573200 -0.9384990
H -4.8054240 -1.2829260 0.2766520
H -3.6409870 -2.7201930 1.9623790
H -1.1895550 -2.4495180 2.3149490
C -1.7937810 2.3647080 -0.9304210
H -0.0528110 1.4665930 -0.1027540
H -0.5495810 0.8142730 -1.6735500
O -1.8896290 3.1323880 0.1953010
O -2.3623340 2.6454140 -1.9640370
H -2.4881820 3.8672370 -0.0236100
H 0.6228920 -0.4818640 2.1668380

- **(m): 5.30 kJ/mol**

C -0.9516700 -0.5290800 0.6970680
C -0.9275090 0.7648240 1.2686700
C -2.0283570 1.6186220 1.2181920
C -3.2203460 1.1841720 0.6386170
C -3.3087880 -0.1052090 0.1098010
C -2.1886230 -0.9295280 0.1367520
Cl 0.5111440 1.3216180 2.1124100
H -1.9436430 2.6134500 1.6442080
H -4.0780310 1.8495890 0.5947270
H -4.2252720 -0.4628830 -0.3491650
Cl -2.2997310 -2.5351690 -0.5875810
N 0.1479180 -1.3857360 0.7250010
C 1.4561470 -0.9902990 0.2956710
C 1.6766690 -0.2960160 -0.9159070
C 2.9957460 0.0791880 -1.2330260
C 4.0716410 -0.2486260 -0.4050820
C 3.8432350 -0.9819860 0.7640770
C 2.5407360 -1.3412370 1.1110690
C 0.5669640 0.0084440 -1.8950330
H 3.1776150 0.6108930 -2.1667500
H 5.0806260 0.0500440 -0.6806650
H 4.6724820 -1.2551040 1.4131590
H 2.3354460 -1.8696420 2.0390120
C -0.0890210 1.4001470 -1.8278020
H 0.9668270 -0.0598920 -2.9161890
H -0.2415070 -0.7233150 -1.8371110
O 0.5846040 2.3612160 -1.1392990
O -1.1145970 1.6605940 -2.4069190
H 1.3299510 1.9524590 -0.6643390
H -0.0849520 -2.3500410 0.5173500

- **(n): 5.39 kJ/mol**

C 1.0156540 -0.4950680 0.5638060
C 1.0882770 -1.7068120 -0.1634960
C 2.2580280 -2.1103490 -0.8097500
C 3.4153540 -1.3380290 -0.7038820
C 3.4035810 -0.1657040 0.0554270
C 2.2225040 0.2402210 0.6680670
Cl -0.3060490 -2.7724920 -0.2409150
H 2.2547810 -3.0400910 -1.3709190
H 4.3271730 -1.6530450 -1.2041650
H 4.2935770 0.4475500 0.1570110
Cl 2.2223490 1.7222820 1.6125890
N -0.1341180 -0.0466150 1.2030220
C -1.4647990 -0.0649300 0.7289710
C -1.8051610 0.1866760 -0.6250280
C -3.1649480 0.1528750 -0.9811540
C -4.1722890 -0.0742410 -0.0418790
C -3.8250320 -0.2723650 1.2992200
C -2.4830540 -0.2782120 1.6747890
C -0.7775960 0.5748900 -1.6610230
H -3.4307090 0.3330550 -2.0219610
H -5.2146760 -0.0880610 -0.3513540
H -4.5953800 -0.4433680 2.0481770
H -2.1994960 -0.4767680 2.7064830
C -0.0744820 1.9224980 -1.4206940
H 0.0143840 -0.1667600 -1.7912830
H -1.2719170 0.6718040 -2.6368670
O -0.7434950 2.8109430 -0.6314560
O 0.9778850 2.2185210 -1.9291000
H -1.5418320 2.3720730 -0.2866760
H 0.0344820 0.5590670 1.9961490

- **(o): 5.64 kJ/mol**

C 1.4259910 -0.5102940 0.2279560
C 1.4536890 -0.9113410 -1.1314650
C 2.4628630 -0.4988720 -2.0031340
C 3.5151560 0.2917110 -1.5388860
C 3.5572680 0.6663560 -0.1933990
C 2.5270630 0.2762390 0.6562290
Cl 0.2286790 -2.0021670 -1.7583880
H 2.4266470 -0.8273600 -3.0377610
H 4.3049140 0.6030130 -2.2172970
H 4.3698470 1.2717090 0.1971210
Cl 2.5813920 0.7933890 2.3415470
N 0.4348220 -0.8786540 1.1229630
C -0.9640610 -0.9499580 0.8658010
C -1.6505720 0.0382450 0.1265570
C -3.0236310 -0.1413030 -0.1000120
C -3.7176250 -1.2293690 0.4324980
C -3.0374970 -2.1729430 1.2095460
C -1.6649750 -2.0370140 1.4100270
C -0.9236980 1.2644930 -0.4009730
H -3.5632710 0.5952080 -0.6910590
H -4.7844930 -1.3340920 0.2475920
H -3.5670440 -3.0220870 1.6363900
H -1.1065600 -2.7863890 1.9670830
C -1.8097750 2.4937970 -0.4539860
H -0.0948860 1.5127750 0.2677210
H -0.5066670 1.0678470 -1.3964060
O -2.3193460 2.7010930 -1.7079250
O -2.0572630 3.2254630 0.4784100
H -2.8712260 3.5007340 -1.6490930
H 0.6894930 -0.7724910 2.0968290

- **(p): 5.71 kJ/mol**

C 1.3591260 -0.5630830 0.2993490
C 1.4502430 -1.0588210 -1.0261540
C 2.5222020 -0.7422740 -1.8616450
C 3.5746890 0.0449240 -1.3916330
C 3.5527070 0.5129370 -0.0754140
C 2.4623340 0.2166380 0.7361410
Cl 0.2218710 -2.1465140 -1.6516900
H 2.5324030 -1.1409580 -2.8719100
H 4.4124790 0.2819030 -2.0417830
H 4.3625780 1.1185890 0.3201710
Cl 2.4386940 0.8525810 2.3824370
N 0.3069120 -0.8341730 1.1576890
C -1.0797350 -0.8873910 0.8248340
C -1.6997280 0.0706830 -0.0047360
C -3.0636050 -0.0915410 -0.2943100
C -3.8110270 -1.1317780 0.2579010
C -3.1962830 -2.0446160 1.1224060
C -1.8341110 -1.9269980 1.3905130
C -0.9314220 1.2301770 -0.5926760
H -3.5549980 0.6324230 -0.9396530
H -4.8693020 -1.2228840 0.0232320
H -3.7688040 -2.8564690 1.5661950
H -1.3243800 -2.6551180 2.0178110
C -1.6577410 2.5637780 -0.5679020
H -0.0021170 1.4027700 -0.0366320
H -0.6138740 1.0215600 -1.6228340
O -1.1158800 3.4134760 -1.4956040
O -2.5549880 2.8971120 0.1722790
H -1.5774300 4.2628550 -1.3871800
H 0.5064970 -0.6491220 2.1326290

- **(q): 5.82 kJ/mol**

C 1.3977640 0.1332890 -0.1391210
C 1.6921330 -0.9635240 -0.9782000
C 3.0027590 -1.3779150 -1.2191570
C 4.0698540 -0.6860840 -0.6434800
C 3.8254060 0.4184490 0.1744290
C 2.5090150 0.8037960 0.4211670
Cl 0.3946830 -1.8275030 -1.7794960
H 3.1746810 -2.2304990 -1.8692760
H 5.0911440 -1.0031760 -0.8374500
H 4.6400180 0.9728810 0.6302810
Cl 2.2200370 2.1855510 1.4783010
N 0.0803980 0.5878880 0.0945410
C -0.8837740 -0.3500430 0.6622030
C -2.1665460 -0.4647240 0.0958050
C -3.0892090 -1.3129230 0.7298560
C -2.7450240 -2.0436910 1.8690800
C -1.4559050 -1.9402220 2.4013810
C -0.5299520 -1.0885670 1.7964920
C -2.5544510 0.2339450 -1.1909490
H -4.0878190 -1.4075630 0.3079350
H -3.4794980 -2.6971610 2.3349960
H -1.1753600 -2.5095160 3.2848600
H 0.4759230 -0.9876220 2.1998860
C -2.8249160 1.7377980 -1.0321320
H -1.7585410 0.0910900 -1.9326540
H -3.4729190 -0.2104090 -1.5815640
O -1.7087730 2.5111800 -0.9511730
O -3.9293550 2.2226730 -0.9909590
H -0.9298380 1.9112450 -0.9364390
H 0.1312660 1.4003670 0.7107790

- **(r): 6.00 kJ/mol**

C 1.2102050 -0.4315050 0.3623930
C 1.2301670 -1.5308100 -0.5278320
C 2.3706330 -1.8477230 -1.2740590
C 3.5460370 -1.1178260 -1.1105750
C 3.5905960 -0.0720430 -0.1853320
C 2.4402270 0.2575550 0.5234220
Cl -0.1486730 -2.6031340 -0.6975960
H 2.3275190 -2.6899690 -1.9581800
H 4.4307300 -1.3730280 -1.6878150
H 4.5002960 0.4968820 -0.0196580
Cl 2.5199790 1.5718090 1.6894480
N 0.0922860 0.0418660 1.0773380
C -1.2821970 -0.2558630 0.8269800
C -1.8869420 0.1322720 -0.3870010
C -3.2540100 -0.1297170 -0.5536460
C -4.0146430 -0.7274910 0.4544620
C -3.4074030 -1.0758870 1.6649040
C -2.0428970 -0.8451630 1.8447720
C -1.1313620 0.8536190 -1.4834590
H -3.7283910 0.1607900 -1.4893350
H -5.0750130 -0.9119790 0.2980520
H -3.9873740 -1.5378630 2.4607830
H -1.5511430 -1.1430750 2.7694660
C -1.0088270 2.3676890 -1.2352700
H -0.1196580 0.4491800 -1.6121260
H -1.6541210 0.7360330 -2.4350820
O -0.3772830 2.7278890 -0.0882630
O -1.4289270 3.2019470 -2.0004590
H -0.1066170 1.9266530 0.4083250
H 0.2977590 0.2245210 2.0539360

- **(s): 10.40 kJ/mol**

C 1.3374700 -0.5876500 0.3062700
C 1.4208560 -1.0824990 -1.0204970
C 2.4979900 -0.7808880 -1.8554470
C 3.5628300 -0.0107210 -1.3841660
C 3.5483640 0.4541750 -0.0664350
C 2.4537750 0.1731160 0.7452770
Cl 0.1758360 -2.1490480 -1.6486200
H 2.5035900 -1.1808270 -2.8653560
H 4.4058780 0.2115060 -2.0327790
H 4.3686990 1.0443160 0.3311160
Cl 2.4398440 0.8058460 2.3915530
N 0.2782160 -0.8371780 1.1615500
C -1.1086120 -0.8652110 0.8246100
C -1.7075350 0.1026920 -0.0093420
C -3.0721410 -0.0335700 -0.3080190
C -3.8405680 -1.0587560 0.2437200
C -3.2476250 -1.9804260 1.1139320
C -1.8847890 -1.8887800 1.3891990
C -0.9120700 1.2446760 -0.5943920
H -3.5461220 0.6987690 -0.9557830
H -4.8992250 -1.1303690 0.0045020
H -3.8378370 -2.7799080 1.5569210
H -1.3925650 -2.6253670 2.0205270
C -1.6008620 2.6123830 -0.5761640
H 0.0243400 1.3830140 -0.0407980
H -0.6101810 1.0047840 -1.6265230
O -0.9799500 3.5535900 -1.3626910
O -2.5652960 2.9197130 0.0732730
H -0.2302140 3.1504060 -1.8261350
H 0.4790150 -0.6593060 2.1376580

References

1 I.-F. W. Kuo, C. J. Mundy, M. J. McGrath, J. I. Siepmann, J. VandeVondele, M. Sprik, J. Hutter, B. Chen, M. L. Klein, F. Mohamed, M. Krack and M. Parrinello, *J. Phys. Chem. B*, 2004, **108**, 12990.

2 M. J. Gillan, D. Alfe and A. Michaelides, *J. Chem. Phys.*, 2016, **144**, 130901.

3 A. Bankura, B. Santra, R. A. D. Jr., C. W. Swartz, M. L. Klein and X. Wu, *Mol. Phys.*, 2015, **113**, 2842.

4 J. Sun, D. Bousquet, H. Forbert and D. Marx, *J. Chem. Phys.*, 2010, **133**, 114508.

5 P. Gasparotto, A. A. Hassanali and M. Ceriotti, *J. Chem. Theory Comput.*, 2016, **12**, 1953.

6 F. Ambrosio, G. Miceli and A. Pasquarello, *J. Phys. Chem. B*, 2016, **120**, 7456.

7 T. Morawietz, A. Singraber, C. Dellago and J. Behler, *Proc. Natl. Acad. Sci.*, 2016, **113**, 8368.

8 I. C. Lin, A. P. Seitsonen, I. Tavernelli and U. Rothlisberger, *J. Chem. Theory Comput.*, 2012, **8**, 3902.

9 S. Yoo, X. C. Zeng and S. S. Xantheas, *J. Chem. Phys.*, 2009, **130**, 221102.

10 S. Yoo and S. S. Xantheas, *J. Chem. Phys.*, 2011, **134**, 121105.

11 J. Schmidt, J. VandeVondele, I.-F. W. Kuo, D. Sebastiani, J. I. Siepmann, J. Hutter and C. J. Mundy, *J. Phys. Chem. B*, 2009, **113**, 11959.

12 E. Guardia, I. Skarmoutsos and M. Masia, *J.Phys.Chem.B*, 2015, **119**, 8926.

13 M. Montagna, F. Sterpone and L. Guidoni, *J. Phys. Chem. B*, 2012, **116**, 11695.

14 I. C. Lin, A. P. Seitsonen, M. D. Coutinho-Neto, I. Tavernelli and U. Rothlisberger, *J. Phys. Chem. B*, 2009, **113**, 1127.

15 S. Y. Willow, X. C. Zeng, S. S. Xantheas, K. S. Kim and S. Hirata, *J. Phys. Chem. Lett.*, 2016, **7**, 680.

16 E. Schwegler, J. C. Grossman, F. Gygi and G. Galli, *J. Chem. Phys.*, 2004, **121**, 5400.

17 T. D. Kuhne, M. Krack and M. Parrinello, *J. Chem. Theory Comput.*, 2009, **5**, 235.

18 P. H. Sit and N. Marzari, *J. Chem. Phys.*, 2005, **122**, 204510.

19 T. A. Pham, T. Ogitsu, E. Y. Lau and E. Schwegler, *J. Chem. Phys.*, 2016, **145**, 154501.

20 A. K. Soper, *Chem. Phys.*, 2000, **258**, 121.

21 L. B. Skinner, C. Huang, D. Schlesinger, L. G. M. Pettersson, A. Nilsson and C. J. Benmore, *J. Chem. Phys.*, 2013, **138**, 074506.

22 M. Kozlowska, P. Rodziewicz and A. Kaczmarek-Kedziera, *Struct. Chem.*, 2017, **28**, 999.

23 K. Vanommeslaeghe and A. D. M. Jr., *J. Chem. Inf. Model.*, 2012, **52**, 3144.

24 K. Vanommeslaeghe, E. P. Raman and A. D. M. Jr., *J. Chem. Inf. Model.*, 2012, **52**, 3155.