Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

SUPLEMENTARY MATERIAL

CARBON NANOHORN AS NANOCONTAINER FOR CISPLATIN: INSIGHTS ON THE INTERACTION WITH PLASMA MEMBRANES OF NORMAL AND BREAST CANCER CELLS

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Table S1. Number of lipids that compound the membrane models referring to N_memb and C_memb.

Components (lipids)	**Number of lipids**			
	N_memb[a]		**C_memb[b]**	
	outer monolayer	inner monolayer	outer monolayer	inner monolayer
DOPC	77	37	46	46
DOPE	4	16	18	18
DOPG	2	2	4	4
DOPS	0	26	8	8
CHL	16	16	22	22
Ions	**Number of ions[c]**			
Na^+	99		90	
Cl^-	69		66	

[a]Number of lipids based on the lipid composition of a normal breast tissue cell [47]. [b]Number of lipids based on the lipid composition of the MCF-7 cell line [46]. [c]Total number of ions included to neutralize and represent the molar concentration (0.15 M) of the Na^+ and Cl^- in the membrane models. DOPC: 1,2-dioleoyl-*sn*-glycero-3-phosphocholine. DOPE: 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine. DOPG: 1,2-dioleoyl-*sn*-glycero-3-[phospho-rac-(1-glycerol)]. DOPS: 1,2-dioleoyl-*sn*-glycero-3-phospho-L-serine. CHL: cholesterol.

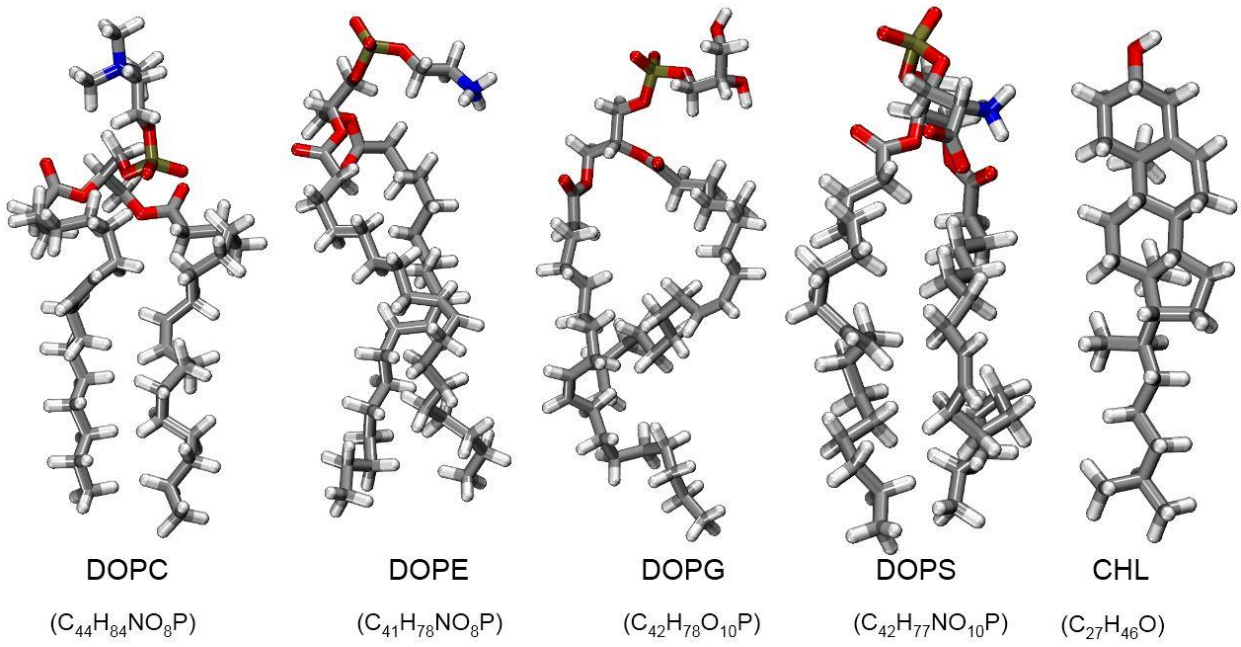

Figure S1. Structures and molecular formulas of the main lipids expressed in plasma membranes of normal and cancer cells referring to the human breast. DOPC: 1,2-dioleoyl-*sn*-glycero-3-phosphocholine. DOPE: 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine. DOPG: 1,2-dioleoyl-sn-glycero-3-[phospho-rac-(1-glycerol)]. DOPS: 1,2-dioleoyl-sn-glycero-3-phospho-L-serine. CHL: cholesterol. The white, gray, red, golden, and blue colors in the licorice representations indicate the H, C, O, P, and N atoms.

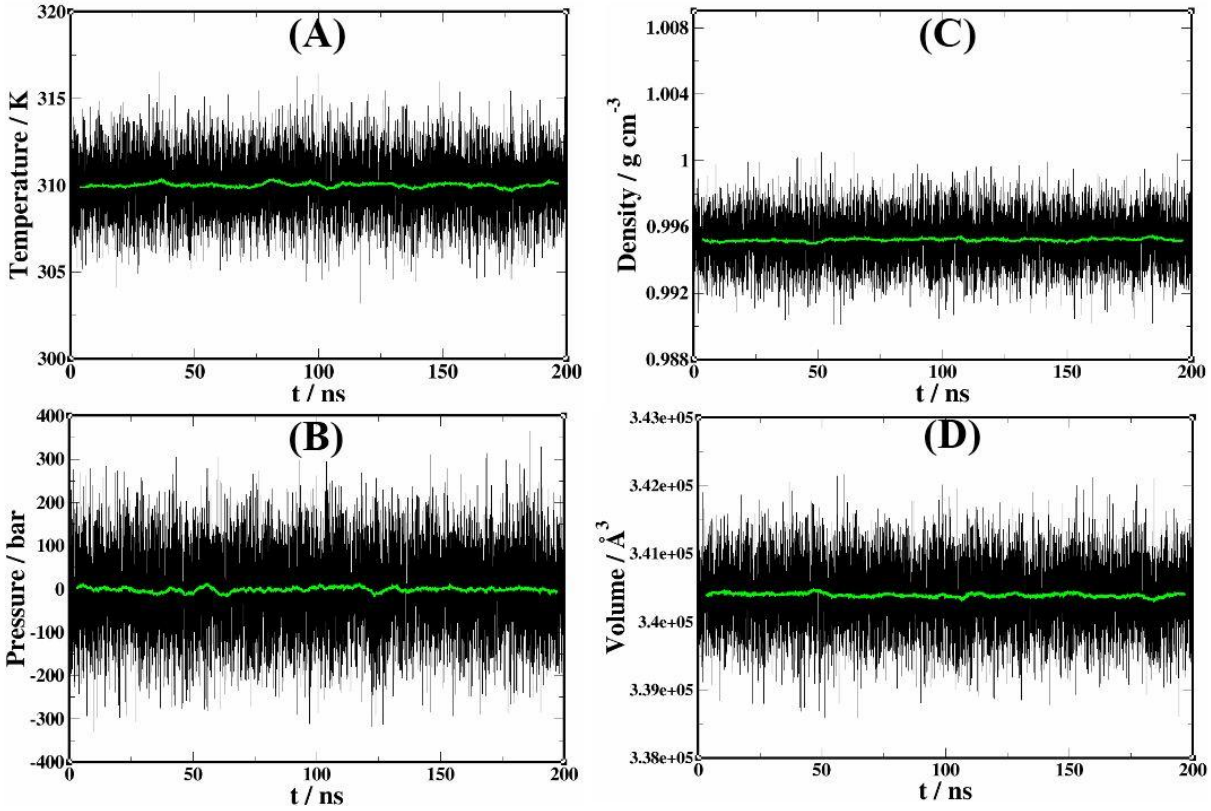

Figure S2. The temporal variation of the temperature (A), pressure (B), density (C) and volume (D) referring to the inclusion complex formed by three cddp molecules encapsulated into one CNHox3cddp@CNHox in aqueous solution with 0.15 M of NaCl during 200 ns simulation run. The green line represents the moving average calculated for sets of 350 frames.

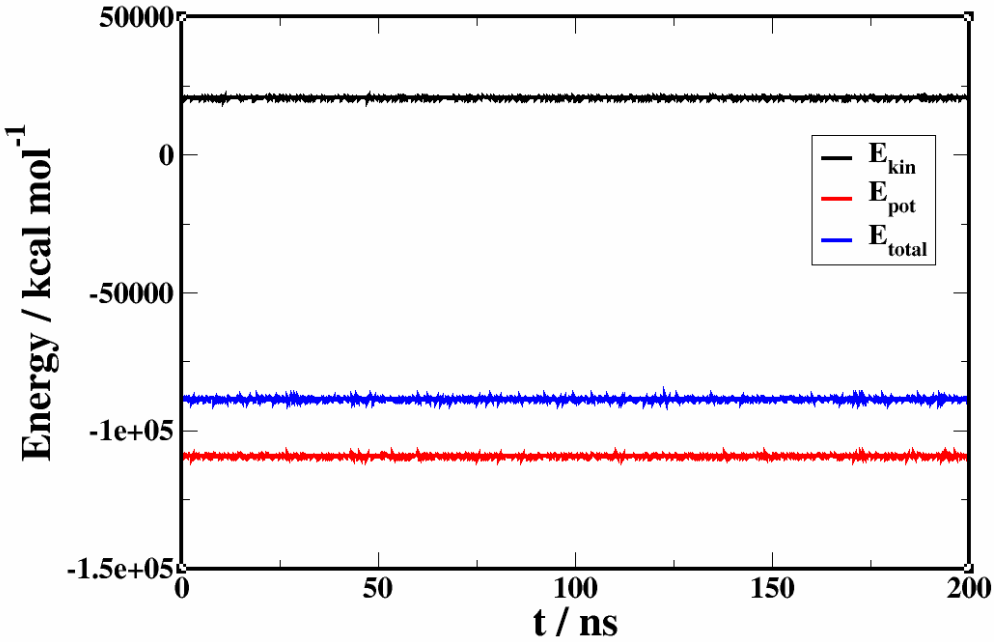

Figure S3. The temporal variation of the kinetic (E_{kin}), potential (E_{pot}), and total (E_{total}) energy of the inclusion complex formed by three cddp molecules encapsulated into one CNHox (3cddp@CNHox) in aqueous solution with 0.15 M of NaCl during 200 ns simulation run.

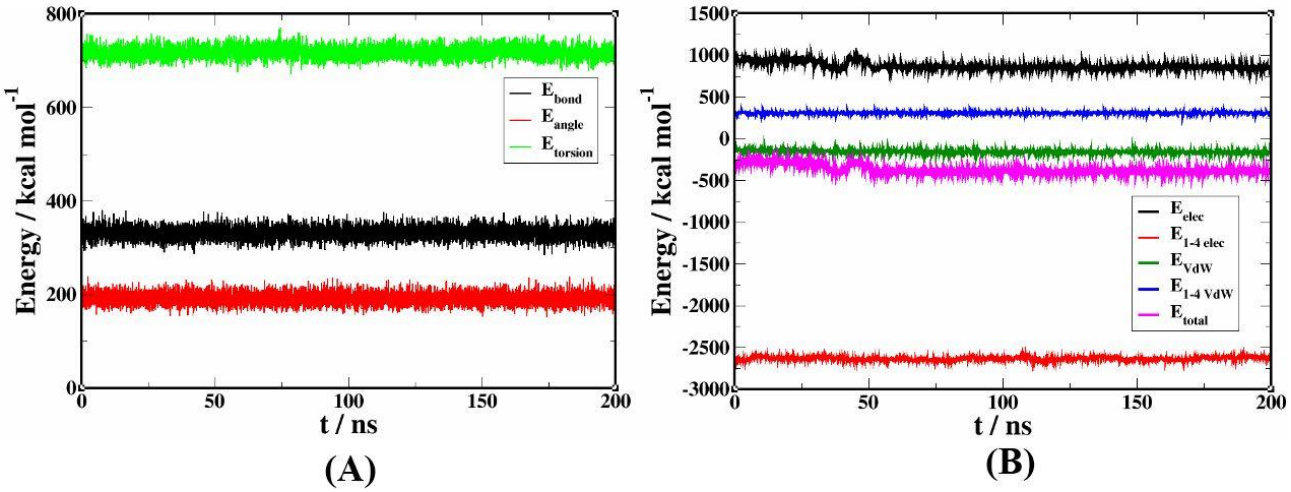

Figure S4. Temporal variation of the energetic components of the solute (3cddp@CNHox) during 200 ns simulation run. (A): energy required to the bond stretching (E_{bond}), angle bending (E_{angle}), and rotations about bonds referring to torsional angles ($E_{torsion}$). (B): electrostatic interaction energy (E_{elec}), electrostatic interaction energy between the end atoms involved in a dihedral angle ($E_{1\text{-}4\ elec}$), van der Waals interaction energy (E_{vdW}), van der Waals interaction energy between the end atoms involved in a dihedral angle ($E_{1\text{-}4\ vdW}$), and total potential energy (E_{tot}).

Table S2. Statistics of the energetic contributions to the total potential energy of the inclusion complex formed by three cddp molecules encapsulated into one CNHox (3cddp@CNHox) during 200 ns simulation. All values are in kcal mol^{-1}.

Components	Average ± Std.	Max.	Min.
E_{bond}	191.46±11.88	239.43	151.03
E_{angle}	331.12±12.69	380.85	285.05
$E_{torsion}$	717.83±12.20	771.83	670.46
$E_{vdW1\text{-}4}$	307.13±5.80	329.17	286.79
E_{vdW}	-156.18±11.86	-101.69	-190.76
$E_{elec1\text{-}4}$	-2635.02±18.33	-2564.59	-2694.60
E_{elec}	872.54±39.87	1006.18	787.64
E_{tot}	-371.12±48.23	-191.43	-459.44

The E_{bond}, E_{angle}, $E_{torsion}$, $E_{vdW1\text{-}4}$, E_{vdW}, $E_{elec1\text{-}4}$, E_{elec}, E_{tot}, Std., Max., and Min. terms refer to the energy required to the bond stretching, angle bending, rotations about bonds referring to torsional angles, van der Waals interaction energy between the end atoms involved in a dihedral angle, van der Waals interaction energy, electrostatic interaction energy between the end atoms involved in a dihedral angle, electrostatic interaction energy, total potential energy, standard deviation, maximum value, and minimum value, respectively.

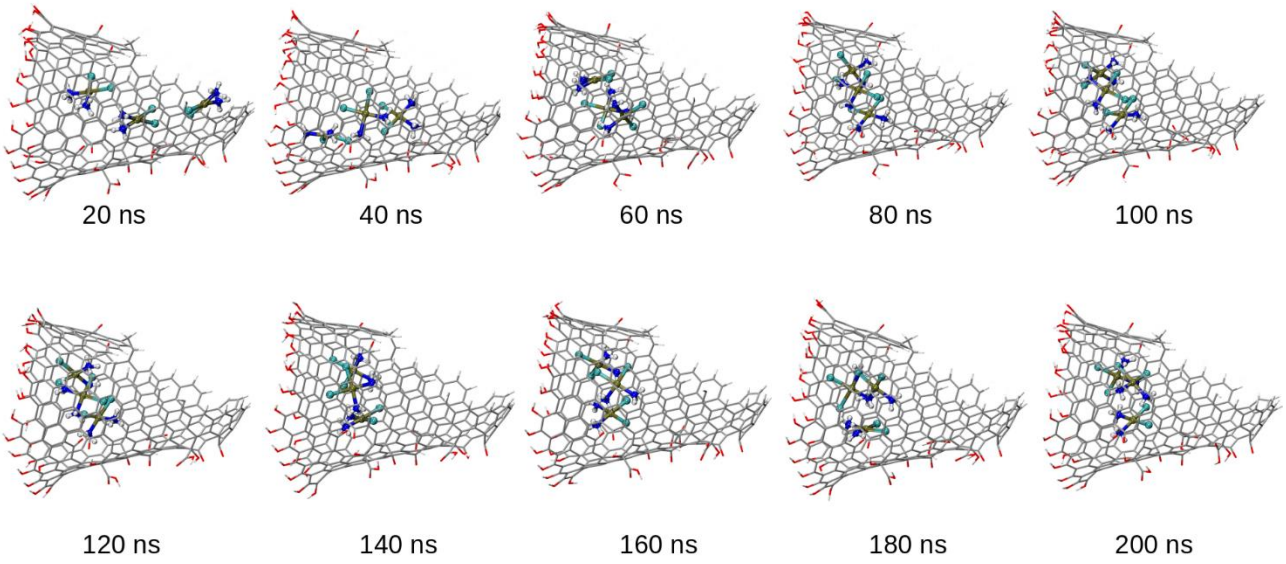

Figure S5. The snapshots of the 200 ns MD trajectory referring to the inclusion complex formed by a cluster of three cddp molecules encapsulated into one CNHox (3cddp@CNHox). The silver, red, blue, white, and cyan colors indicate the CNH structure and the O, N, H, and Cl atoms of the cddp molecule.

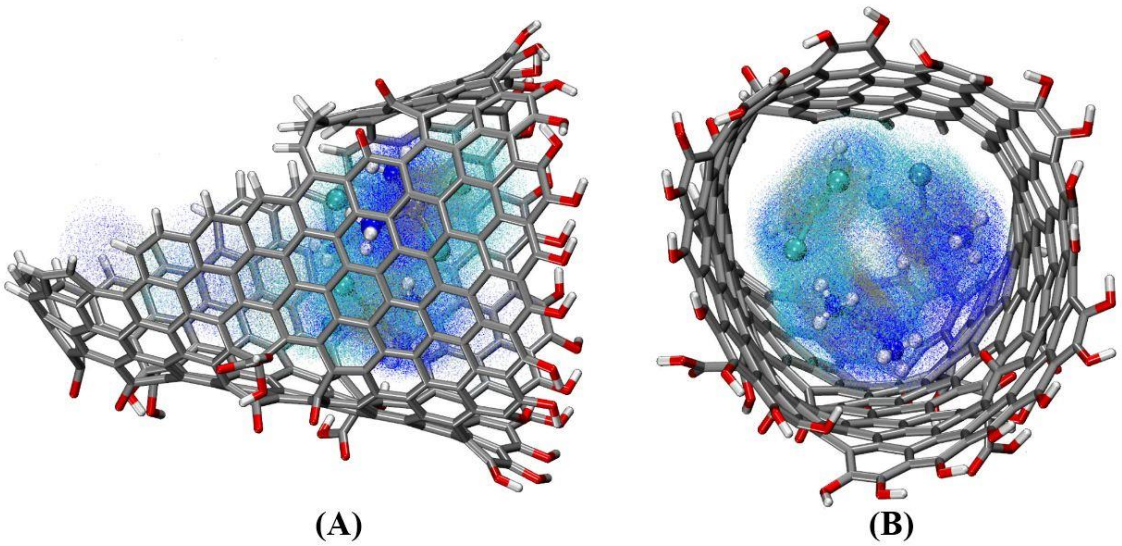

Figure S6. Spatial distribution of the cluster formed by three cddp molecules inside the CNHox cavity: (A) Side view and (B) front view. While the silver, red, and white colors represent the C, O, and H atoms of the CNHox structure, the blue, green, and golden spheres and clouds correspond to the temporal variation of the N, Cl, and Pt atoms. This distribution involves the superposition of 100 frames collected from the 200 ns simulation.

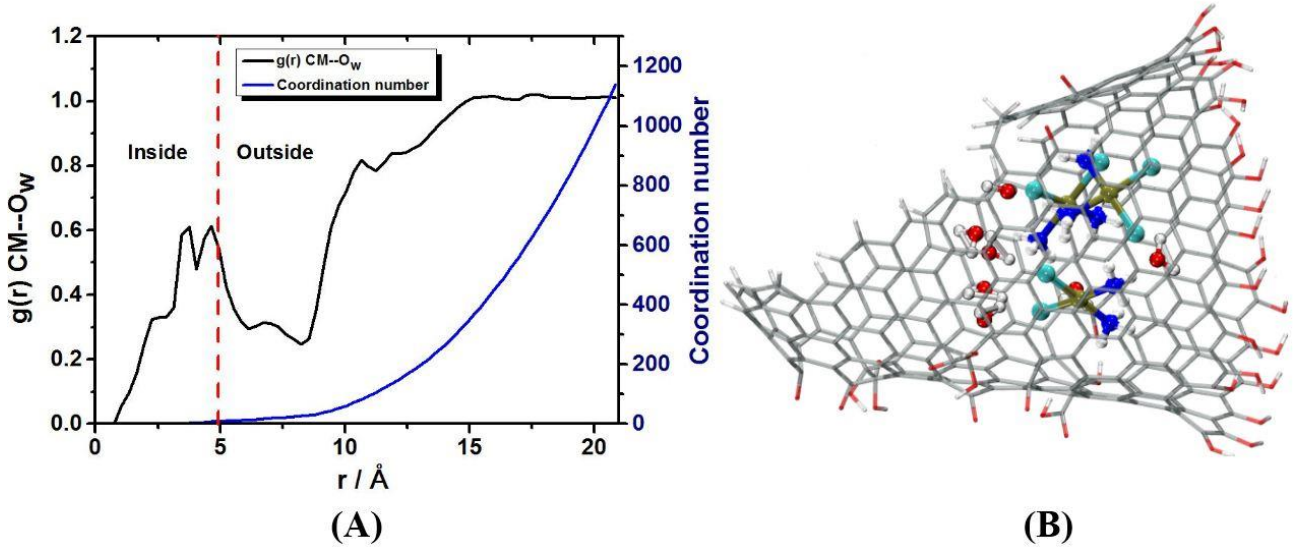

Figure S7. Radial distribution function (g(r) CM--O_w) defined between the CM of the CNHox model and the O atoms (O_w) of the water molecules (A) and the water molecules of the inner solvation shell (B).The red dashed line defines the region internal and external water molecules relative to the CNHox structure. The silver, red, white, blue, golden, and green colors represent the C, O, H, N, Pt, Cl atoms, respectively.

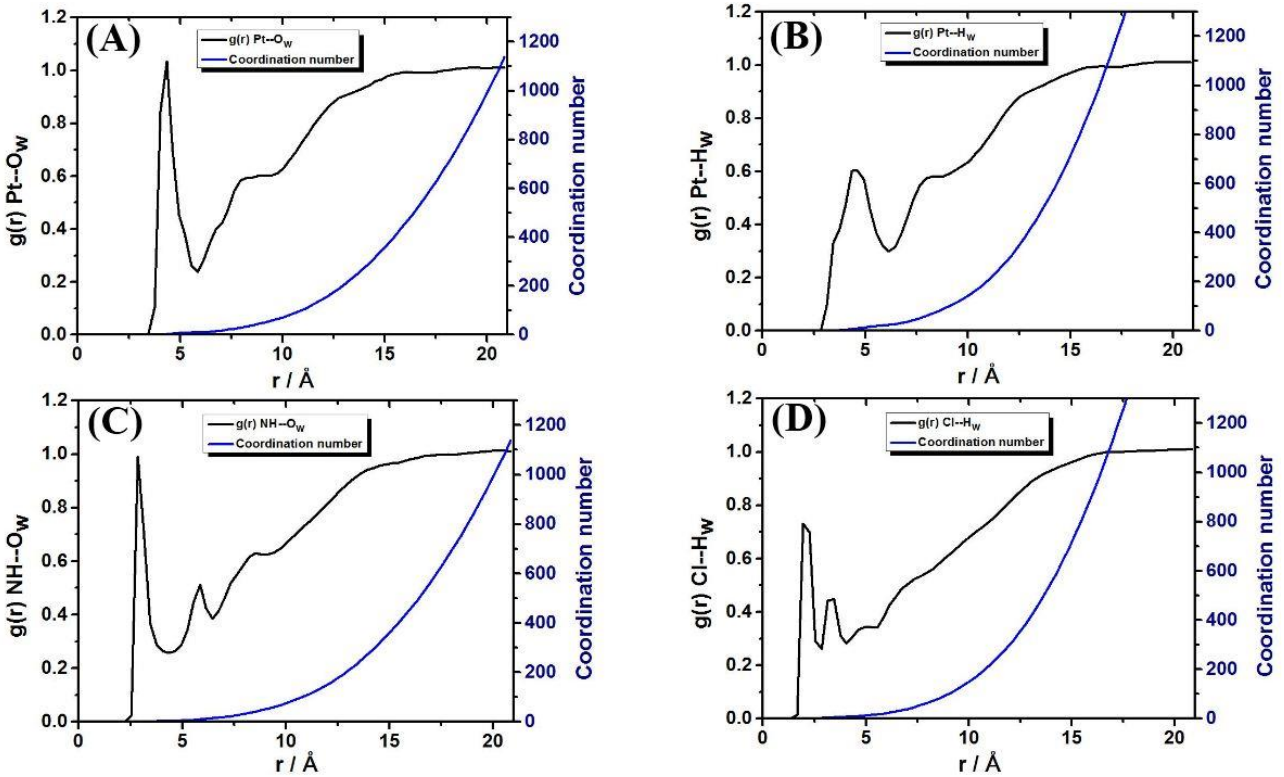

Figure S8. Radial distribution functions (RDF) involving the cddp cluster and the water molecules: g(r) Pt--O_w (A), g(r) Pt--H_w (B), g(r) NH--O_w (C), and g(r) Cl--H_w (D).

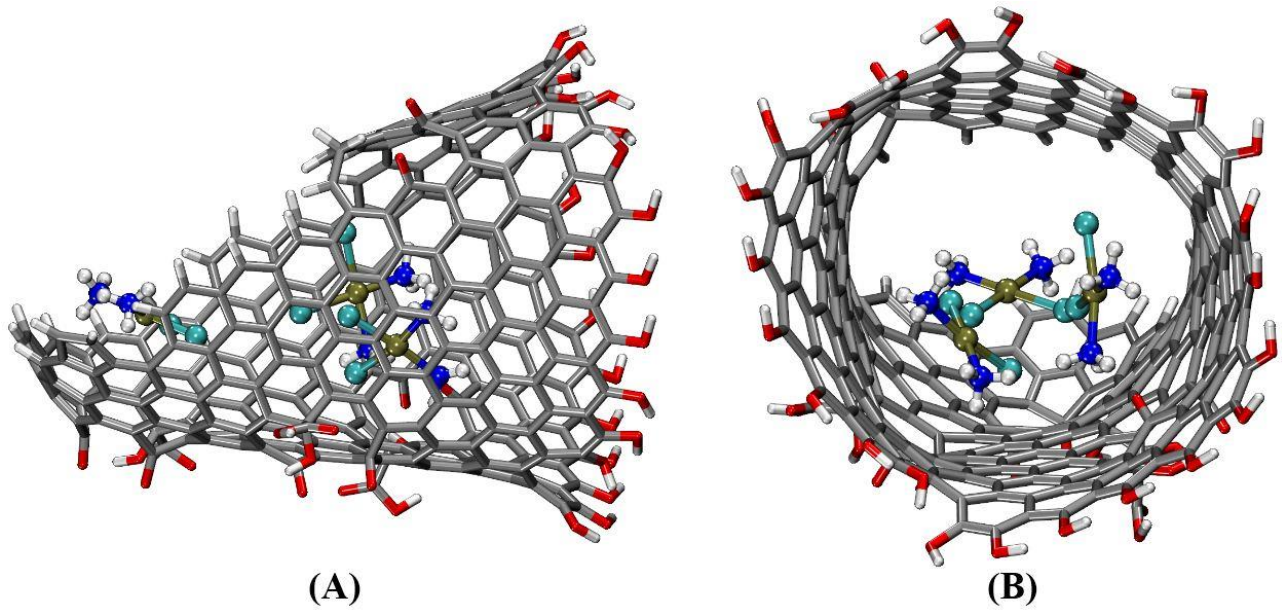

Figure S9. Snapshot of the 3cddp@CNHox complex collected from the 26 ns time of the 200 ns trajectory: (A) Side view and (B) front view from the oxidized end of the CNHox structure.

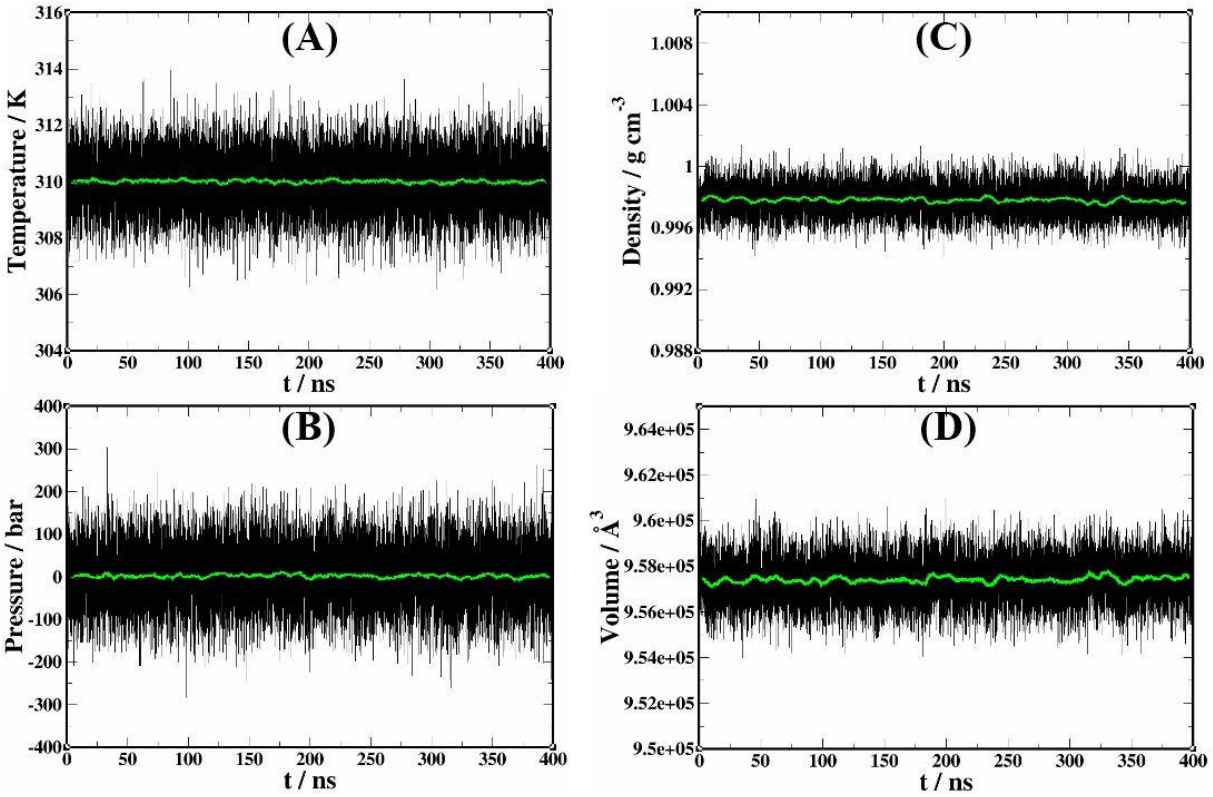

Figure S10. The temporal variation of the temperature (A), pressure (B), density (C) and volume (D) referring to the membrane model of a BC cell (C_memb model) in aqueous solution during 400 ns simulation run. The green line represents the moving average calculated for sets of 350 frames.

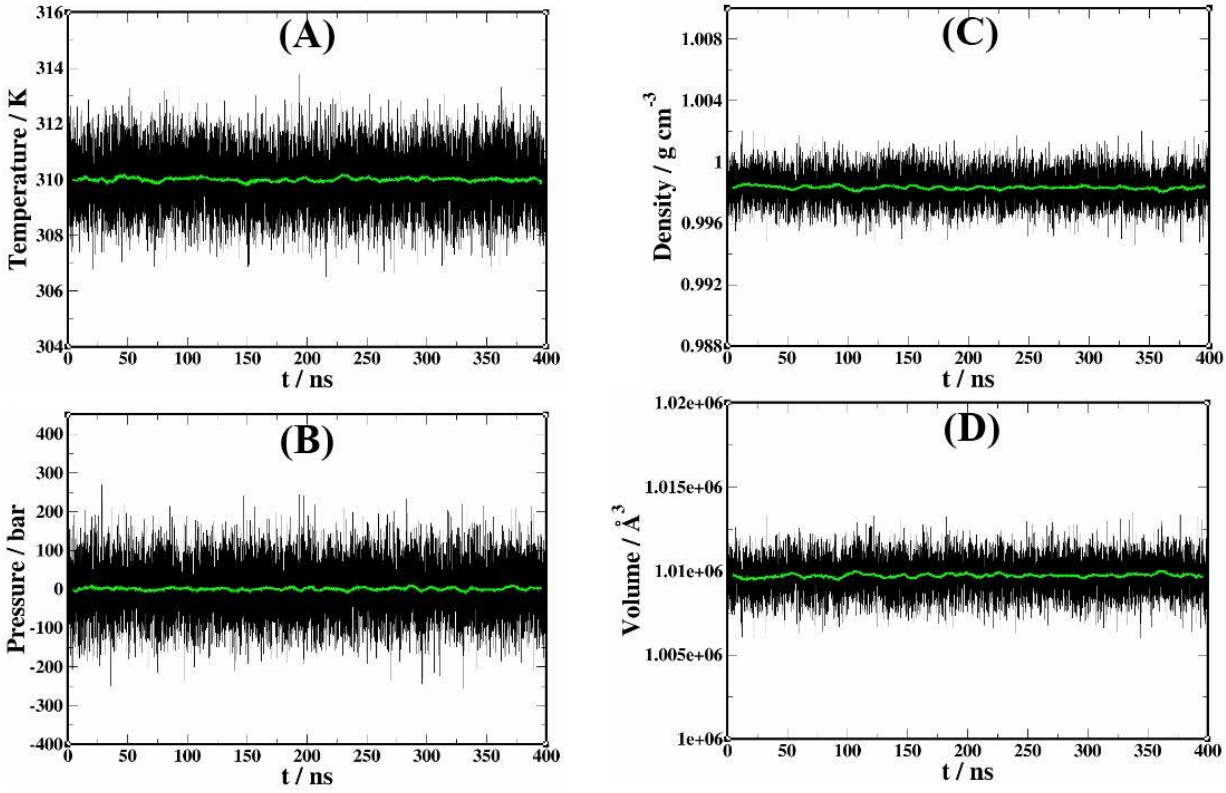

Figure S11. The temporal variation of the temperature (A), pressure (B), density (C) and volume (D) referring to the membrane model of a normal breast cell (N_memb model) in aqueous solution during 400 ns simulation run. The green line represents the moving average calculated for sets of 350 frames.

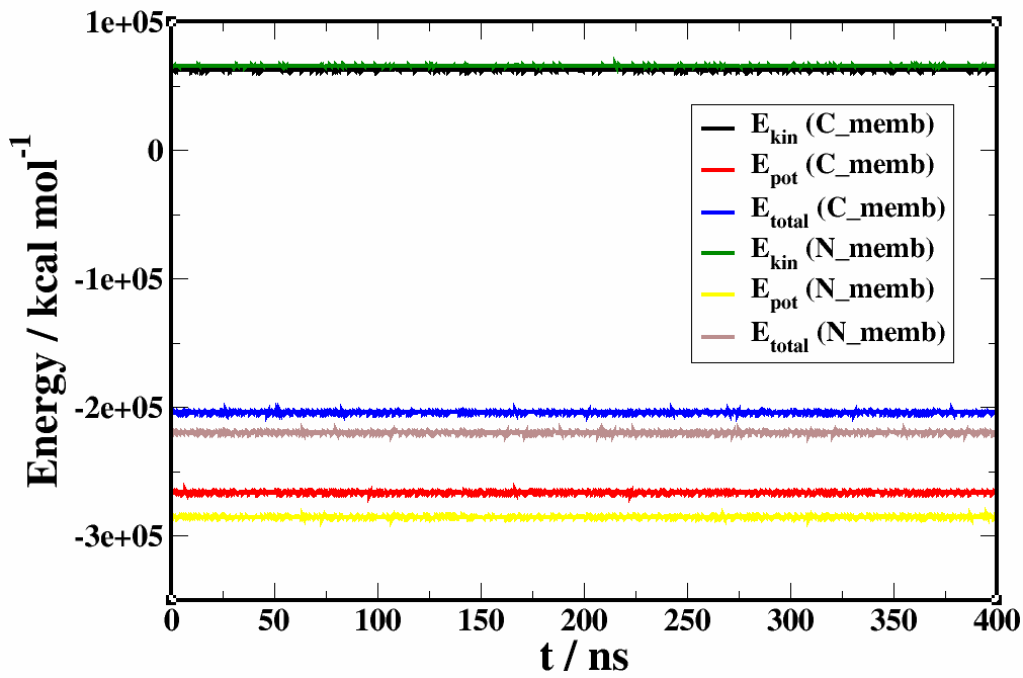

Figure S12. The temporal variation of the kinetic (E_{kin}), potential (E_{pot}), and total (E_{total}) energy of the membrane models referring to a breast cancer cell (C_memb model) and a normal breast cell (N_memb) in aqueous solution over the 400 ns simulation run.

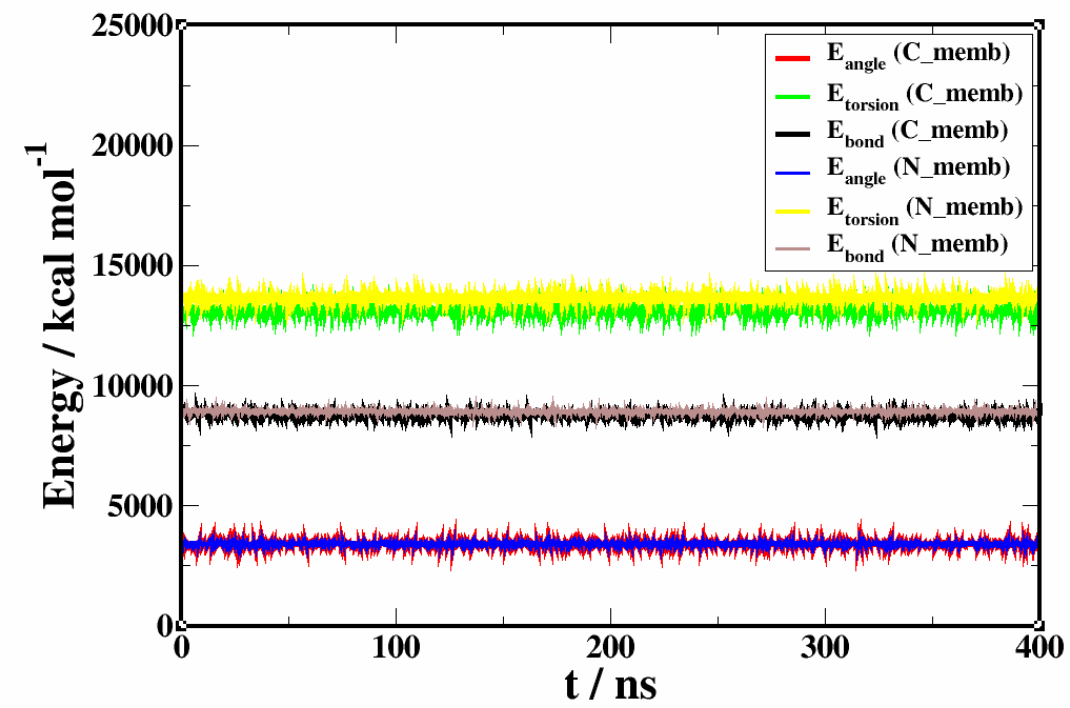

Figure S13. Temporal variation of the bonded energy terms referring to only the membrane models of a BC cell (C_memb) and a normal breast cell (N_memb) during 400 ns of simulation: energy required to the bond stretching (E_{bond}), energy required to the angle bending (E_{angle}), and energy required to the rotations about bonds referring to torsional angles ($E_{torsion}$).

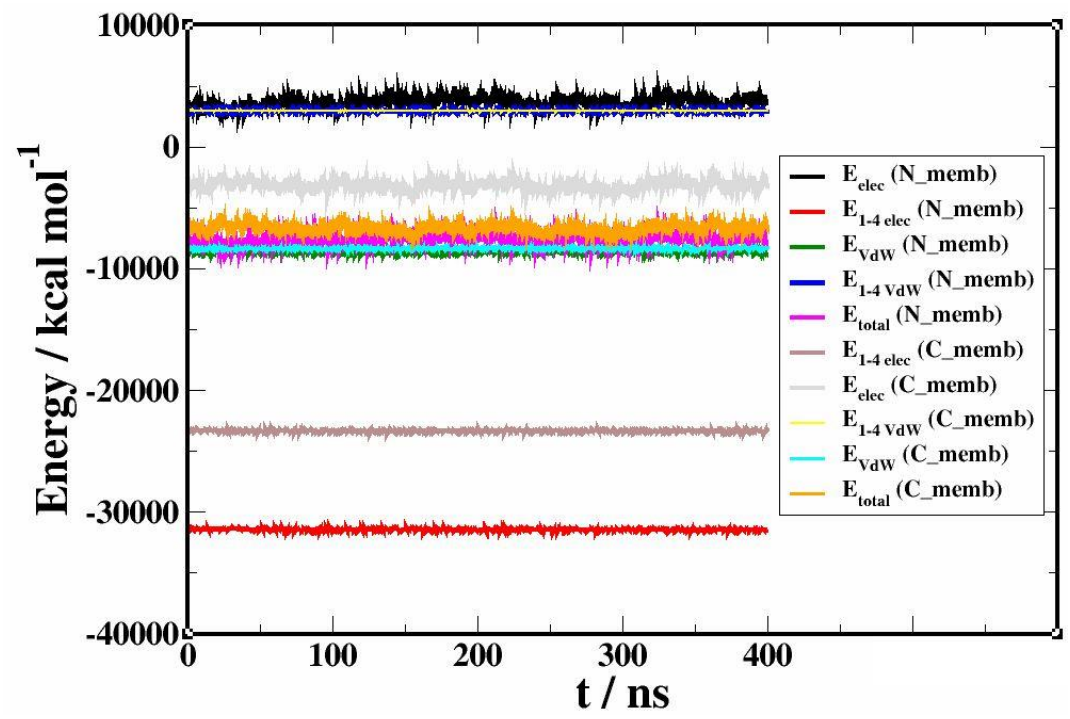

Figure S14. Temporal variation of the non-bonded energy terms referring to only the membrane model of a BC cell (C_memb) and a normal breast cell (N_memb) during 400 ns of simulation: electrostatic interaction energy (E_{elec}), electrostatic interaction energy between the end atoms involved in a dihedral angle ($E_{1\text{-}4\ elec}$), van der Waals interaction energy (E_{vdW}), van der Waals interaction energy between the end atoms involved in a dihedral angle ($E_{1\text{-}4\ vdW}$), and total potential energy (E_{tot}).

Table S3. Statistics of the energetic contributions to the total potential energy of the membrane models (only the solute) of a BC cell (C_memb) and a normal breast cell (N_memb) over 400 ns simulation. All values are in kcal mol^{-1}.

Components	N_memb[a]			C_memb[b]		
	Average ± Std.	Max.	Min.	Average ± Std.	Max.	Min.
E_{bond}	3403.40±48.14	3579.91	3221.03	3288.42±47.77	3502.08	3097.47
E_{angle}	13631.30±89.90	14004.00	13304.70	13125.30±87.09	13507.40	12805.60
$E_{torsion}$	8919.19±46.32	9093.02	8752.87	8774.08±46.58	8965.50	8593.05
E_{vdW1-4}	2971.16±22.76	3073.62	2879.97	2956.93±22.45	3049.50	2875.18
E_{vdW}	-8698.08±62.70	-8455.61	-8935.51	-8339.59±61.52	-8099.17	-8596.65
$E_{elec1-4}$	-31449.40±50.99	-31246.10	-31641.60	-23340.40±48.18	-23152.30	-23524.20
E_{elec}	3625.08±397.58	4999.17	2270.42	-3175.52±343.94	-1842.30	-4540.90
E_{tot}	-7597.37±403.55	-6104.03	-9029.89	-6710.73±367.02	-5327.72	-8119.96

[a]Simulation box dimensions: 118x87x169 Å. [b]Simulation box dimensions: 103x86x175 Å The E_{bond}, E_{angle}, $E_{torsion}$, E_{vdW1-4}, E_{vdW}, $E_{elec1-4}$, E_{elec}, E_{tot}, Std., Max., and Min. terms refer to the energy required to the bond stretching, energy required to the angle bending, energy required to the rotations about bonds referring to torsional angles, van der Waals interaction energy between the end atoms involved in a dihedral angle, van der Waals interaction energy, electrostatic interaction energy between the end atoms involved in a dihedral angle, electrostatic interaction energy, total potential energy, standard deviation, maximum value, and minimum value, respectively.

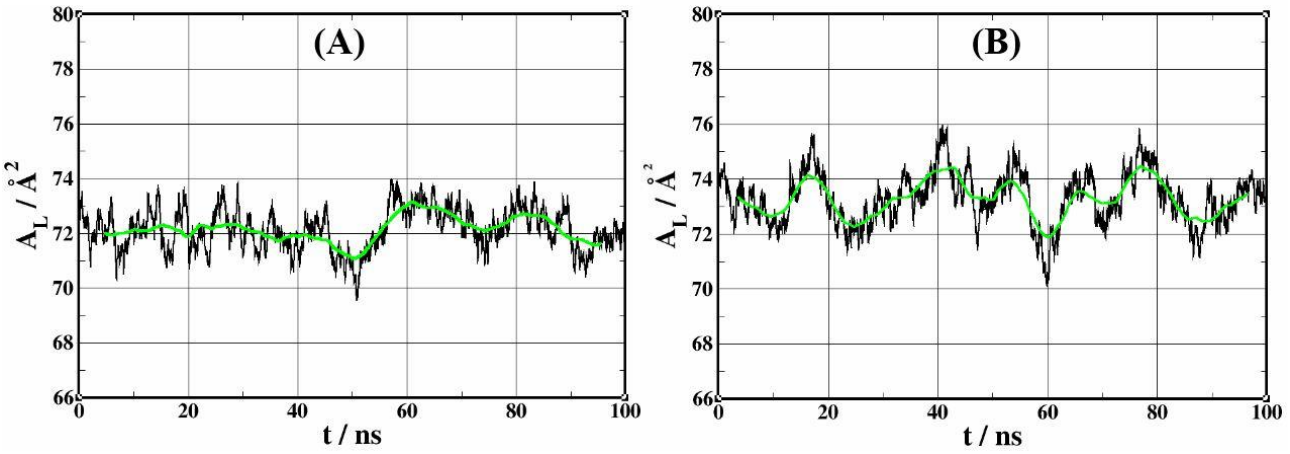

Figure S15. Temporal variation of the area per lipid (A_L) calculated from the membrane models referring to a normal breast cell (N_memb) and a BC cell (C_memb) over the last 100 ns of the 400 ns simulation: N_memb (A) and C_memb (B).

The volume per lipid (V_L) and the volume per molecule (V_M) were calculated as average values over the last 100 ns of the 400 ns simulation by taking into account the volume of the simulation box (V_{xyz}), the volume of a TIP3P water molecule (V_w), and the total number of water (n_w), lipids (n_{lipid}), and cholesterol (n_{CHL}) molecules, as shown in Equation S1-S2.

$$V_L = \frac{V_{xyz} - n_w V_w}{n_{lipid}} \quad \text{S1}$$

$$V_M = \frac{V_{xyz} - n_w V_w}{n_{lipid} + n_{CHL}} \quad \text{S2}$$

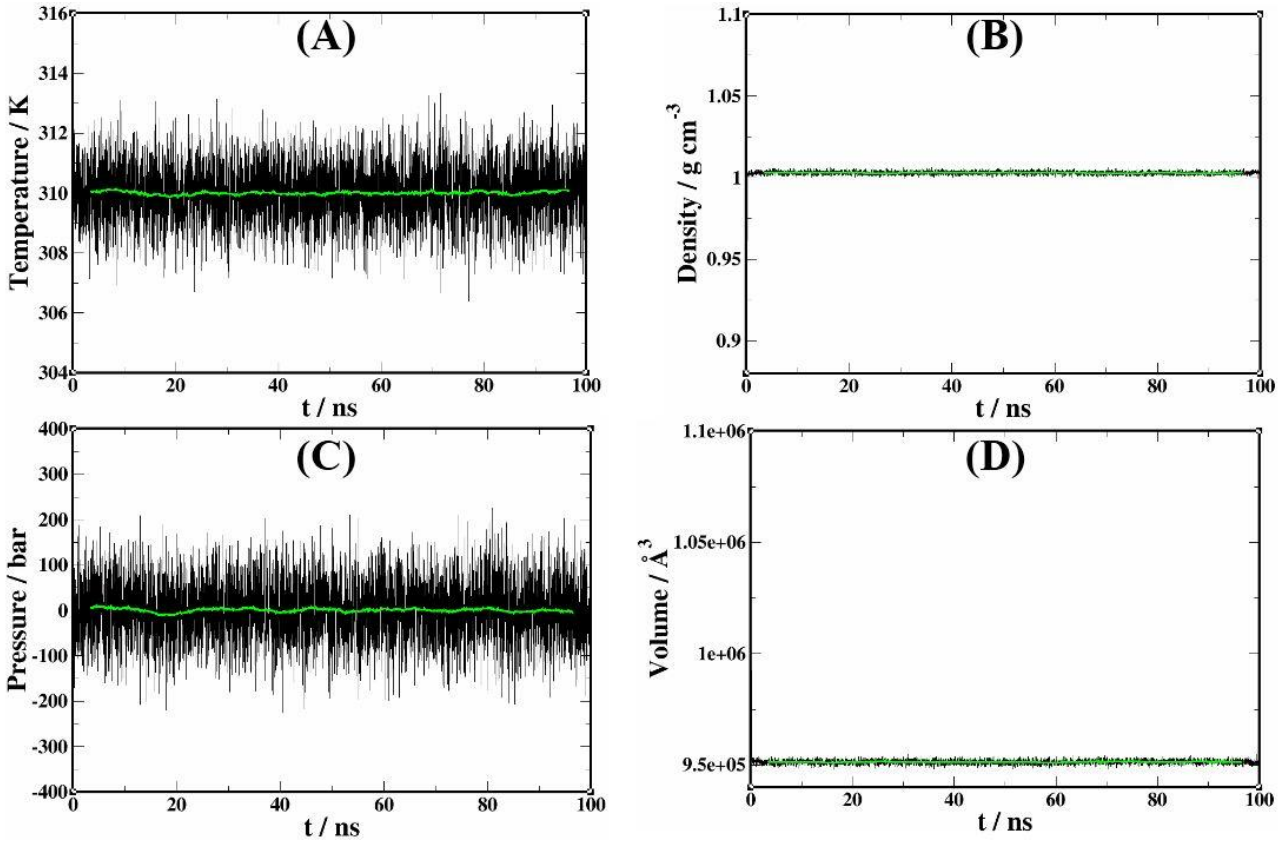

Figure S16. The temporal variation of the temperature (A), pressure (B), density (C) and volume (D) referring to the 3cddp@CNHox>C_memb system in aqueous solution during the first 100 ns of the 800 ns trajectory. The green line represents the moving average calculated for sets of 350 frames.

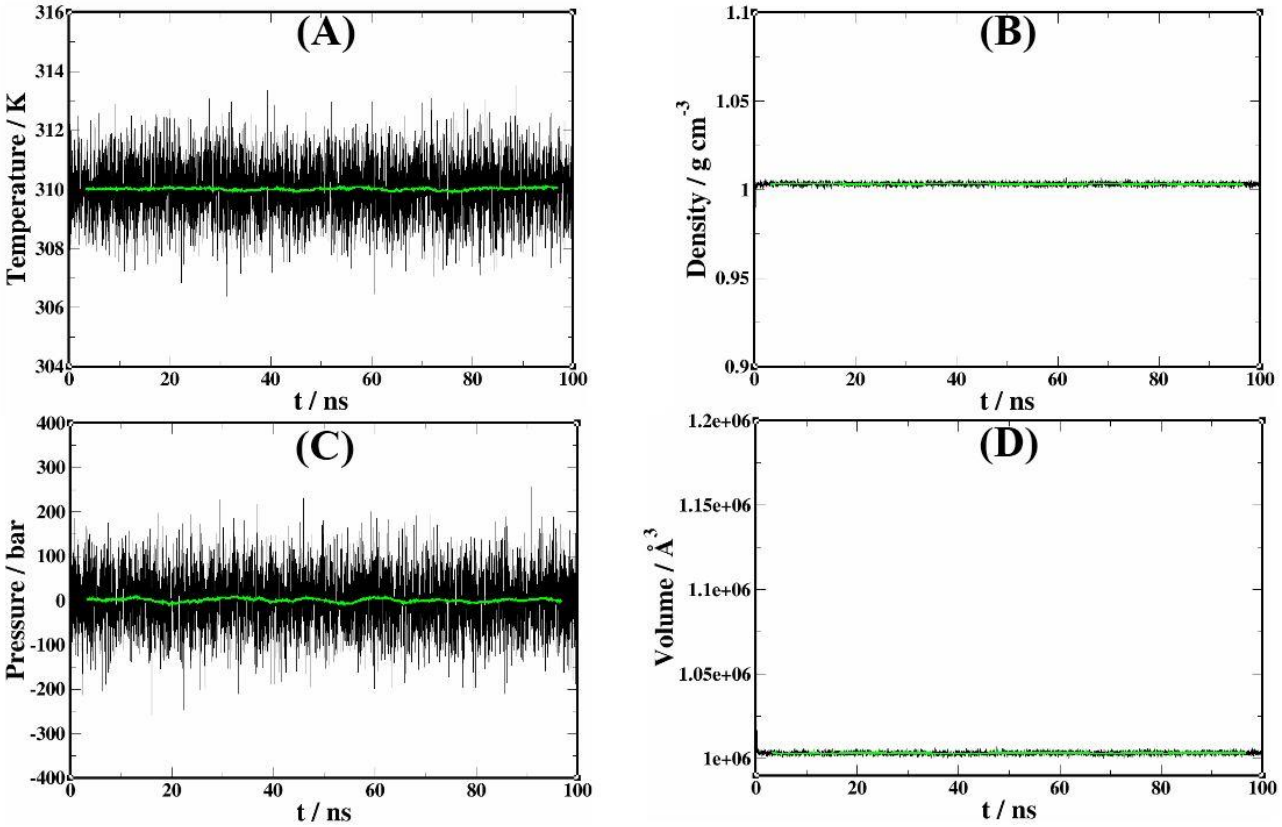

Figure S17. The temporal variation of the temperature (A), pressure (B), density (C) and volume (D) referring to the 3cddp@CNHox>N_memb system in aqueous solution during the first 100 ns of the 800 ns trajectory. The green line represents the moving average calculated for sets of 350 frames.

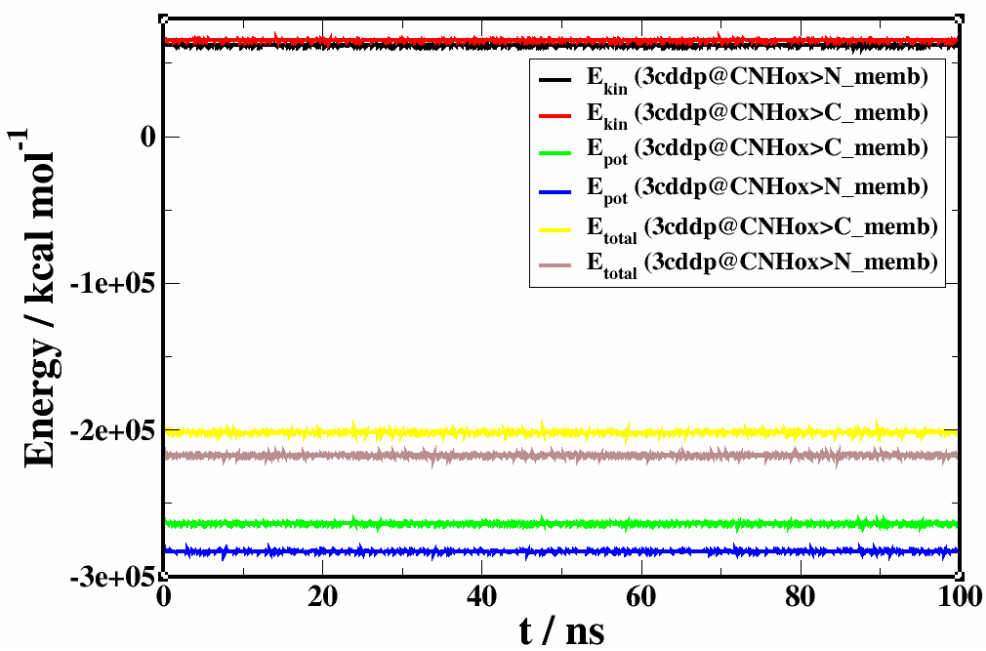

Figure S18. The temporal variation of the kinetic (E_{kin}), potential (E_{pot}), and total (E_{total}) energy of the 3cddp@CNHox>C_memb and 3cddp@CNHox>N_memb systems in aqueous solution the first 100 ns of the 800 ns simulation.

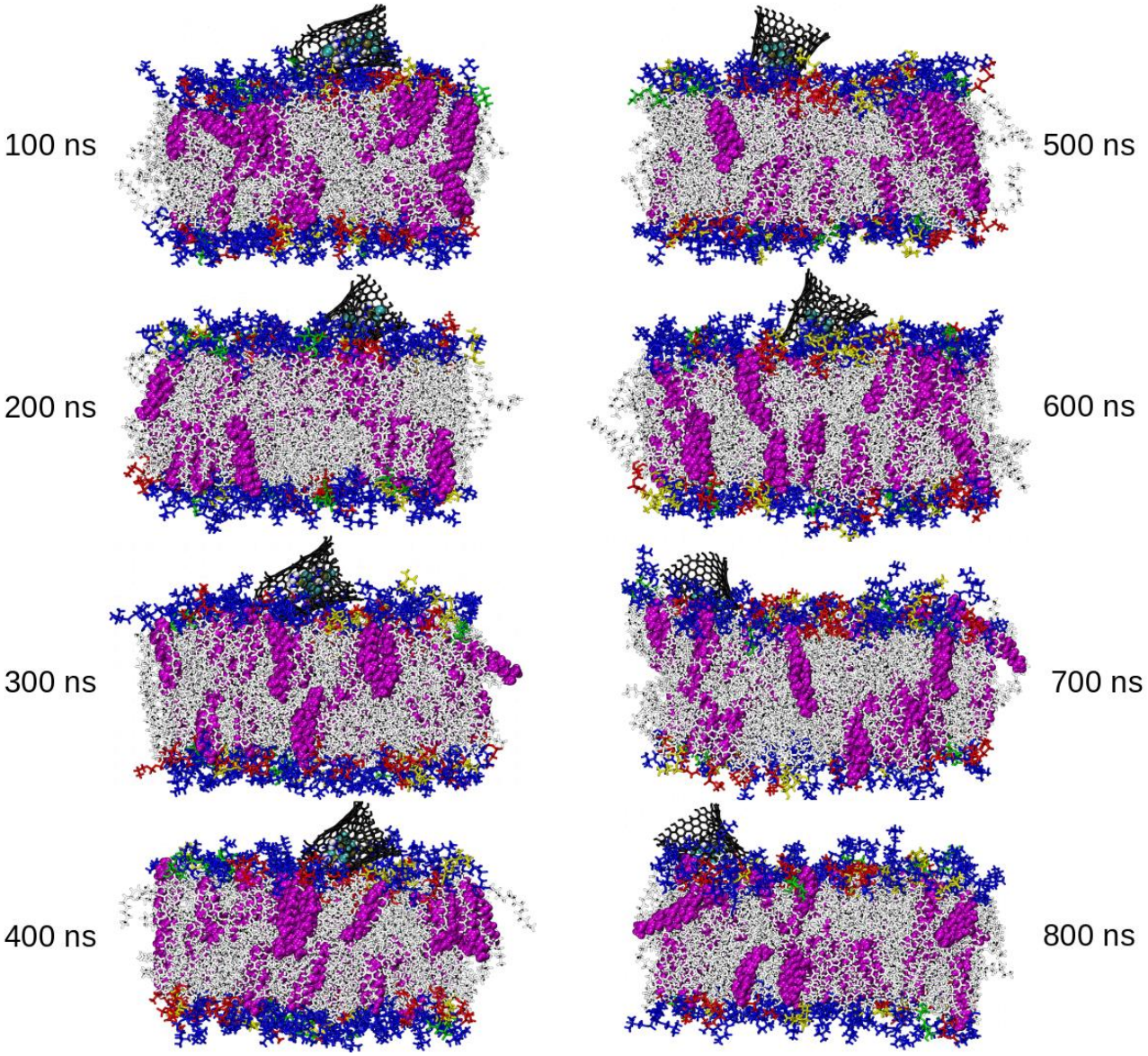

Figure S19. Snapshots of the 800 ns simulation referring to the system 3cddp@CNHox>C_memb, which corresponds to the interaction between the inclusion complex formed by a cluster of three cddp molecules encapsulated into one CNHox structure (3cddp@CNHox) and a plasma membrane model of a BC cell (C_memb). In the membrane structure, the blue, red, yellow, green, magenta, and white colors correspond to the DOPC, DOPE, DOPS, DOPG, CHL, and OL species. In the inclusion complex, while the black color indicated the CNH structure, the blue, white, cyan, and golden colors indicate the N, H, Cl, and Pt atoms of the cddp molecule.

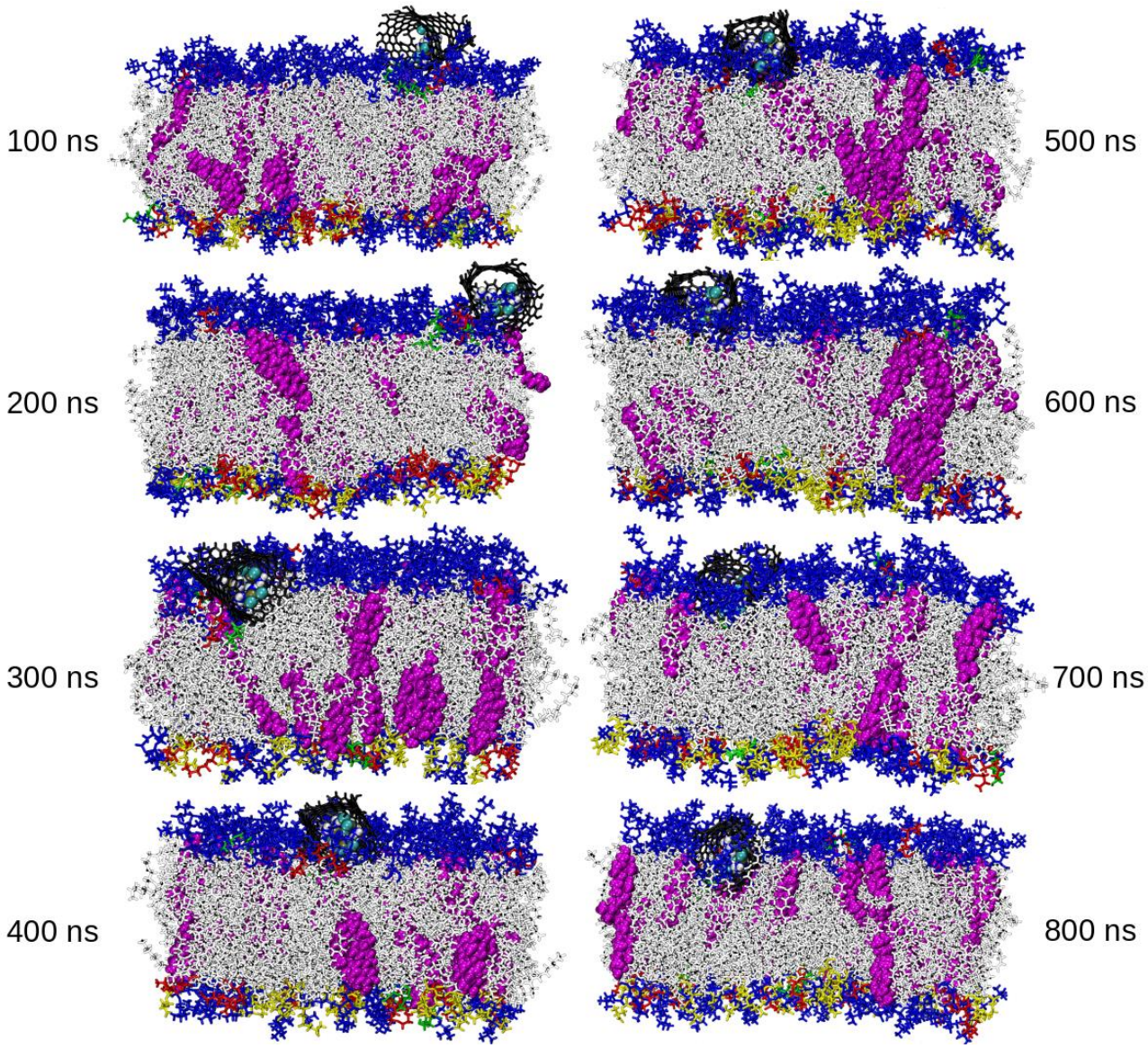

Figure S20. Snapshots of the 800 ns simulation referring to the system 3cddp@CNHox>N_memb, which corresponds to the interaction between the inclusion complex formed by a cluster of three cddp molecules encapsulated into one CNHox) structure (3cddp@CNHox), and a plasma membrane model of a normal breast cell (N_memb). In the membrane structure, the blue, red, yellow, green, magenta, and white colors correspond to the DOPC, DOPE, DOPS, DOPG, CHL, and OL species. In the inclusion complex, while the black color indicated the CNH structure, the blue, white, cyan, and ochre colors indicate the N, H, Cl, and Pt atoms of the cddp molecule.

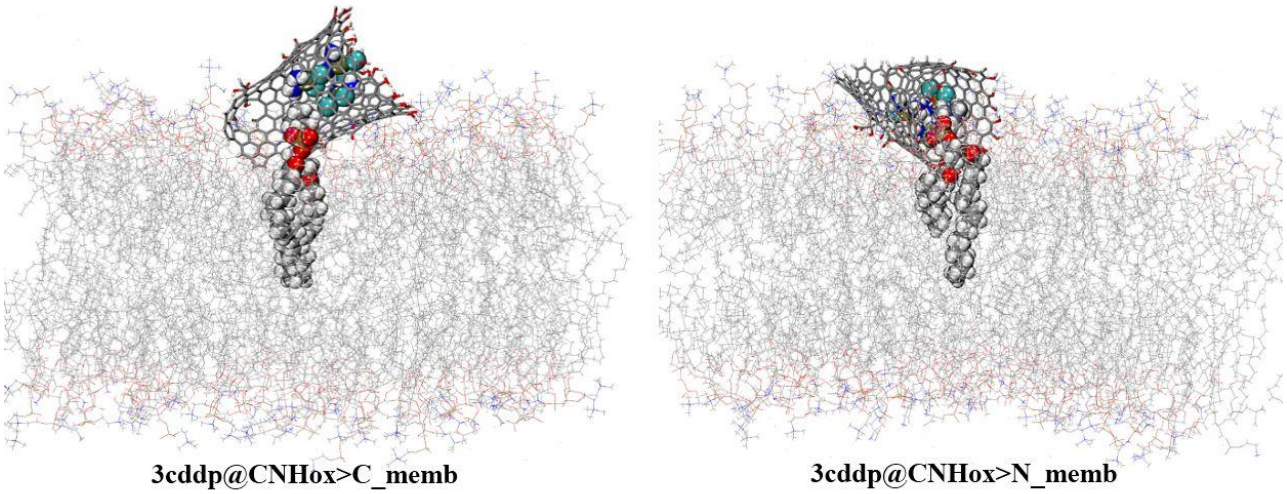

Figure S21. Insertion of the PC headgroup of the 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) lipid located in both C_memb (A) and N_memb (B) models into the cavity of the CNHox) by the time of 260 ns and 280 ns, respectively.