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


# Robustness of Heteroaggregates Involving Hydrophobic Cholesterol and its Mimetics

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## Supplementary Information

Table SI-1: Composition of the systems

| System | No. of lipid molecules | | Length of simulation (ns) |
|---|---|---|---|
| | $L_1$ | $L_2$ | |
| 10 $CHL_B$ | 10 | 0 | 100 |
| 20 $CHL_B$ | 20 | 0 | 100 |
| 40 $CHM_B$ | 40 | 0 | 330 |
| 40 $CAM_B$ | 40 | 0 | 330 |
| 40 $ARJ_B$ | 40 | 0 | 330 |
| 1:1 CHL:CHM | 10 | 10 | 330 |
| 1:1 CHL:CAM | 10 | 10 | 330 |
| 1:1 CHL:ARJ | 10 | 10 | 330 |
| 1:4 CHL:CHM | 10 | 40 | 330 |
| 1:4 CHL:CAM | 10 | 40 | 330 |
| 1:4 CHL:ARJ | 10 | 40 | 330 |
| 4:1 CHL:CHM | 40 | 10 | 330 |
| 4:1 CHL:CAM | 40 | 10 | 330 |
| 4:1 CHL:ARJ | 40 | 10 | 330 |

CHL: Cholesterol; CHM: Cholesteryl hemisuccinate; CAM: Campesterol; ARJ: Arjunic acid. The subscript ‘B’ refers to blank systems containing only one pure component solvated in TIP3P water.

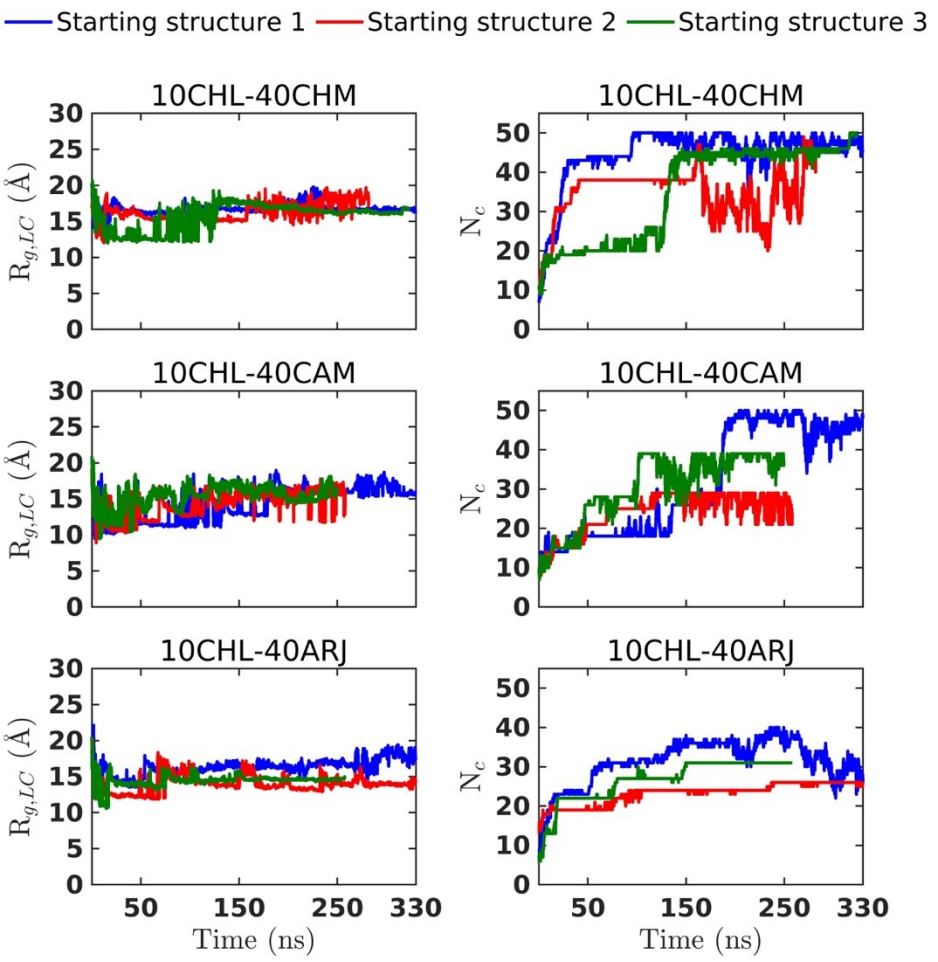



**Figure SI-1.** Simulation trajectories showing convergence of $R_g$ and $N_c$ starting from different initial configuration of the (1:4) CHL: Lipid compositions. The color code for each trajectory is given in the top panel.

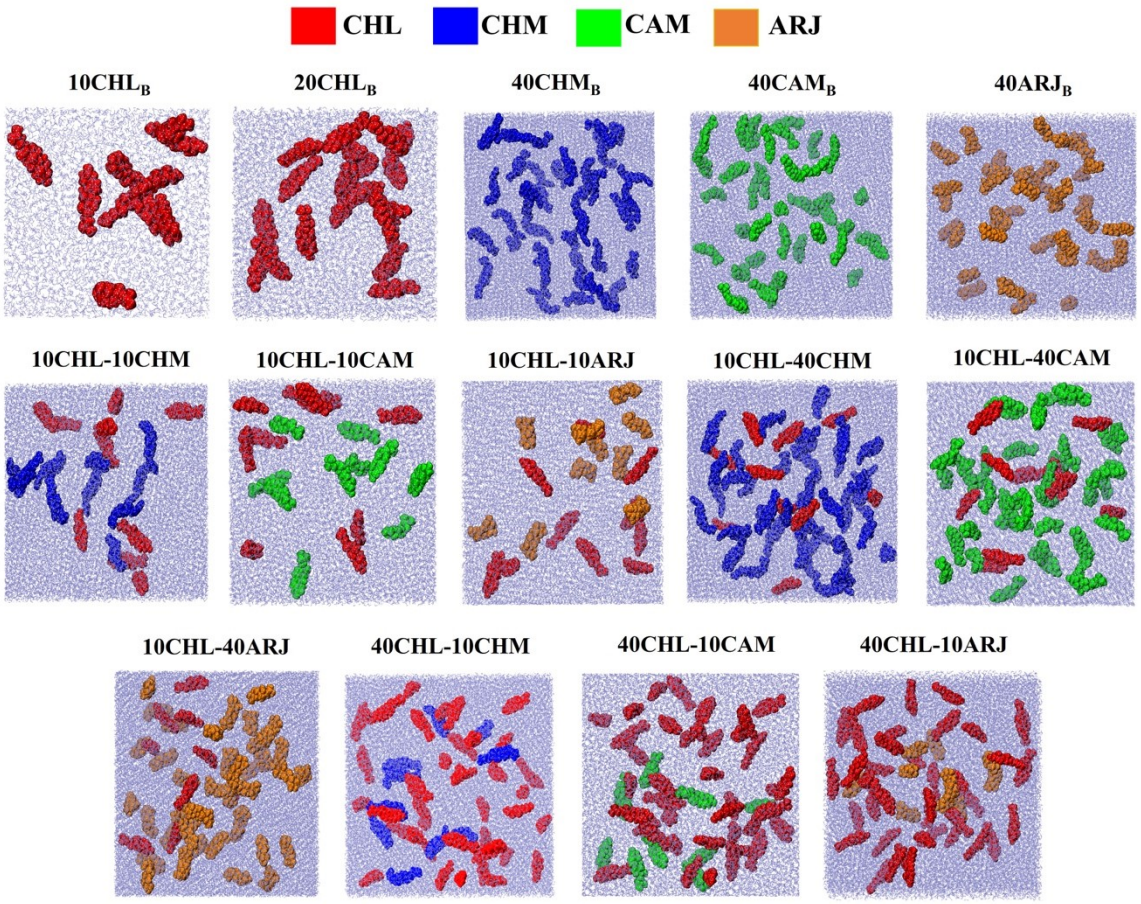



**Figure SI-2.** Initial configurations of the simulation cell for all the systems. The color codes used for each lipid type is given in the top panel.

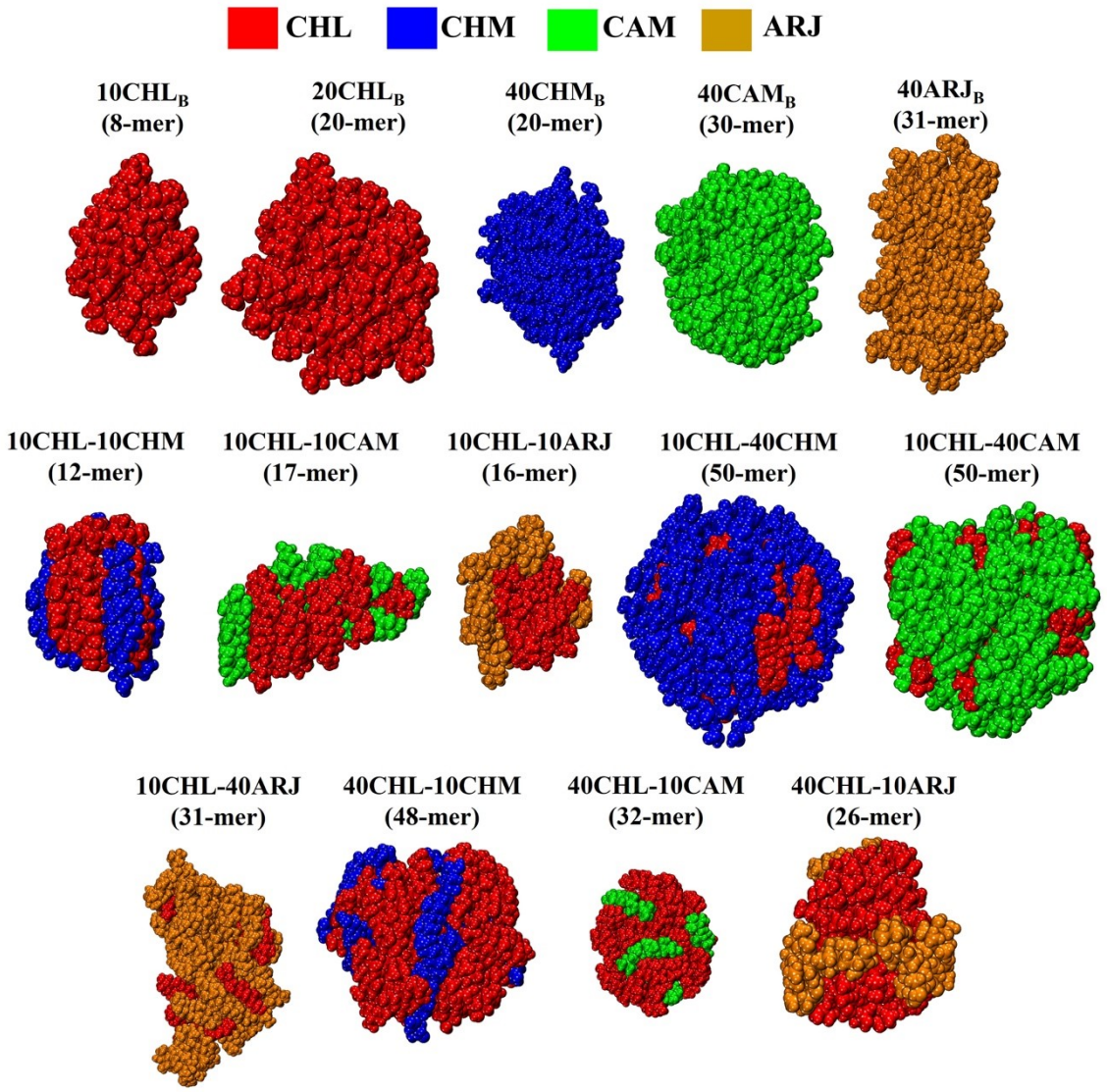



**Figure SI-3.** Representative structures of the largest cluster observed along the course of simulations for each system. The total number of lipid monomers present in the cluster is given within parentheses. The color codes used for each lipid type is given in the top panel.

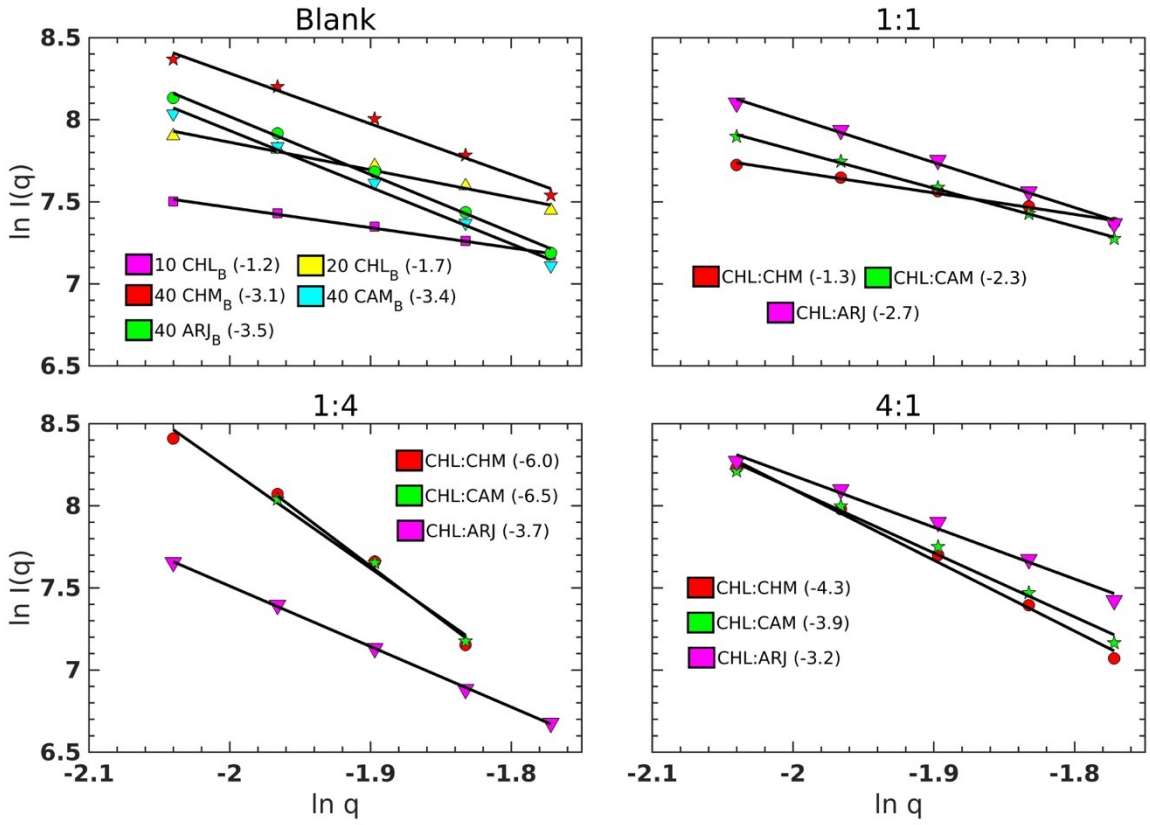
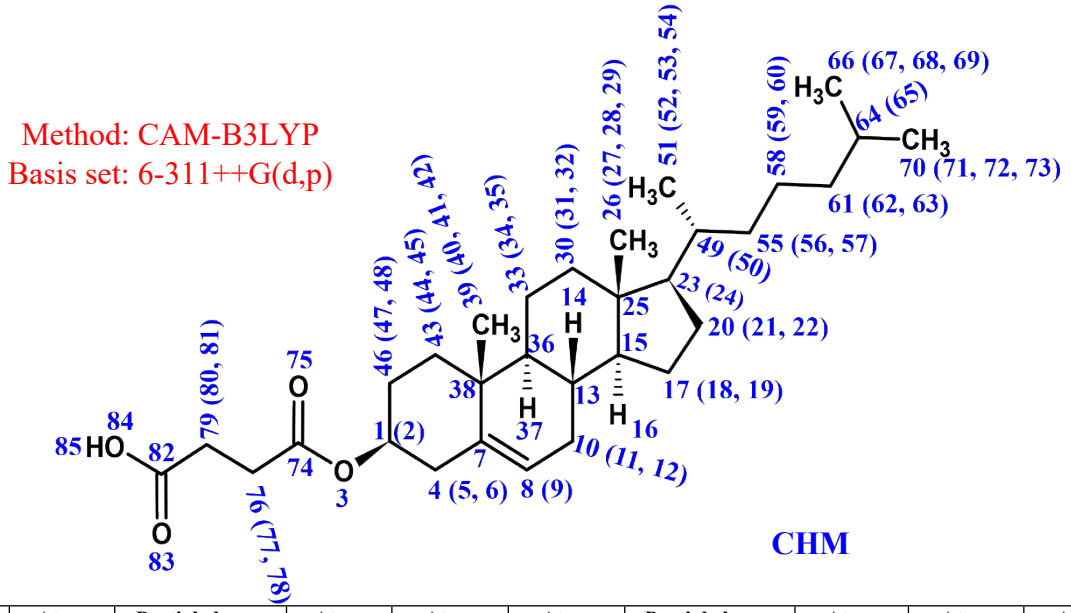



**Figure SI-4.** Porod plots constructed from small angle scattering data of the aggregated phases for the pure (suffix B) and mixed micellar systems. The slopes of each plot denoting the '*Porod exponent*' are shown within parentheses.

## Force Field Parameters for CHM, CAM and ARJ:

For each molecule, the bonding and non-bonding parameters are taken from the closest atom type in CHARMM36. Charges are taken from the optimized geometry of the molecules obtained using CAM-B3LYP functional and 6-311++g(d,p) basis set in the Gaussian 09 platform.

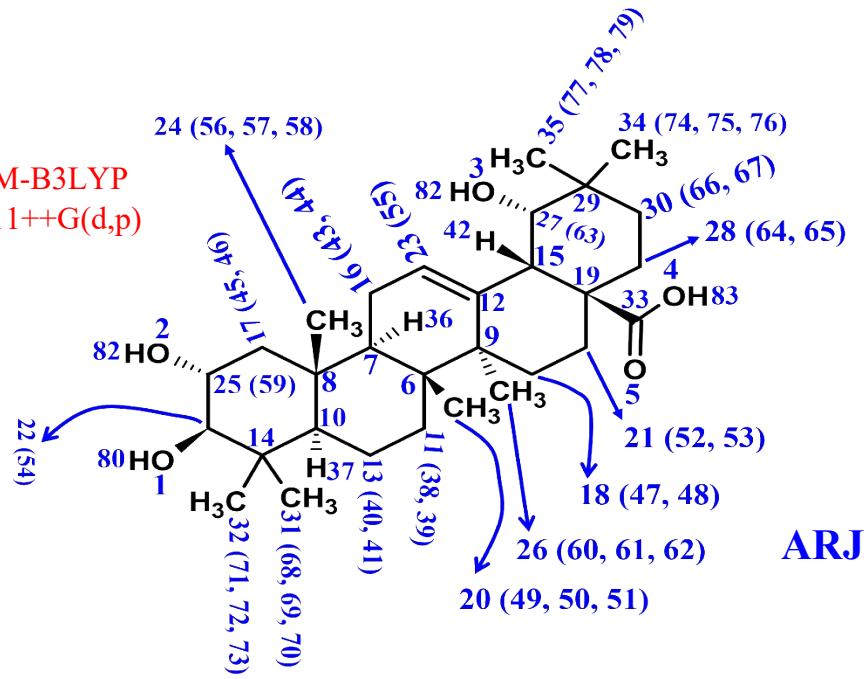
**Table SI-2: Force field parameters for CHM**




| Atom index | Atom name | Atom type | Partial charge | Atom index | Atom name | Atom type | Partial charge | Atom index | Atom name | Atom type | Partial charge |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | C3 | CRL1 | 0.582277 | 33 | C11 | CRL2 | -0.021019 | 65 | H25 | HAL1 | -0.043250 |
| 2 | H3 | HGA1 | -0.004251 | 34 | H11A | HGA2 | 0.016156 | 66 | C26 | CTL3 | -0.435655 |
| 3 | O3 | OSL | -0.646302 | 35 | H11B | HGA2 | 0.020881 | 67 | H26A | HAL3 | 0.097601 |
| 4 | C4 | CRL2 | -0.367038 | 36 | C9 | CRL1 | -0.157893 | 68 | H26B | HAL3 | 0.094463 |
| 5 | H4A | HGA2 | 0.128398 | 37 | H9 | HGA1 | 0.032746 | 69 | H26C | HAL3 | 0.092248 |
| 6 | H4B | HGA2 | 0.131352 | 38 | C10 | CRL1 | 0.446215 | 70 | C27 | CTL3 | -0.437002 |
| 7 | C5 | CEL1 | -0.136633 | 39 | C19 | CTL3 | -0.355719 | 71 | H27A | HAL3 | 0.097111 |
| 8 | C6 | CEL1 | -0.236086 | 40 | H19A | HAL3 | 0.063898 | 72 | H27B | HAL3 | 0.092627 |
| 9 | H6 | HEL1 | 0.147327 | 41 | H19B | HAL3 | 0.091989 | 73 | H27C | HAL3 | 0.096375 |
| 10 | C7 | CRL2 | -0.165341 | 42 | H19C | HAL3 | 0.075964 | 74 | C28 | CL | 0.879366 |
| 11 | H7A | HGA2 | 0.069370 | 43 | C1 | CRL2 | -0.205895 | 75 | O28 | OCL | -0.597207 |
| 12 | H7B | HGA2 | 0.076832 | 44 | H1A | HGA2 | 0.039908 | 76 | C29 | CTL2 | -0.384925 |
| 13 | C8 | CRL1 | 0.180131 | 45 | H1B | HGA2 | 0.075689 | 77 | H29A | HAL2 | 0.138458 |
| 14 | H8 | HGA1 | -0.002772 | 46 | C2 | CRL2 | -0.206092 | 78 | H29B | HAL2 | 0.139571 |
| 15 | C14 | CRL1 | -0.003822 | 47 | H2A | HGA2 | 0.078251 | 79 | C30 | CTL2 | -0.074587 |
| 16 | H14 | HGA1 | -0.006738 | 48 | H2B | HGA2 | 0.070298 | 80 | H30A | HAL2 | 0.076960 |
| 17 | C15 | CRL2 | -0.337397 | 49 | C20 | CTL1 | 0.150113 | 81 | H30B | HAL2 | 0.078535 |
| 18 | H15A | HGA2 | 0.069246 | 50 | H20 | HAL1 | -0.013197 | 82 | C31 | CL | 0.766838 |
| 19 | H15B | HGA2 | 0.073557 | 51 | C21 | CTL3 | -0.392536 | 83 | O31 | OCL | -0.587298 |
| 20 | C16 | CRL2 | 0.045611 | 52 | H21A | HAL3 | 0.080033 | 84 | O32 | OHL | -0.669639 |
| 21 | H16A | HGA2 | -0.006404 | 53 | H21B | HAL3 | 0.067831 | 85 | H32 | HGA1 | 0.449167 |
| 22 | H16B | HGA2 | 0.011095 | 54 | H21C | HAL3 | 0.100738 | | | | |
| 23 | C17 | CRL1 | 0.150109 | 55 | C22 | CTL2 | -0.230871 | | | | |
| 24 | H17 | HGA1 | -0.102873 | 56 | H22A | HAL2 | 0.060804 | | | | |
| 25 | C13 | CRL1 | 0.561434 | 57 | H22B | HAL2 | 0.014377 | | | | |
| 26 | C18 | CTL3 | -0.677601 | 58 | C23 | CTL2 | 0.250634 | | | | |
| 27 | H18A | HAL3 | 0.136962 | 59 | H23A | HAL2 | -0.011427 | | | | |
| 28 | H18B | HAL3 | 0.137266 | 60 | H23B | HAL2 | -0.010493 | | | | |
| 29 | H18C | HAL3 | 0.149098 | 61 | C24 | CTL2 | -0.382619 | | | | |
| 30 | C12 | CRL2 | -0.244385 | 62 | H24A | HAL2 | 0.069229 | | | | |
| 31 | H12A | HGA2 | 0.052453 | 63 | H24B | HAL2 | 0.074425 | | | | |
| 32 | H12B | HGA2 | 0.020357 | 64 | C25 | CTL1 | 0.452593 | | | | |

## Table SI-3: Force field parameters for ARJ

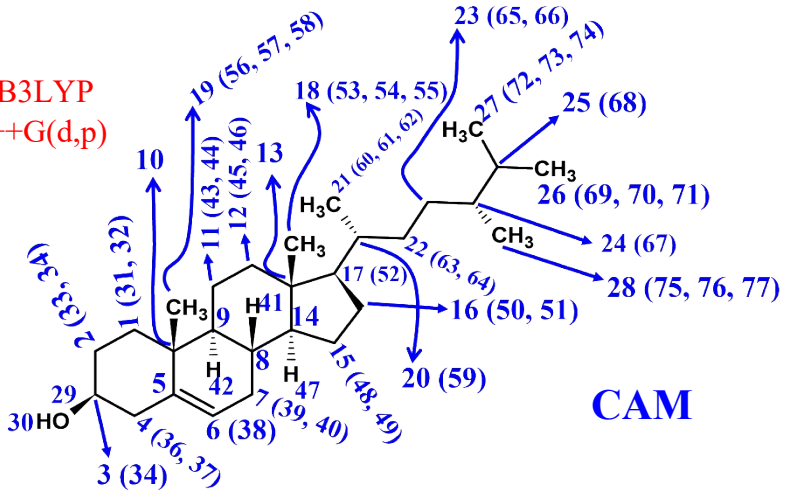
Method: CAM-B3LYP
Basis set: 6-311++G(d,p)




| Atom index | Atom name | Atom type | Partial charge | Atom index | Atom name | Atom type | Partial charge | Atom index | Atom name | Atom type | Partial charge |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | O10 | OHL | -0.685343 | 30 | C3 | CRL2 | -0.160350 | 59 | H11 | HGA1 | 0.093063 |
| 2 | O11 | OHL | -0.725790 | 31 | C9A | CTL3 | -0.478530 | 60 | H261 | HAL3 | 0.190585 |
| 3 | O1 | OHL | -0.833193 | 32 | C9B | CTL3 | -0.676560 | 61 | H262 | HAL3 | 0.064955 |
| 4 | O4 | OCL | -0.607574 | 33 | C33 | CL | 0.698977 | 62 | H263 | HAL3 | 0.088115 |
| 5 | O33 | OCL | -0.589698 | 34 | C34 | CTL3 | -0.406686 | 63 | H1 | HGA1 | -0.082614 |
| 6 | C6B | CEL1 | 0.397907 | 35 | C35 | CTL3 | -0.564686 | 64 | H41 | HGA2 | -0.003376 |
| 7 | C12B | CRL1 | 0.051008 | 36 | H12B | HGA1 | 0.001582 | 65 | H42 | HGA2 | 0.041161 |
| 8 | C12A | CEL1 | 0.189002 | 37 | H8A | HGA1 | -0.030944 | 66 | H31 | HGA2 | 0.030211 |
| 9 | C6A | CEL1 | 0.776108 | 38 | H71 | HGA2 | -0.014409 | 67 | H32 | HGA2 | 0.048288 |
| 10 | C8A | CRL1 | -0.107219 | 39 | H72 | HGA2 | 0.006390 | 68 | H9A3 | HAL3 | 0.090076 |
| 11 | C7 | CRL2 | -0.071151 | 40 | H81 | HGA2 | 0.059832 | 69 | H9A2 | HAL3 | 0.131854 |
| 12 | C14A | CEL1 | -0.635771 | 41 | H82 | HGA2 | 0.038955 | 70 | H9A1 | HAL3 | 0.087262 |
| 13 | C8 | CRL2 | -0.178783 | 42 | H14B | HGA1 | 0.023470 | 71 | H9B2 | HAL3 | 0.137256 |
| 14 | C9 | CEL1 | 0.745572 | 43 | H131 | HGA2 | 0.064761 | 72 | H9B3 | HAL3 | 0.128191 |
| 15 | C14B | CRL1 | 0.209725 | 44 | H132 | HGA2 | 0.048916 | 73 | H9B1 | HAL3 | 0.167575 |
| 16 | C13 | CRL2 | -0.102231 | 45 | H121 | HGA2 | 0.074637 | 74 | H341 | HAL3 | 0.090113 |
| 17 | C12 | CRL2 | -0.431649 | 46 | H122 | HGA2 | 0.123890 | 75 | H342 | HAL3 | 0.064532 |
| 18 | C6 | CRL2 | -0.004823 | 47 | H61 | HGA2 | -0.023825 | 76 | H343 | HAL3 | 0.111889 |
| 19 | C4A | CEL1 | 0.072151 | 48 | H62 | HGA2 | -0.028716 | 77 | H351 | HAL3 | 0.144053 |
| 20 | C20 | CTL3 | -0.461668 | 49 | H201 | HAL3 | 0.074210 | 78 | H352 | HAL3 | 0.108905 |
| 21 | C5 | CRL2 | -0.238301 | 50 | H202 | HAL3 | 0.100978 | 79 | H353 | HAL3 | 0.123202 |
| 22 | C10 | CRL1 | -0.012954 | 51 | H203 | HAL3 | 0.081235 | 80 | HO10 | HOL | 0.432849 |
| 23 | C14 | CEL1 | -0.094975 | 52 | H51 | HGA2 | 0.072522 | 81 | HO11 | HOL | 0.420271 |
| 24 | C24 | CTL3 | -0.552582 | 53 | H52 | HGA2 | 0.027611 | 82 | HO1 | HOL | 0.436276 |
| 25 | C11 | CRL1 | 0.387834 | 54 | H10 | HGA1 | 0.026590 | 83 | HO4 | HGA1 | 0.422501 |
| 26 | C26 | CTL3 | -0.581387 | 55 | H14 | HEL1 | 0.070106 | | | | |
| 27 | C1 | CRL1 | 0.697452 | 56 | H241 | HAL3 | 0.160759 | | | | |
| 28 | C4 | CRL2 | -0.085766 | 57 | H242 | HAL3 | 0.127175 | | | | |
| 29 | C2 | CEL1 | 0.286103 | 58 | H243 | HAL3 | 0.122907 | | | | |

## Table SI-4: Force field parameters for CAM

Method: CAM-B3LYP
Basis set: 6-311++G(d,p)




| Atom index | Atom name | Atom type | Partial charge | Atom index | Atom name | Atom type | Partial charge | Atom index | Atom name | Atom type | Partial charge |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | C1 | CRL2 | -0.285008 | 27 | C27 | CTL3 | -0.473687 | 53 | H18A | HAL3 | 0.127735 |
| 2 | C2 | CRL2 | -0.052119 | 28 | C28 | CTL3 | -0.498230 | 54 | H18B | HAL3 | 0.122471 |
| 3 | C3 | CRL1 | 0.431198 | 29 | O3 | OHL | -0.746890 | 55 | H18C | HAL3 | 0.117945 |
| 4 | C4 | CRL2 | -0.392705 | 30 | H3´ | HOL | 0.423701 | 56 | H19A | HAL3 | 0.120746 |
| 5 | C5 | CEL1 | -0.052916 | 31 | H1A | HGA2 | 0.068530 | 57 | H19B | HAL3 | 0.088407 |
| 6 | C6 | CEL1 | -0.320694 | 32 | H1B | HGA2 | 0.054247 | 58 | H19C | HAL3 | 0.094874 |
| 7 | C7 | CRL2 | 0.007818 | 33 | H2A | HGA2 | 0.052846 | 59 | H20 | HAL1 | -0.040908 |
| 8 | C8 | CRL1 | 0.016196 | 34 | H2B | HGA2 | 0.061834 | 60 | H21A | HAL3 | 0.079228 |
| 9 | C9 | CRL1 | 0.011474 | 35 | H3 | HGA1 | -0.013132 | 61 | H21B | HAL3 | 0.101511 |
| 10 | C10 | CRL1 | 0.446120 | 36 | H4A | HGA2 | 0.134015 | 62 | H21C | HAL3 | 0.076740 |
| 11 | C11 | CRL2 | -0.048447 | 37 | H4B | HGA2 | 0.108738 | 63 | H22A | HAL2 | -0.005737 |
| 12 | C12 | CRL2 | -0.261726 | 38 | H6 | HEL1 | 0.149745 | 64 | H22B | HAL2 | 0.063783 |
| 13 | C13 | CRL1 | 0.609305 | 39 | H7A | HGA2 | 0.029278 | 65 | H23A | HAL2 | 0.064195 |
| 14 | C14 | CRL1 | -0.022443 | 40 | H7B | HGA2 | 0.038737 | 66 | H23B | HAL2 | 0.078167 |
| 15 | C15 | CRL2 | -0.258537 | 41 | H8 | HGA1 | 0.017981 | 67 | H24 | HAL1 | -0.016559 |
| 16 | C16 | CRL2 | -0.095213 | 42 | H9 | HGA1 | -0.012897 | 68 | H25 | HAL1 | -0.080294 |
| 17 | C17 | CRL1 | 0.165964 | 43 | H11A | HGA2 | 0.028344 | 69 | H26A | HAL3 | 0.087039 |
| 18 | C18 | CTL3 | -0.620508 | 44 | H11B | HGA2 | 0.018356 | 70 | H26B | HAL3 | 0.115913 |
| 19 | C19 | CTL3 | -0.456997 | 45 | H12A | HGA2 | 0.048780 | 71 | H26C | HAL3 | 0.115832 |
| 20 | C20 | CTL1 | 0.234229 | 46 | H12B | HGA2 | 0.018275 | 72 | H27A | HAL3 | 0.101797 |
| 21 | C21 | CTL3 | -0.415009 | 47 | H14 | HGA1 | 0.001196 | 73 | H27B | HAL3 | 0.098645 |
| 22 | C22 | CTL2 | -0.189478 | 48 | H15A | HGA2 | 0.060487 | 74 | H27C | HAL3 | 0.099151 |
| 23 | C23 | CTL2 | -0.204118 | 49 | H15B | HGA2 | 0.060177 | 75 | H28A | HAL3 | 0.107817 |
| 24 | C24 | CTL1 | 0.228758 | 50 | H16A | HGA2 | 0.047679 | 76 | H28B | HAL3 | 0.106094 |
| 25 | C25 | CTL1 | 0.495573 | 51 | H16B | HGA2 | 0.026372 | 77 | H28C | HAL3 | 0.117405 |
| 26 | C26 | CTL3 | -0.513396 | 52 | H17 | HGA1 | -0.103801 | | | | |

Some bonding parameters for CHM and ARJ that could not be retrieved straight forwardly from CHARMM36 force field are mentioned below. The equilibrium bond length ($b_0$), angle ($\theta_0$), and dihedral ($\psi_0$) values are obtained from the respective optimized geometries of the molecules. The corresponding force constants ($k_b$, $k_\theta$, $k_\psi$) are extracted from the existing CHARMM36 Lipid FF by finding the closest match of a combination of atom types that fits the chemical nature of the bonding reasonably.

**Table SI-5: Bonding parameters for CHM and ARJ**

| Molecule | Bond connectivity | $b_0$ (Å) | $k_b$ (kcal mol$^{-1}$ Å$^{-2}$) | Source |
|---|---|---|---|---|
| CHM | HGA1-OHL | 0.960 | 545.0 | CHARMM |
| | OSL-CRL1 | 1.334 | 150.0 | CHARMM |
| ARJ | HGA1-OCL | 0.9803 | 545.0 | CHARMM |
| | CEL1-CL | 1.5196 | 200.0 | CHARMM |

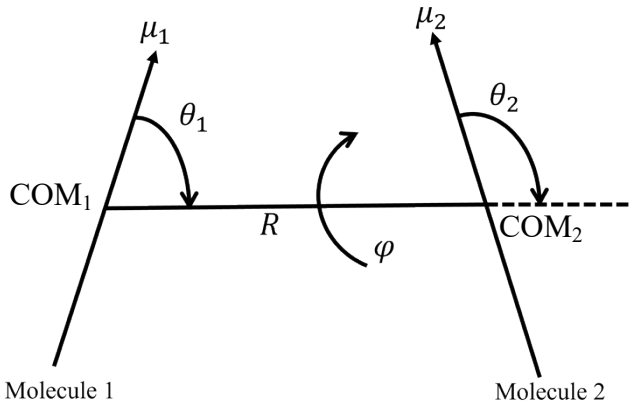
| Molecule | Angle connectivity | $k_\theta$ (kcal mol$^{-1}$ rad$^{-2}$) | $\theta_0$ (°) | Source |
|---|---|---|---|---|
| CHM | HGA1-CRL1-OSL | 56.205 | 107.8374 | Swissparam |
| | CRL2-CRL1-OSL | 71.390 | 107.1322 | Swissparam |
| ARJ | OHL-CRL1-CRL1 | 75.700 | 110.10 | CHARMM |
| | CTL3-CEL1-CRL2 | 42.00 | 108.9927 | CHARMM |
| | CTL3-CEL1-CTL3 | 47.00 | 107.2517 | CHARMM |
| | CEL1-CRL1-OHL | 75.700 | 113.3336 | CHARMM |
| | CEL1-CRL1-CEL1 | 53.350 | 117.4994 | CHARMM |
| | CRL1-CEL1-CTL3 | 48.00 | 113.6067 | CHARMM |
| | CEL1-CL-OCL | 55.00 | 126.2707 | CHARMM |
| | CRL2-CEL1-CRL2 | 58.350 | 109.2143 | CHARMM |
| | CL-CEL1-CRL2 | 58.350 | 106.5039 | CHARMM |
| | CL-CEL1-CRL1 | 34.500 | 108.3469 | CHARMM |
| | CL-OCL-HGA1 | 41.956 | 111.8971 | CHARMM |

| Molecule | Dihedral connectivity | $k_\chi$ (kcal mol$^{-1}$) | Multiplicity (n) | δ (°) | Source |
|---|---|---|---|---|---|
| CHM | CRL2-CRL1-OSL-CL | 0.160 | 3 | 154.86 | Swissparam |
| | HGA1-CRL1-OSL-CL | -0.152 | 3 | 35.529 | Swissparam |
| ARJ | HAL3-CTL3-CEL1-CRL2 | 0.0500 | 3 | -61.9507 | CHARMM |
| | CTL3-CEL1-CRL2-CRL1 | 0.5000 | 1 | -85.9406 | CHARMM |
| | OCL-CL-CEL1-CRL2 | 0.0000 | 6 | 60.0684 | CHARMM |
| | OCL -CL-CEL1-CRL1 | 0.0000 | 6 | -177.3779 | CHARMM |
| | OCL-CL-OCL-HGA1 | 2.05 | 2 | -0.0293 | CHARMM |
| | CRL1-CEL1-CTL3-HAL3 | 0.0500 | 3 | 152.0083 | CHARMM |
| | CRL1-CEL1-CRL2-CRL2 | 0.9100 | 1 | -45.364 | CHARMM |
| | CRL2-CRL2-CEL1-CTL3 | 0.5000 | 1 | 73.4013 | CHARMM |
| | CRL2-CRL2-CEL1-CL | 0.1800 | 2 | 68.232 | CHARMM |
| | CRL2-CRL2-CEL1-CRL2 | 0.5000 | 1 | -178.9013 | CHARMM |
| | X-CL-OCL-X | 2.05 | 2 | 180.00 | CHARMM |
| | CTL3-CEL1-CRL2-HGA2 | 0.0300 | 3 | -166.5415 | CHARMM |
| | CRL2-CEL1-CRL2-HGA2 | 0.0300 | 3 | -78.872 | CHARMM |
| | CTL3-CEL1-CTL3-HAL3 | 0.0500 | 3 | -171.9531 | CHARMM |
| | CL-CEL1-CRL2-HGA2 | 0.3000 | 3 | -173.6041 | CHARMM |

## Calculation of Intermolecular Interactions from MD trajectories:[1,2]

The weak forces, primarily the short ranged vdW interactions are vital in sustaining the micellar structures. We have calculated the magnitudes of such interaction energies from the instantaneous configurations of the molecular systems as collected from the molecular dynamics trajectories.

**1. van der Waals Interactions:**




**1.1. Dipole-dipole Interaction (Keesom force):** The dipole-dipole interaction potential is given by

$$V(R,\theta,\varphi) = \frac{-\mu_1\mu_2(2cos\theta_1 cos\theta_2 - sin\theta_1 sin\theta_2 cos\varphi)}{4\pi\epsilon_0 R^3}$$

Here $\mu_1$ and $\mu_2$ are the dipole moments of molecule 1 and molecule 2 respectively. The dipole moment of the molecule can be written as $\mu_i = \sum_{i=1}^{N} q_i \vec{r}_i$, where $N$ is the total number of atoms, $q_i$ is the partial charge of atom $i$ and $r_i$ is a vector representing the cartesian coordinates of atom $i$ as $(x_i, y_i, z_i)$. The coordinates of all the atoms present in the cluster is translated to the centre of mass of the respective molecule for calculating the dipole moments. The net dipole moment is given by $\mu = \sqrt{(\mu_x^2 + \mu_y^2 + \mu_z^2)}$.

$R$ is the distance between centre of mass of molecule 1 ($COM_1$) and centre of mass of molecule 2 ($COM_2$). $\theta_1$ is the angle between $\mu_1$ and $R$, similarly $\theta_2$ is the angle between $\mu_2$ and $R$. $\varphi$ is the angle between the planes $(R,\mu_1)$ and $(R,\mu_2)$, $\epsilon_0$ is the absolute dielectric permittivity of vacuum ($8.854 \times 10^{-12}$ $Fm^{-1}$).

**1.2. Dipole-induced dipole Interaction (Debye force):** The dipole-induced dipole interaction energy is given by

$$V(R,\theta) = -\left[\mu_1^2\alpha_2'\left(3cos^2\theta_1 + 1\right) + \mu_2^2\alpha_1'\left(3cos^2\theta_2 + 1\right)\right]/\left(2\left(4\pi\epsilon_0\right)R^6\right)$$

Here definition of $\mu_1$, $\mu_2$, $\theta_1$, $\theta_2$, $\epsilon_0$, and $R$ are the same as those of **section 1.1**. $\alpha_1'$ and $\alpha_2'$ are the polarizability volumes of molecule 1 and molecule 2 respectively, obtained from DFT calculations using CAM-B3LYP functional with 6-311++g(d,p) basis set in the Gaussian 09 platform. The polarizability volume of CHL, CHM, CAM, and ARJ are 45.62, 53.37, 47.06, 50.66 $Å^3$ respectively.

**1.3. Induced dipole-induced dipole Interaction (Dispersion or London force)**: The induced dipole-induced dipole interaction energy is given by

$$V(R) = -\frac{\frac{3}{2}\frac{I_1 I_2}{I_1 + I_2}\alpha_1'\alpha_2'}{R^6}$$

Here $I_1$ and $I_2$ are the first ionization potential of molecule 1 and molecule 2 respectively. The remaining parameters are the same as those of **section 1.1** and **1.2**. The first ionization potentials are obtained from DFT geometry optimization. The values are 7.96, 8.08, 7.99, 7.84 eV respectively for CHL, CHM, CAM, and ARJ.

***Note:*** *The formulae are written for a pair of molecules. The actual calculation involves all pairwise combinations between the molecules present in the cluster. The total energy is normalized with respect to the number of molecules present in the cluster.*

**References:**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