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

Supplementary material

Phenolic compounds alter the ion permeability of phospholipid bilayers via specific lipid interactions

Sheikh I. Hossain[a], Suvash C. Saha[b], Evelyne Deplazes[a,c]

[a] School of Life Sciences, University of Technology Sydney, Ultimo NSW 2007, Australia.

[b] School of Mechanical and Mechatronic Engineering, University of Technology Sydney, Ultimo NSW 2007, Australia.

[c] School of Chemistry and Molecular Biosciences, University of Queensland, St Lucia QLD 4072, Australia.

*Corresponding author: Evelyne Deplazes, e.deplazes@uq.edu.au

Table S1. Octanol-water logP values for phenolic compounds. LogP values were calculated from the free energy of partioning using umbrella sampling simulations.

Phenolic compound	**Calculated logP**	**Reference logP**
Caffeic acid methyl ester (CAME)	2.35 ± 0.02	1.21 [1]
Caffeic acid (CA)	0.98 ± 0.02	1.15 [2, 3]
3,4 dihydroxybenzoic acid (DBHA)	0.50 ± 0.13	0.86 [4]
Chlorogenic acid (CGA)	0.30 ± 0.10	-0.7 [5]
Syringic acid (SGA)	1.05 ± 0.25	1.04 [6]
p-Coumaric acid (pCA)	1.10 ± 0.13	1.46 [7]

Table S2. Area per lipid (APL) calculated from simluations of POPC in the absence (POPC only) and presence of phenolic compounds. APL was averaged over the last 200 ns of a 500-ns simulation. Errors are given as standard deviations.

Compound	**Area per lipid (nm)**
POPC only	0.651 ± 0.007
POPC + Caffeic acid methyl ester (CAME)	0.652 ± 0.006
POPC + Caffeic acid (CA)	0.648 ± 0.007
POPC + 3,4 dihydroxybenzoic acid (DBHA)	0.646 ± 0.006
POPC + Chlorogenic acid (CGA)	0.651 ± 0.007
POPC + Syringic acid (SGA)	0.646 ± 0.006
POPC + p-Coumaric acid (pCA)	0.649 ± 0.006

Table S3. Proximity to membrane surface. A phenolic compound was considered to be bound to the membrane surface if any of its atoms were within 0.2 nm of the POPC phosphate atom. Percentages are calculated for each compound separately, using the last 200 ns of the 500-ns simulation and averaged over the 10 compounds in the system. Errors are given as standard deviations.

Compound	**% simulation time spent bound to the membrane surface**										**Average**
	1	2	3	4	5	6	7	8	9	10	
CAME	100	99.98	95.38	99.84	100	99.74	100	99.92	100	99.98	99.5 ± 1.4
CA	97.48	97.60	98.38	92.24	90.70	85.68	99.40	59.77	97.30	95.32	91.4 ± 11.3
DHBA	94.14	93.78	95.76	99.16	91.66	91.34	94.54	80.04	87.42	93.12	92.1 ± 4.9
CGA	100	100	0	100	3.92	100	100	44.15	100	100	74.8 ± 40
SGA	13.64	7.18	19.16	10.44	11.82	8.28	15.24	15.30	11.28	14.88	12.7 ± 3.4
pCA	44.15	45.95	40.59	35.41	30.45	35.39	30.01	39.33	53.87	41.75	39.7 ± 6.9

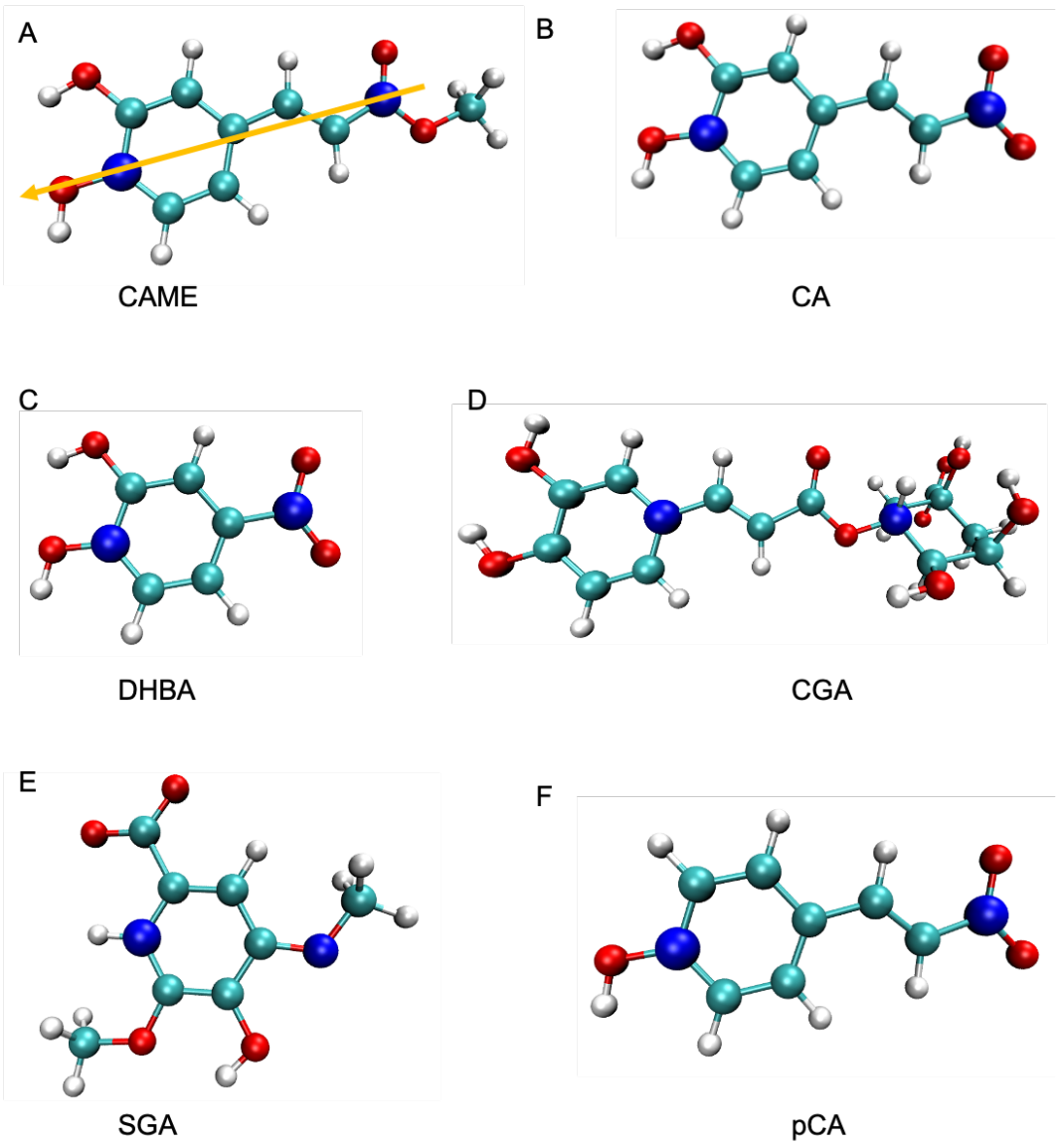

Figure S1. Atoms selected to define the orientation of the phenolic compound with respect to the membrane. The atoms indicated in blue were used to define a vector running along the phenolic compound shown in orange in CAME. These atoms are C5 and C9 for CAME, C5 and C9 for CAME, C5 and C7 for DHBA, C2 and C11 for CGA, C5 and O2 for SGA, and C6 and C9 for pCA. The angle between the vector and the *z*-axis of the simulation system defines the orientation of the phenolic compound on the membrane.

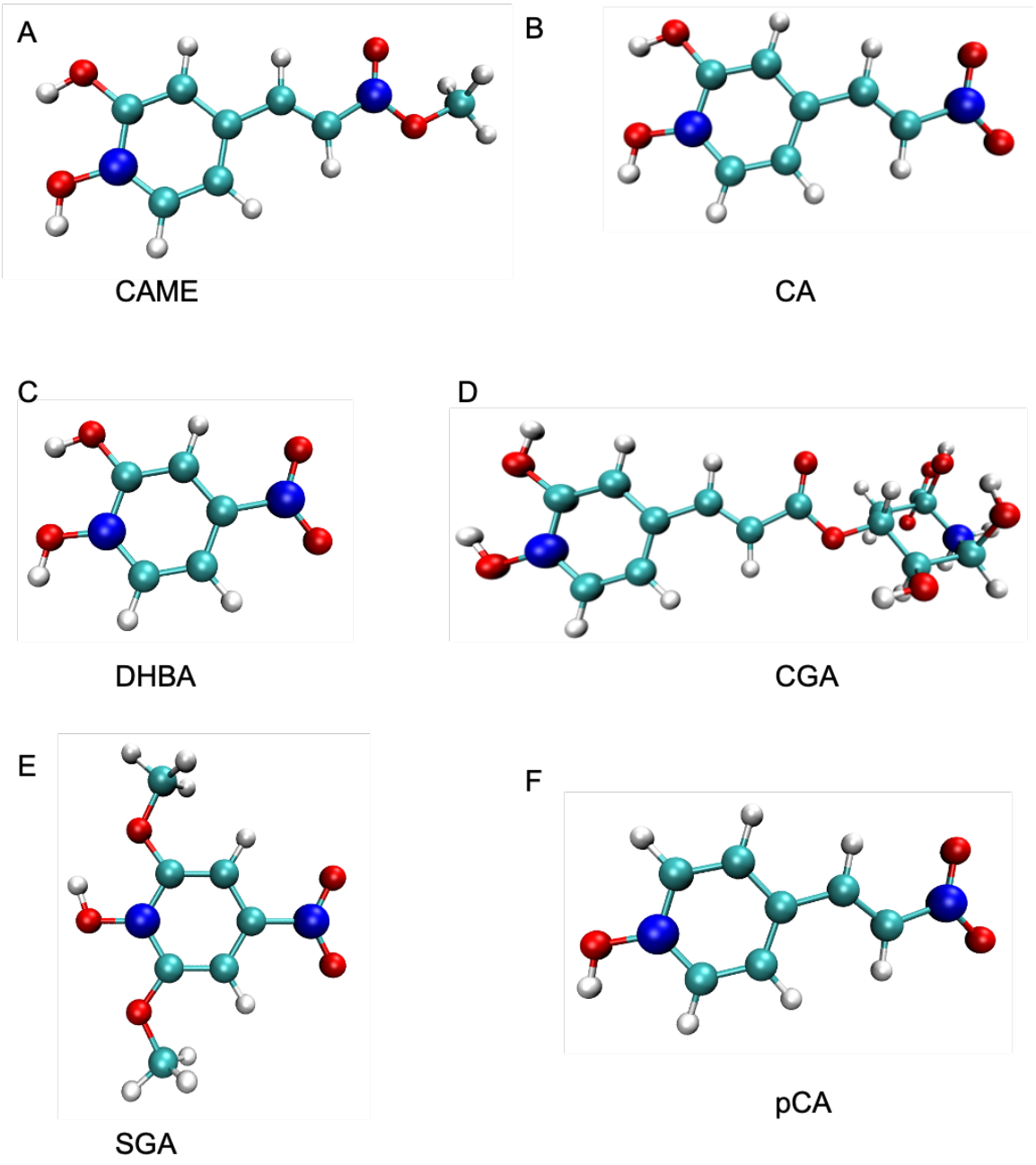

Figure S2. Atoms selected to define the head and tail of the phenolic compounds, used to calculate insertion depth. These atoms are indicated in blue and are C5 and C9 for CAME, C5 and C9 for CA, C5 and C7 for DHBA, C4 and C16 for CGA, C4 and C7 for SGA and C6 and C9 for pCA.

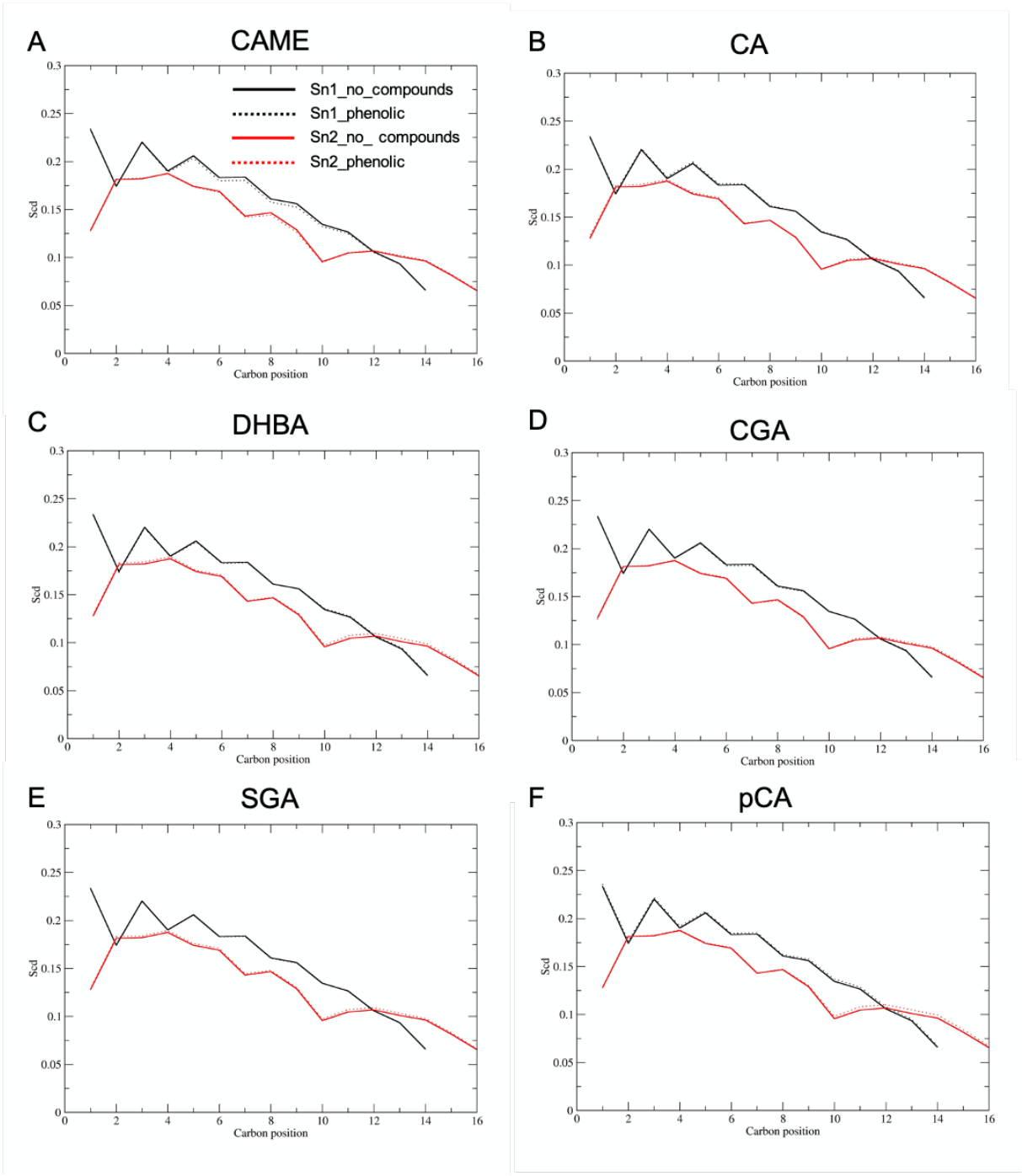

Figure S3. Order parameters of POPC in the absence and presence of phenolic compounds (A) Caffeic acid methyl ester (CAME), (B) caffeic acid (CA), (C) 3,4-Dihydroxybenzoic acid (DHBA), (D) Chlorogenic acid (CGA), (E) Syringic acid (SGA) and (F) p-Coumaric (pCA). Order parameters for the *sn1* and *sn2* chains are shown in black and red, respectively, with solid lines for POPC only and dotted lines for POPC in the presence of the phenolic compounds.

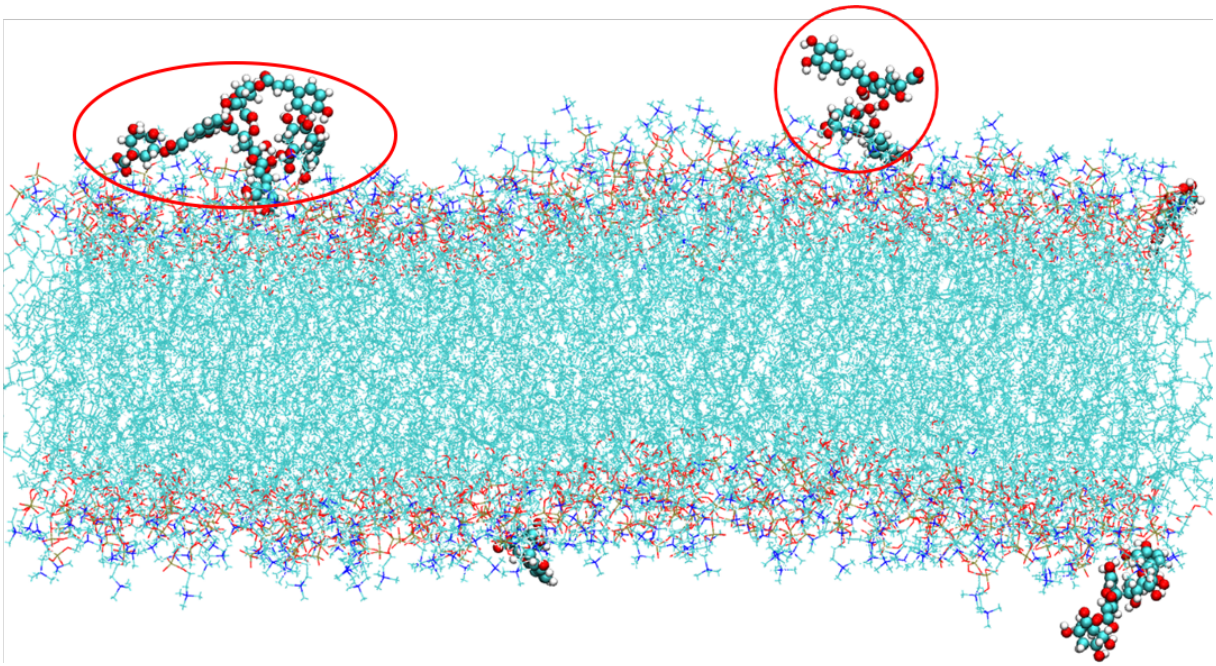

Figure S4. Aggregation of chlorogenic acid molecules on a POPC bilayer surface. CGA aggregates in a way such that one or two molecules are superficially bound to the membrane surface while the other molecules in the cluster remain in the water phase. Water has been removed for clarity.

References

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