

Supplementary Material

I. Atom types and partial charges

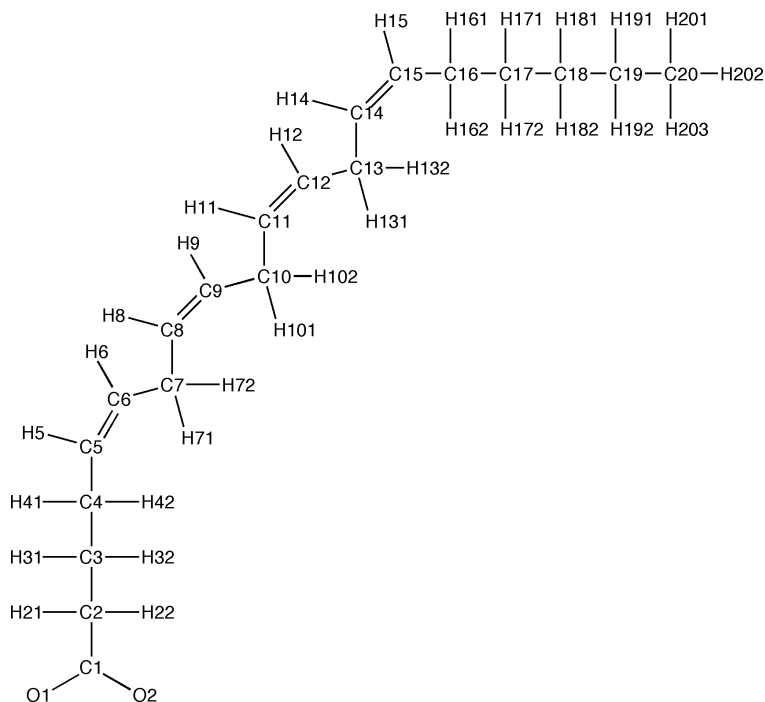


Figure 1. Arachidonate

Atom	Atom Type	Charge	Atom	AtomType	Charge
O1	O2	-0.811171	H11	HA	0.147859
C1	C	0.762308	C12	CE	-0.390927
O2	O2	-0.811171	H12	HA	0.169130
C2	CT	-0.015634	C13	CT	0.123394
H21	HC	-0.015870	H131	HC	0.042885
H22	HC	-0.015870	H132	HC	0.042885
C3	CT	0.089950	C14	CE	-0.112461
H31	HC	-0.015841	H14	HA	0.103696
H32	HC	-0.015841	C15	CE	-0.265169
C4	CT	-0.010998	H15	HA	0.130690
H41	HC	0.008264	C16	CT	-0.038861
H42	HC	0.008264	H161	HC	0.049073
C5	CE	-0.202746	H162	HC	0.049073
H5	HA	0.116380	C17	CT	-0.094888
C6	CE	-0.235123	H171	HC	0.036349
H6	HA	0.128573	H172	HC	0.036349
C7	CT	-0.028435	C18	CT	0.042591
H71	HC	0.077629	H181	HC	0.003300
H72	HC	0.077629	H182	HC	0.003300
C8	CE	-0.085005	C19	CT	0.025082
H8	HA	0.112510	H191	HC	-0.004119
C9	CE	-0.315904	H192	HC	-0.004119
H9	HA	0.136387	C20	CT	-0.089275
C10	CT	0.065034	H201	HC	0.016405
H101	HC	0.046590	H202	HC	0.016405
H102	HC	0.046590	H203	HC	0.016405
C11	CE	-0.151551			

II. Potential function parameters

Additional parameters needed for arachidonate, including the definition of new atom type CE for homoconjugated cis double bonded carbons

Table 1: Parameters for bond terms:

$$E_{\text{bond}} = K_b (R - R_b)^2$$

	K_b	R_b
CE-CE	560.	1.320
CE-HA	367.	1.080
CE-CT	317.	1.510

Table 2: Parameters for bond angle terms:

$$E_{\text{angle}} = K_{\theta} (R - \theta)^2$$

	K_{θ}	θ
CE-CE-HA	35.	113.3
CE-CE-CT	63.	127.0
CE-CT-HC	50.	109.5
CE-CT-CT	70.	109.5
CT-CE-HA	50.	119.7
CE-CT-CE	50.	118.5

Table 3: Parameters for torsion angle terms:

$$E_{\text{tors}} = (PK / \text{IDIVF}) * (1 + \cos (PN * \text{phi} - \text{PHASE}))$$

	IDIVF	PK	PHASE	PN
X-CE-CE-X	4	26.6	180.	2.
X-CE-CT-X	6	0.0	0.	1.
CE-CE-CT-CT	1	0.15	180.	-5.
CE-CE-CT-CT	1	0.30	180.	-4.
CE-CE-CT-CT	1	0.80	180.	-3.
CE-CE-CT-CT	1	0.20	0.	-2.
CE-CE-CT-CT	1	0.80	0.	1.
CE-CE-CT-CE	1	0.08	0.	-4.
CE-CE-CT-CE	1	0.60	180.	-3.
CE-CE-CT-CE	1	0.65	0.	-2.
CE-CE-CT-CE	1	1.10	0.	1.

Table 4: Parameters for improper torsion terms:

$$E_{\text{tors}} = (PK) * (1 + \cos (PN * \text{phi} - \text{PHASE}))$$

	PK	PHASE	PN
X-X-CE-HA	1.1	180.	2.

Table 5: Parameters for nonbonded interaction terms:

	R^*	ϵ
CE	1.9080	0.0860

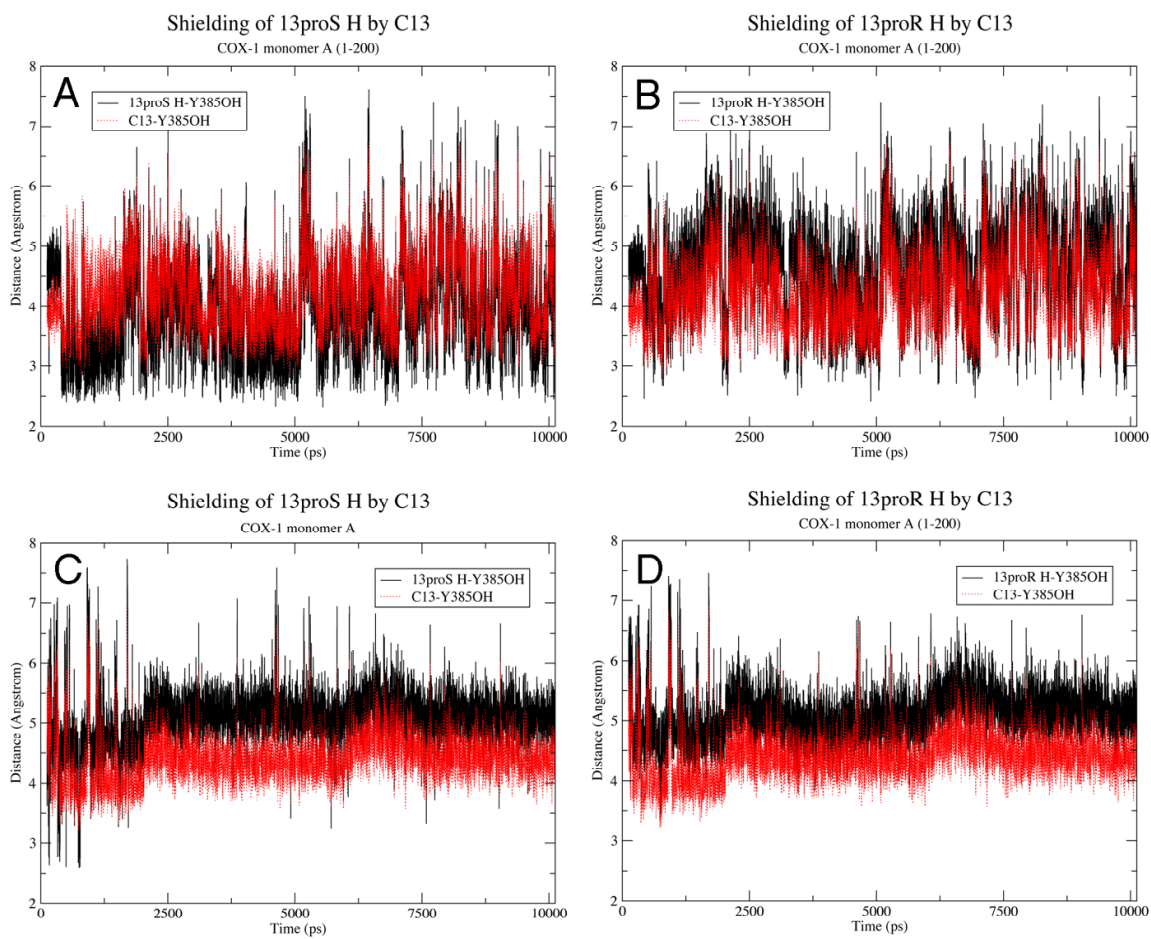


Figure 2. Distances between C13, 13pro-*S* or 13pro-*R* hydrogens and the oxygen atom of Tyr-385 over the COX-1/ACD simulation for monomer A (A, B) and monomer B (C, D). Comparison of all three distances gives an approximate picture of the degree to which C13 shields one or both hydrogens from abstraction. Panels A and B demonstrate that for COX-1 monomer A, the 13pro-*S* hydrogen is consistently more accessible to Tyr-385 (shorter pro-*S*–Tyr-385-O distance) than the 13pro-*R* hydrogen, suggesting a catalytically productive conformation where the 13pro-*S* hydrogen would be preferentially abstracted by Tyr-385. Panels C and D show that for COX-1 monomer B, C13 is nearly always closer to Tyr-385 than either hydrogen, apparently shielding them from abstraction and suggesting a catalytically unproductive conformation.

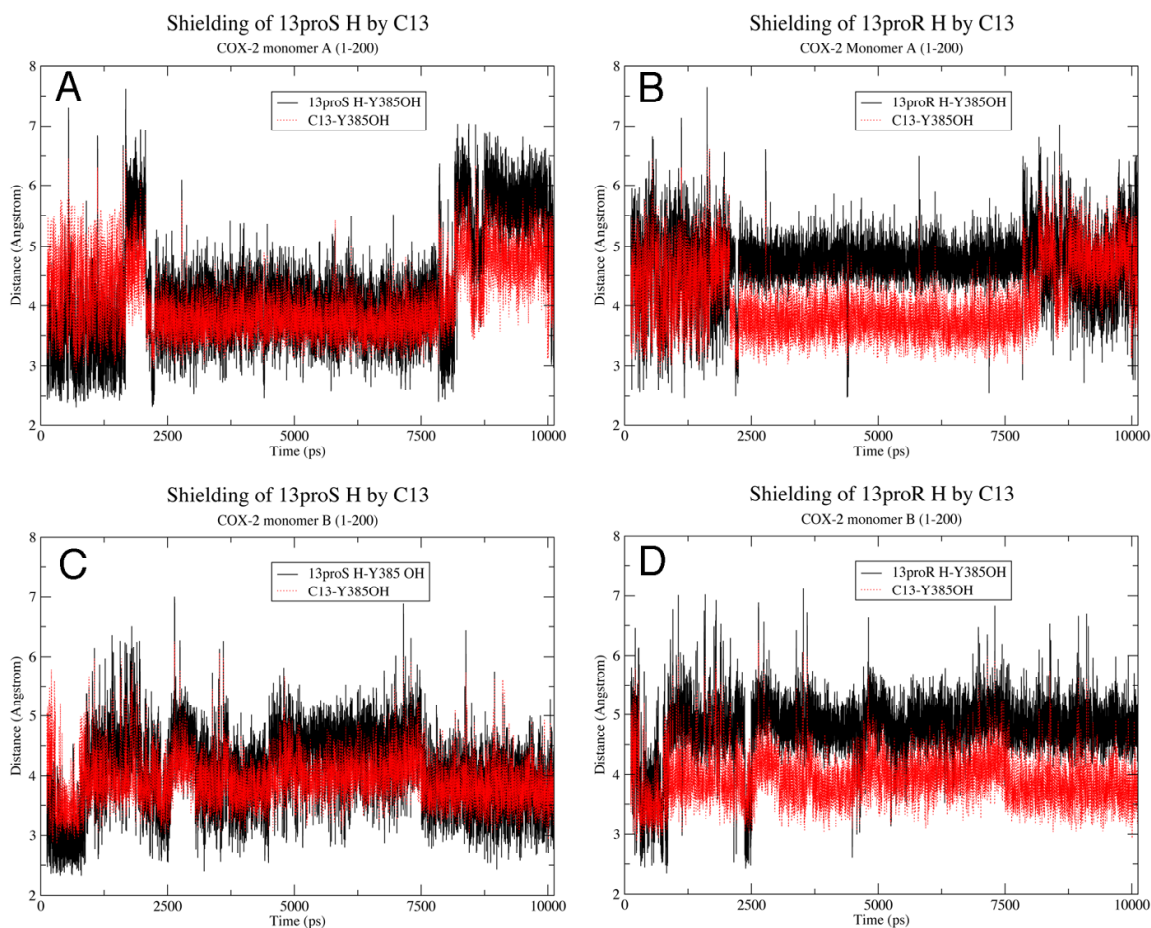


Figure 3. Distances between C13, 13pro-*S* or 13pro-*R* hydrogens and the oxygen atom of Tyr-385 over the COX-2/ACD simulation for monomer A (A, B) and monomer B (C, D). Unlike COX-1 (Figure 2), which demonstrated clear catalytically productive behavior in one monomer (Figure 2A,B), and clear catalytically unproductive behavior the other monomer (Figure 2C,D), COX-2 demonstrates intermediate behavior in both monomers. For both monomers the pro-*S* hydrogen is significantly exposed to Tyr-385 (panels A and C, pro-*S*—Tyr385 O distance shorter than C13—Tyr385 O distance), while the 13pro-*R* hydrogen is nearly always shielded by C13 (panels B and D). However, in the final 2 ns, it appears that the 13pro-*R* hydrogen is preferentially exposed in monomer A (panels A and B).