Supporting Information for:

Does Compound I vary significantly between isoforms of Cytochrome P450?

Richard Lonsdale, Julianna Oláh[1], Adrian J. Mulholland and Jeremy N. Harvey**

Centre for Computational Chemistry, School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, UK.

Corresponding authors: Jeremy.Harvey@bris.ac.uk; Adrian.Mulholland@bris.ac.uk

[1]Present address: Materials Structure and Modeling Research Group of the Hungarian Academy of Sciences, Budapest University of Technology and Economics, P.O. Box 91, 1521 Budapest, Hungary

Contents

Full reference for ref. 48:

MacKerell, A. D.; Bashford, D.; Bellott, M.; Dunbrack, R. L.; Evanseck, J. D.; Field, M. J.; Fischer, S.; Gao, J.; Guo, H.; Ha, S.; Joseph-McCarthy, D.; Kuchnir, L.; Kuczera, K.; Lau, F. T. K.; Mattos, C.; Michnick, S.; Ngo, T.; Nguyen, D. T.; Prodhom, B.; Reiher, W. E.; Roux, B.; Schlenkrich, M.; Smith, J. C.; Stote, R.; Straub, J.; Watanabe, M.; Wiorkiewicz-Kuczera, J.; Yin, D.; Karplus, M. *J. Phys. Chem. B* **1998**, *102*, 3586.

Part A - Details of molecular dynamics simulations.

Hydrogen atoms were added to the crystal structures used, according to standard pK_a values, using the HBUILD module of the CHARMM program, version 30b2,[1] and their positions then optimized. The CHARMM27 force field was used throughout.[2] Previous calculations on $P450_{cam}$ have revealed the necessity to protonate the residue Asp297 at the OD2 oxygen.[3] This proton forms a hydrogen bond with the O2A atom of a haem propionate, the absence of which results in structures that are inconsistent with experiment after MD simulation. Hence in this work, models of $P450_{cam}$ were used in which the O2D oxygen of Asp297 was protonated. Histidine tautomers were assigned based on their local hydrogen-bonding environment. Each system was then truncated to a sphere of 25 Å centred on the haem iron. Charged residues (Arg, Asp, Lys, Glu) located 20 Å or further from the centre of each system were neutralized for MD simulation in order to avoid any unrealistic effects due to protein truncation and insufficient screening of charges by the solvent.

Unlike propene, no topology or force field parameters exist for warfarin and dextromethorphan in the standard CHARMM force field. The same parameters for dextromethorphan were used here as in previous work, and are shown below.[4] Charges were based on electrostatic potential (ESP) charges obtained from gas-phase QM calculations of warfarin at the B3LYP/LACVP** level of theory. Angle and bond parameters were derived from these QM calculations together with chemically similar bonds and angles available in the CHARMM force field. The topology and parameters for warfarin and dextromethorphan are detailed below. Modified haem parameters were used to model Compound I, as used in previous work, these are shown below.[5]

The systems were each solvated in a 25 Å sphere of pre-equilibrated water molecules, represented by the TIP3P model.[6] All overlapping water molecules, i.e. those whose oxygen atom was 2.6 Å or closer to existing heavy atoms were deleted. The positions of the added water molecules were then optimized using 1000 steps of steepest descent (SD) followed by 500 steps of conjugate gradient (CG) minimization. A 13 Å cut-off for non-bonded interactions was used in all molecular mechanics energy minimizations and MD simulations. Further minimizations were carried out on both the added and crystallographic water molecules using 600 steps of SD and 1500 steps using the Adopted Basis Newton-Raphson (ABNR) algorithm. The water was

then heated from 0 to 300 K over 1 ps and then equilibrated for 25 ps in stochastic boundary molecular dynamics (SBMD) simulations where water molecules within 20 Å of the haem iron were treated with full Newtonian dynamics and the remainder treated with Langevin dynamics. The water atoms were kept within 25 Å of the haem iron by the application of a deformable boundary potential. Each whole system was then minimized and equilibrated for 100 ps using SBMD. Friction coefficients used in the Langevin dynamics were 62 ps^{-1} for water oxygen atoms and 250 ps^{-1} for protein heavy atoms. Protein atoms more than 20 Å from the haem iron were harmonically restrained to their initial positions with force constants increasing with distance from the centre of the system. The energy of each system was then minimized with 500 steps of SD and 1750 steps of ABNR. These optimized geometries were then used as starting points for 5 ns SBMD simulations following the same protocol as above. A time step of 1 fs was used, which was chosen to be small compared to the highest frequency motion, the C–H bond, which occurs on the 10 fs timescale. The SHAKE algorithm was used to constrain the bonds to hydrogen atoms and reduce the computational expense.[7]

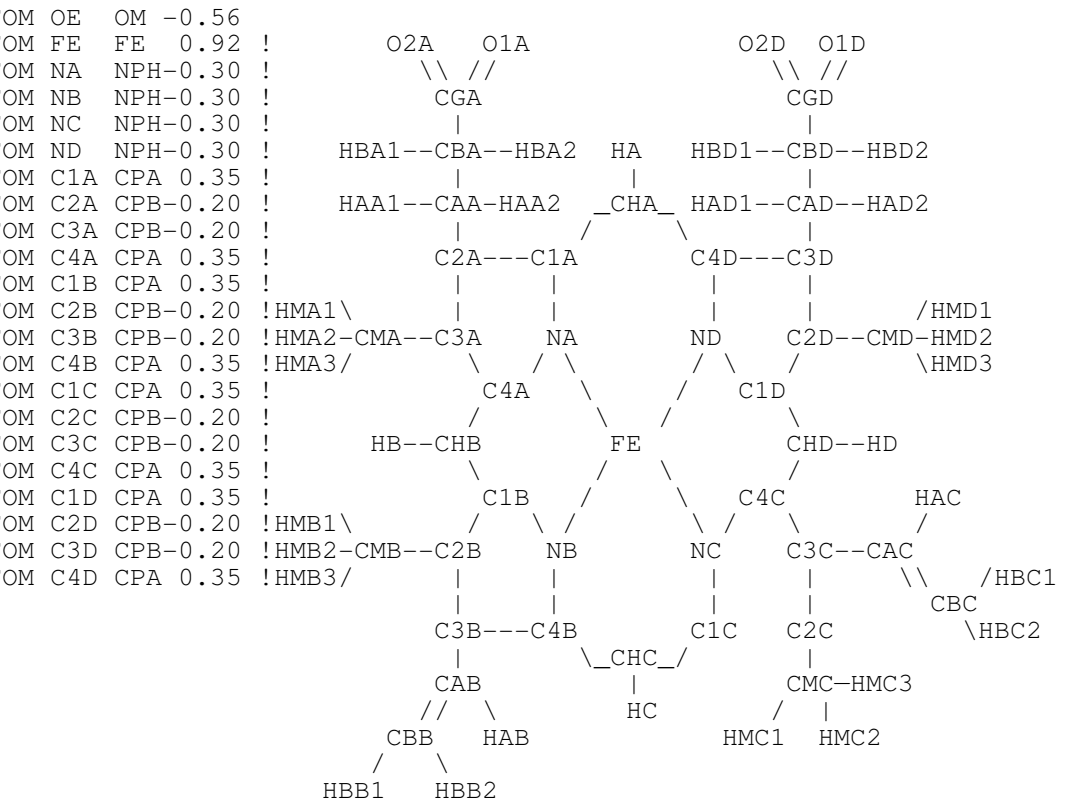
Modified heme MM parameters for Compound I:

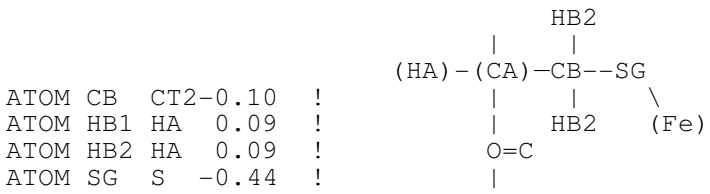
The heme group parameters contained in the CHARMM27 force field do not contain any axial ligands to the iron center. These parameters were modified to include an oxygen atom and a thiolate ligand, to represent the Compound I species in cytochrome P450. The atomic charges on the α-, β- and *meso*-carbons, as well as on the pyrrole nitrogens were adjusted to account for the different charge distribution in Compound I, as detailed previously (Bathelt et al., *J. Am. Chem. Soc*., **2005**, *127*, 12900).

Additional bond and angle parameters were derived from the QM optimized Compound I model and from analogy to chemically similar bond lengths and angles available in the CHARMM27 force field.

atom name type charge

GROUP
ATOM OE OM -0.56
ATOM FE FE 0.92 !
ATOM NA NPH-0.30 !
ATOM NB NPH-0.30 !
ATOM NC NPH-0.30 !
ATOM ND NPH-0.30 !
ATOM C1A CPA 0.35 !
ATOM C2A CPB-0.20 !
ATOM C3A CPB-0.20 !
ATOM C4A CPA 0.35 !
ATOM C1B CPA 0.35 !
ATOM C2B CPB-0.20 !
ATOM C3B CPB-0.20 !
ATOM C4B CPA 0.35 !
ATOM C1C CPA 0.35 !
ATOM C2C CPB-0.20 !
ATOM C3C CPB-0.20 !
ATOM C4C CPA 0.35 !
ATOM C1D CPA 0.35 !
ATOM C2D CPB-0.20 !
ATOM C3D CPB-0.20 !
ATOM C4D CPA 0.35 !





ATOM CB CT2-0.10 !
ATOM HB1 HA 0.09 !
ATOM HB2 HA 0.09 !
ATOM SG S -0.44 !

bonds: k_B b_0

OM FE 350.000 1.6300

b_0 from QM calculation;
k_B increased from value in the original CHARMM set to account for higher bond order of oxygen in Compound I

angles: k_θ θ_0

FE S CT2 38.8 113.0

θ_0 from QM calculation;
k_θ from HS S CT2 parameters

OM FE NPH 50.0 90.0

θ_0 from original CHARMM parameter set
k_θ increased to account for tighter binding of oxygen in Compound I compared to O2 ligand

S FE NPH 5.000 90.0000

from original OM-FE-NPH CHARMM parameters

MM parameters for warfarin:

```
RESI WARF  0.000
GROUP
ATOM C1 C  0.603 !
ATOM C2 CA -0.382 !
ATOM C3 CA  0.001 !
ATOM C4 CA -0.228 !
ATOM C5 CA -0.021 !
ATOM C6 CA -0.337 !
ATOM C8 C  0.597 !
ATOM C10 CA -0.636 !
ATOM C12 C  0.911 !
ATOM O1 OS -0.573 !
ATOM O2 OH1 -0.666 !
ATOM O3 O -0.559 !
ATOM C14 CT1  0.350 !
ATOM C16 CT2 -0.390 !
ATOM C18 C  0.658 !
ATOM C7 CT3 -0.427 !
ATOM O4 O -0.540 !
ATOM C9 CA -0.146 !
ATOM C11 CA -0.144 !
ATOM C13 CA -0.225 !
ATOM C15 CA  0.083 !
ATOM C17 CA -0.144 !
ATOM C19 CA -0.117 !
ATOM H1 HP  0.083 !
ATOM H2 HP  0.153 !
ATOM H3 HP  0.130 !
ATOM H4 HP  0.190 !
ATOM H8 H   0.489 !
ATOM H10 HA  0.123
ATOM H12 HA  0.123
ATOM H14 HA  0.123
ATOM H5 HB  0.110
ATOM H6 HB  0.110
ATOM H7 HB  0.090
ATOM H9 HP  0.117
ATOM H11 HP  0.110
ATOM H13 HP  0.150
ATOM H15 HP  0.115
ATOM H16 HP  0.116
BOND C1 C2
BOND C1 C6
BOND C1 O1
BOND C2 C3
BOND C2 C8
BOND C3 C4
BOND C3 H1
BOND C4 C5
BOND C4 H2
BOND C5 C6
BOND C5 H3
BOND C6 H4
BOND C8 C10
BOND C8 O2
BOND C10 C12
BOND C10 C14
BOND C12 O1
BOND C12 O3
BOND O2 H8
BOND C14 C16
BOND C14 H7
BOND C14 C15
BOND C16 C18
BOND C16 H5
BOND C16 H6
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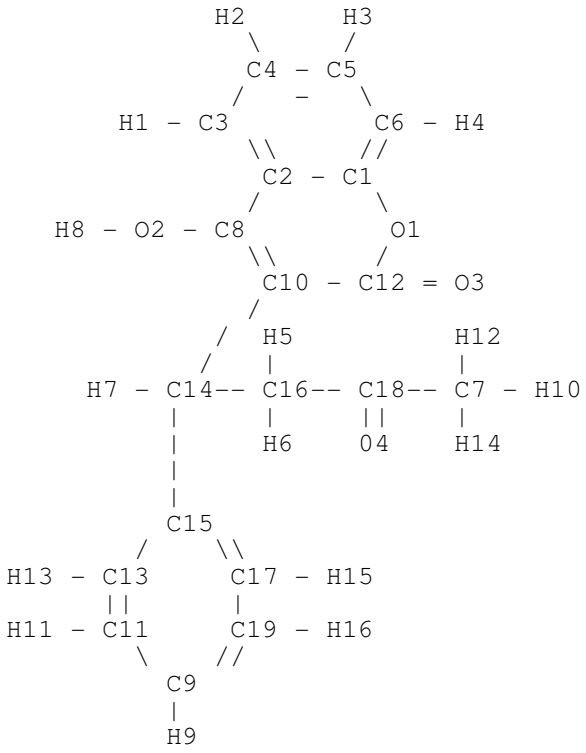

```
BOND C18 C7
BOND C18 O4
BOND C7 H10
BOND C7 H12
BOND C7 H14
BOND C9 C11
BOND C9 C19
BOND C9 H9
BOND C11 C13
BOND C11 H11
BOND C13 C15
BOND C13 H13
BOND C15 C17
BOND C17 C19
BOND C17 H15
BOND C19 H16
IMPH C6 C1 C2 C3
IMPH C2 C1 C6 C5
IMPH C1 C2 C3 C4
IMPH C2 C3 C4 C5
IMPH C3 C4 C5 C6
IMPH C4 C5 C6 C1
IMPH C19 C9 C11 C13
IMPH C11 C9 C19 C17
IMPH C9 C11 C13 C15
IMPH C11 C13 C15 C17
IMPH C13 C15 C17 C19
IMPH C15 C17 C19 C9
IMPH C1 C2 C6 O1
IMPH C2 C1 C3 C8
IMPH C3 C2 C4 H1
IMPH C4 C3 C5 H2
IMPH C5 C4 C6 H3
IMPH C6 C1 C5 H4
IMPH C8 C2 O2 C10
IMPH C10 C12 C14 C8
IMPH C12 C10 O1 O3
IMPH C18 C7 O4 C16
IMPH C9 C11 C19 H9
IMPH C11 C9 C13 H11
IMPH C13 C11 C15 H13
IMPH C15 C13 C17 C14
IMPH C17 C15 C19 H15
IMPH C19 C9 C17 H16
IC C6 C1  C2 C3   1.40 121.85  -0.36 117.92   1.41
IC O1 C1  C2 C3   1.38 120.83 179.34 117.92   1.41
IC C6 C1  C2 C8   1.40 121.85 179.37 117.13   1.45
IC C2 C6 *C1 O1   1.41 121.85 -179.71 117.32   1.38
IC C1 C3 *C2 C8   1.41 117.92 -179.70 124.95   1.45
IC C1 C2  C3 C4   1.41 117.92   0.37 120.72   1.39
IC C8 C2  C3 C4   1.45 124.95 -179.34 120.72   1.39
IC C1 C2  C3 H1   1.41 117.92 -179.23 120.94   1.09
IC C2 C4 *C3 H1   1.41 120.72 179.61 118.34   1.09
IC C2 C3  C4 C5   1.41 120.72  -0.12 120.11   1.41
IC H1 C3  C4 C5   1.09 118.34 179.49 120.11   1.41
IC C2 C3  C4 H2   1.41 120.72 -179.96 119.86   1.08
IC C3 C5 *C4 H2   1.39 120.11 179.84 120.03   1.08
IC C3 C4  C5 C6   1.39 120.11  -0.15 120.29   1.39
IC H2 C4  C5 C6   1.08 120.03 179.69 120.29   1.39
IC C3 C4  C5 H3   1.39 120.11 -179.97 119.94   1.08
IC C4 C6 *C5 H3   1.41 120.29 179.82 119.77   1.08
IC C4 C5  C6 C1   1.41 120.29   0.16 119.11   1.40
IC H3 C5  C6 C1   1.08 119.77 179.98 119.11   1.40
IC C4 C5  C6 H4   1.41 120.29 -179.70 122.19   1.08
IC C1 C5 *C6 H4   1.40 119.11 -179.86 122.19   1.08
IC C5 C6  C1 C2   1.39 119.11   0.10 121.85   1.41
IC H4 C6  C1 C2   1.08 118.70 179.97 121.85   1.41
IC C5 C6  C1 O1   1.39 119.11 -179.61 117.32   1.38
IC C1 C2  C8 C10   1.41 117.13   0.65 122.76   1.37
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IC C3 C2  C8 C10   1.41 124.95 -179.64 122.76   1.37
IC C1 C2  C8 O2   1.41 117.13 -179.41 119.99   1.38
IC C2 C10 *C8 O2   1.45 122.76 -179.94 117.25   1.38
IC C2 C8  C10 C12   1.45 122.76   1.45 119.43   1.45
IC O2 C8  C10 C12   1.38 117.25 -178.50 119.43   1.45
IC C2 C8  C10 C14   1.45 122.76 179.42 120.29   1.53
IC C8 C12 *C10 C14   1.37 119.43 -177.98 120.25   1.53
IC C8 C10  C12 O1   1.37 119.43  -3.18 117.15   1.43
IC C14 C10  C12 O1   1.53 120.25 178.85 117.15   1.43
IC C8 C10  C12 O3   1.37 119.43 177.26 127.29   1.23
IC C10 O1 *C12 O3   1.45 117.15 179.62 115.56   1.23
IC C10 C12  O1 C1   1.45 117.15   2.99 122.62   1.38
IC O3 C12  O1 C1   1.23 115.56 -177.39 122.62   1.38
IC C12 O1  C1 C2   1.43 122.62  -0.94 120.83   1.41
IC C12 O1  C1 C6   1.43 122.62 178.78 117.32   1.40
IC C8 C10  C14 C16   1.37 120.29 138.16 113.48   1.55
IC C12 C10  C14 C16   1.45 120.25 -43.88 113.48   1.55
IC C8 C10  C14 H7   1.37 120.29  22.25 106.13   1.09
IC C8 C10  C14 C15   1.37 120.29 -93.41 111.87   1.54
IC C10 C14  C16 C18   1.53 113.48 -157.22 112.40   1.52
IC H7 C14  C16 C18   1.09 105.92 -41.18 112.40   1.52
IC C15 C14  C16 C18   1.54 112.37  74.61 112.40   1.52
IC C10 C14  C16 H5   1.53 113.48  78.28 111.70   1.09
IC C10 C14  C16 H6   1.53 113.48 -38.34 109.85   1.10
IC C14 C16  C18 C7   1.55 112.40 -160.12 116.56   1.51
IC H5 C16  C18 C7   1.09 110.23 -34.81 116.56   1.51
IC H6 C16  C18 C7   1.10 106.89  79.28 116.56   1.51
IC C14 C16  C18 O4   1.55 112.40  20.35 122.10   1.24
IC C16 C7 *C18 O4   1.52 116.56 179.53 121.34   1.24
IC C16 C18  C7 H10   1.52 116.56 -167.49 110.12   1.09
IC O4 C18  C7 H10   1.24 121.34  12.04 110.12   1.09
IC C16 C18  C7 H12   1.52 116.56 -45.31 111.25   1.10
IC C16 C18  C7 H14   1.52 116.56  72.84 109.41   1.10
IC C10 C14  C15 C13   1.53 111.87 114.37 119.46   1.40
IC C16 C14  C15 C13   1.55 112.37 -116.61 119.46   1.40
IC H7 C14  C15 C13   1.09 106.41  -1.12 119.46   1.40
IC C10 C14  C15 C17   1.53 111.87 -65.43 121.83   1.41
IC C14 C13 *C15 C17   1.54 119.46 179.81 118.70   1.41
IC C14 C15  C13 C11   1.54 119.46 -179.71 120.79   1.40
IC C17 C15  C13 C11   1.41 118.70   0.10 120.79   1.40
IC C14 C15  C13 H13   1.54 119.46   0.91 119.11   1.09
IC C11 C15 *C13 H13   1.40 120.79 -179.38 119.11   1.09
IC C15 C13  C11 C9   1.40 120.79   0.05 120.16   1.40
IC H13 C13  C11 C9   1.09 120.10 179.43 120.16   1.40
IC C15 C13  C11 H11   1.40 120.79 -179.85 119.69   1.09
IC C9 C13 *C11 H11   1.40 120.16 -179.90 119.69   1.09
IC C13 C11  C9 C19   1.40 120.16  -0.13 119.50   1.40
IC H11 C11  C9 C19   1.09 120.16 179.77 119.50   1.40
IC C13 C11  C9 H9   1.40 120.16 179.90 120.26   1.09
IC C11 C19 *C9 H9   1.40 119.50 179.97 120.24   1.09
IC C11 C9  C19 C17   1.40 119.50   0.05 120.39   1.40
IC H9 C9  C19 C17   1.09 120.24 -179.97 120.39   1.40
IC C11 C9  C19 H16   1.40 119.50 -179.96 119.97   1.09
IC C9 C17 *C19 H16   1.40 120.39 -179.99 119.64   1.09
IC C9 C19  C17 C15   1.40 120.39   0.10 120.47   1.41
IC H16 C19  C17 C15   1.09 119.64 -179.89 120.47   1.41
IC C9 C19  C17 H15   1.40 120.39 179.67 119.77   1.09
IC C15 C19 *C17 H15   1.41 120.47 179.57 119.77   1.09
IC C19 C17  C15 C14   1.40 120.47 179.63 121.83   1.54
IC H15 C17  C15 C14   1.09 119.76   0.06 121.83   1.54
IC C19 C17  C15 C13   1.40 120.47  -0.18 118.70   1.40
IC C2 C8  O2 H8   1.45 119.99   3.06 113.37   0.97
IC C10 C8  O2 H8   1.37 117.25 -176.99 113.37   0.97

BONDS
!
!V(bond) = Kb(b - b0)**2
!
!Kb: kcal/mole/A**2
```

```
!b0: A
!
!atom type Kb          b0
C   CA     450.000     1.398 ! b0 from Jag. Kb from CPB C
C   OS     340.000     1.381 ! b0 from Jag. Kb from OS CT3
C  OH1     340.000     1.380 ! b0 from Jag. Kb from OS CT3
CA  OS     340.000     1.381 ! b0 from Jag. Kb from OS CT3
CA   O     340.000     1.235 ! b0 from Jag. Kb from OS CT3

ANGLES
!
!V(angle) = Ktheta(Theta - Theta0)**2
!
!Ktheta: kcal/mole/rad**2
!Theta0: degrees
!
!atom types     Ktheta    Theta0
CA    C   CA      40.0      122.3         ! ALL ANGLES FROM JAGUAR
CA    C   OS      55.0      118.4
C    CA   CA      40.0      122.2
C    CA    C      40.0      119.5
C    CA   HP      30.0      118.7
CA    C  OH1      55.0      118.5
C    CA  CT1      45.8      120.3
CA    C    O      80.0      127.3
OS    C    O      90.0      115.6
C    OS    C      40.0      122.6
C   OH1    H      55.0      113.3
CA  CT1   CA      45.8      111.9
CA  CT1  CT2      51.8      113.5
CA  CT1   HB      50.0      106.1
CT1 CT2    C      52.0      112,4
CT1 CT2   HB      50.0      110.8
CT2   C  CT3      40.0      116.6
CA   CA   OS      55.0      118.0
CA   OS   CA      40.0      122.3
OS   CA    C      55.0      116.8
OS   CA    O      50.0      116.6
C    CA    O      40.0      126.6
CA    C  CT1      45.8      122.3
CA   CA    O      40.0      114.5
C   CT1   CA      52.0      113.6
CA    O    C      40.0      118.2
O     C  OH1      50.0      105.4
OH1   C  CT3      55.0      112.0
CT2   C  OH1      55.0      106.9


DIHEDRALS
!
!V(dihedral) = Kchi(1 + cos(n(chi) - delta))
!
!Kchi: kcal/mole
!n: multiplicity
!delta: degrees
!
!atom types             Kchi    n   delta
C   CA   CA   HP        4.2     1   180.00   !  from HP CA CA CA
CA   C   CA   HP        4.2     1   180.00   !  from HP CA CA CA
CA   C  OH1    H        0.99    1   180.00   !  from H OH1 CA CA
OS   C   CA   HP        0.00    1     0.00   !  from O  C CT1 HB
CT2  C  CT3   HA        0.04    3     0.00   !  from HA CT3 CT2 CA
CT3  C  CT2   HB        0.00    1     0.00   !  from HB CT2 C CT3
C   CA   CA   CA        3.10    2   180.00   !  from CA CA CA CA
C   CA    C   CA        3.10    2   180.00   !  from CA CA CA CA
C   CA    C  OH1        3.10    2   180.00   !  from CA CA CA OH1
C   OS    C   CA        3.10    2   180.00   !  from CA CA CA CA
C   OS    C    O        3.10    2   180.00   !  from CA CA CA OC
CA   C   CA   CA        3.10    2   180.00   !  from CA CA CA CA
```

```
CA   C   CA  CT1        3.10    2   180.00   !  from CA CA CA CA
CA  CA    C   OS        3.10    2   180.00   !  from CA CA CA OH1
CA  CA    C  OH1        3.10    2   180.00   !  from CA CA CA OH1
C   CA    C   OS        3.10    2   180.00   !  from CA CA CA OH1
C   CA    C    O        3.10    2   180.00   !  from CA CA CA OH1
OS   C   CA  CT1        3.10    2   180.00   !  from CA CA CA OH1
OH1  C   CA  CT1        3.10    2   180.00   !  from CA CA CA OH1
O    C   CA  CT1        3.10    2   180.00   !  from CA CA CA OH1
CT1 CT2   C  CT3        3.10    2   180.00   !  from CA CA CA CA
CT1 CT2   C    O        3.10    2   180.00   !  from CA CA CA OH1
OS  CA   CA   HP        4.20    2   180.00   !  from OC CA CA HP
CA   C  CT1   HB        0.04    3     0.00   !  from CA CT1 CT2 HA
O    C  OH1    H        2.50    2   180.00   !  from O C NH1 H
CT2  C  OH1    H        1.30    1     0.00   !  from H OH1 CT2 CT2
HB  CT2   C  OH1        4.20    2   180.00   !  from OH1 CA CA HP
OH1  C  CT3   HA        4.20    2   180.00   !  from OH1 CA CA HP
H   OH1   C  CT3        1.33    1     0.00   !  from H OH1 CT1 CT3
CA  CA   OS   CA        3.10    2   180.00   !  from CA CA CA CA
CA  CA    C  CT1        0.20    1     0.00   !  from CT1 CT2 CPH1
CPH1
CA  CA    O    C        0.23    2   180.00   !  from CT3 CT2 CA CA
CA  CA   CA    O        3.10    2   180.00   !  from CT2 CA CA CA
CA  OS   CA    C        2.05    2   180.00   !  from X CD OS X
CA  OS   CA    O        2.05    2   180.00   !  from X CD OS X
OS  CA   CA   CA        3.10    2   180.00   !  from CT2 CA CA CA
OS  CA    C   CA        3.10    2   180.00   !  from OC CA CA CA
OS  CA    C  CT1        0.40    1   180.00   !  from O C CP1 CP2
CA   C   CA    O        1.40    1     0.00   !  from O C CT1 CT2
CA   C  CT1  CT2        0.23    2   180.00   !  from CT1 CT2 CA CA
CA   C  CT1   CA        0.23    2   180.00   !  from CT1 CT2 CA CA
CA   O    C  CT2        3.10    2   180.00   !  from X CD OS X
CA   O    C  OH1        3.10    2   180.00   !  from X CD OS X
CA   O    C  CT3        3.10    2   180.00   !  from X CD OS X
O   CA    C  CT1        1.40    1     0.00   !  from O C CT1 CT2
CT1 CT2   C  OH1        1.40    1     0.00   !  from O C CT1 CT2
C   CA    O    C        3.10    2   180.00   !  from X CD OS X

IMPROPER
!
!V(improper) = Kpsi(psi - psi0)**2
!
!Kpsi: kcal/mole/rad**2
!psi0: degrees
!note that the second column of numbers (0) is ignored
!
!atom types           Kpsi                   psi0
CA  CA  CA  HP        20.000    0    0.000   ! from HA CPB C C (heme)
CA  C   CA  HP        20.000    0    0.000   ! from HA CPB C C (heme)
CA  C   CA  CA        96.000    0    0.000   ! from CC X X CT1
C   CA  CA  CA        96.000    0    0.000   ! from CC X X CT1
CA  CA  CA  CA        96.000    0    0.000   ! from CC X X CT1
C   CA  CA  OS        96.000    0    0.000   ! from CC X X CT1
CA  C   CA  C         96.000    0    0.000   ! from CC X X CT1
C   CA  OH1 CA        96.000    0    0.000   ! from CC X X CT1
CA  C   CT1 C         96.000    0    0.000   ! from CC X X CT1
C   CT3 O   CT2       96.000    0    0.000   ! from CC X X CT1
CA  CA  CA  CT1       96.000    0    0.000   ! from CC X X CT1
CA  CA  CA  OS        96.000    0    0.000   ! from CC X X CT1
CA  OS  C   O        120.000    0    0.000   ! from O X X C
C   CA  CA  CT1       96.000    0    0.000   ! from CC X X CT1
CA  C   CA  O        120.000    0    0.000   ! from O X X C
```

MM parameters for dextrometorphan:

```
Non standard atom types:

MASS   210 OCE   15.99900 O ! aromatic ether oxygen
MASS   211 NT    14.00700 N ! protonated tertiary amine nitrogen
```

```
MASS   212 CT0   12.01100 C ! aliphatic sp3 C bonded to 4 carbon
atoms,
MASS   213 N3    14.00700 N ! tertiary amine nitrogen


RESI  DEX          +1.000 ! protonated dextromethorphan
GROUP
ATOM   C1  CT2     -0.180
ATOM   C2  CT0      0.000
ATOM   C3  CT1     -0.090
ATOM   C4  CT2     -0.180
ATOM   C5  CT2     -0.180
ATOM   C6  CT2     -0.180
ATOM   C7  CT1      0.120
ATOM   C8  CT2     -0.180
ATOM   C9   CA      0.000
ATOM  C10   CA      0.000
ATOM  C11   CA     -0.110
ATOM  C12   CA     -0.110
ATOM  C13   CA      0.170
ATOM  C14   CA     -0.110
ATOM  N15  NT       0.050
ATOM  C16  CT2      0.030
ATOM  C17  CT2     -0.180
ATOM  O18  OCE     -0.340
ATOM  C19  CT3     -0.100
ATOM  C20  CT3     -0.060
ATOM  H21   HA      0.090
ATOM  H22   HA      0.090
ATOM  H23   HA      0.090
ATOM  H24   HP      0.110
ATOM  H25   HA      0.090
ATOM  H26   HA      0.090
ATOM  H27   HA      0.090
ATOM  H28   HA      0.090
ATOM  H29   HA      0.090
ATOM  H30   HA      0.090
ATOM  H31   HA      0.090
ATOM  H32   HA      0.090
ATOM  H33   HA      0.090
ATOM  H34   HA      0.090
ATOM  H35   HA      0.090
ATOM  H36   HP      0.110
ATOM  H37   HP      0.110
ATOM  H38   HA      0.090
ATOM  H39   HA      0.090
ATOM  H40   HA      0.090
ATOM  H41   HA      0.090
ATOM  H42   HA      0.090
ATOM  H43   HA      0.090
ATOM  H44   HA      0.090
ATOM  H45   HA      0.090
ATOM  H46   HC      0.320
BOND   C1   C2    C1   C6    C1  H44    C1  H45
BOND   C2   C3    C2  C10    C2  C17    C3   C4
BOND   C3   C7    C3  H25    C4   C5    C4  H38
BOND   C4  H39    C5   C6    C5  H40    C5  H41
BOND   C6  H42    C6  H43    C7   C8    C7  N15
```

```
BOND   C7  H26    C8   C9    C8  H34    C8  H35
BOND   C9  C10    C9  C11   C10  C14   C11  C12
BOND  C11  H36   C12  C13   C12  H37   C13  C14
BOND  C13  O18   C14  H24   N15  C16   N15  C20
BOND  N15  H46   C16  C17   C16  H30   C16  H31
BOND  C17  H32   C17  H33   O18  C19   C19  H21
BOND  C19  H22   C19  H23   C20  H27   C20  H28
BOND  C20  H29
IMPR   C9   C10  C11  C8
IMPR   C10  C9   C14  C2
IMPR   C14  C10  C13  H24
IMPR   C13  O18  C12  C14
IMPR   C12  C13  C11  H37
IMPR   C11  C12  C9   H36
PATCHING FIRS NONE LAST NONE

RESI  DEP         +0.000 ! non-protonated dextromethorphan
GROUP
ATOM   C1  CT2     -0.180
ATOM   C2  CT0      0.000
ATOM   C3  CT1     -0.090
ATOM   C4  CT2     -0.180
ATOM   C5  CT2     -0.180
ATOM   C6  CT2     -0.180
ATOM   C7  CT1      0.120
ATOM   C8  CT2     -0.180
ATOM   C9   CA      0.000
ATOM  C10   CA      0.000
ATOM  C11   CA     -0.110
ATOM  C12   CA     -0.110
ATOM  C13   CA      0.170
ATOM  C14   CA     -0.110
ATOM  N15  N3      -0.630
ATOM  C16  CT2      0.030
ATOM  C17  CT2     -0.180
ATOM  O18  OCE     -0.340
ATOM  C19  CT3     -0.100
ATOM  C20  CT3     -0.060
ATOM  H21   HA      0.090
ATOM  H22   HA      0.090
ATOM  H23   HA      0.090
ATOM  H24   HP      0.110
ATOM  H25   HA      0.090
ATOM  H26   HA      0.090
ATOM  H27   HA      0.090
ATOM  H28   HA      0.090
ATOM  H29   HA      0.090
ATOM  H30   HA      0.090
ATOM  H31   HA      0.090
ATOM  H32   HA      0.090
ATOM  H33   HA      0.090
ATOM  H34   HA      0.090
ATOM  H35   HA      0.090
ATOM  H36   HP      0.110
ATOM  H37   HP      0.110
ATOM  H38   HA      0.090
ATOM  H39   HA      0.090
ATOM  H40   HA      0.090
```

```
ATOM  H41   HA      0.090
ATOM  H42   HA      0.090
ATOM  H43   HA      0.090
ATOM  H44   HA      0.090
ATOM  H45   HA      0.090
BOND   C1   C2    C1   C6    C1  H44    C1  H45
BOND   C2   C3    C2  C10    C2  C17    C3   C4
BOND   C3   C7    C3  H25    C4   C5    C4  H38
BOND   C4  H39    C5   C6    C5  H40    C5  H41
BOND   C6  H42    C6  H43    C7   C8    C7  N15
BOND   C7  H26    C8   C9    C8  H34    C8  H35
BOND   C9  C10    C9  C11   C10  C14   C11  C12
BOND  C11  H36   C12  C13   C12  H37   C13  C14
BOND  C13  O18   C14  H24   N15  C16   N15  C20
BOND  C16  C17   C16  H30   C16  H31
BOND  C17  H32   C17  H33   O18  C19   C19  H21
BOND  C19  H22   C19  H23   C20  H27   C20  H28
BOND  C20  H29
IMPR   C9   C10  C11  C8
IMPR   C10  C9   C14  C2
IMPR   C14  C10  C13  H24
IMPR   C13  O18  C12  C14
IMPR   C12  C13  C11  H37
IMPR   C11  C12  C9   H36
ACCEPTOR N15
ACCEPTOR O18
PATCHING FIRS NONE LAST NONE

BONDS
!
!V(bond) = Kb(b - b0)**2
!
!Kb: kcal/mole/A**2
!b0: A
!
!atom type   Kb         b0
!

CT1  NT   119.686    1.5470
CA   OCE  369.634    1.3543
NT   CT2  176.892    1.5194
NT   CT3  254.400    1.4990
NT   HC   385.785    1.0259
CT3  OCE  113.647    1.415
CT0  CT1  218.894    1.5000
CT0  CT2  211.180    1.5380
CT0  CA   387.525    1.4900
!parameters for deprotonated DEX (DEP) values are taken from the
amine stream files
!the amine nitrogen is N3 in this case
!N3   CNT3    235.000   1.4540
N3   CT3    235.000   1.4540
N3   CT1    235.000   1.4540
N3   CT2    235.000   1.4540


ANGLES
!
```

```
!V(angle) = Ktheta(Theta - Theta0)**2
!
!V(Urey-Bradley) = Kub(S - S0)**2
!
!Ktheta: kcal/mole/rad**2
!Theta0: degrees
!Kub: kcal/mole/A**2 (Urey-Bradley)
!S0: A
!
!atom types     Ktheta    Theta0    Kub      S0
!

NT   CT1  CT1   67.700   110.0
NT   CT1  CT2   67.700    110.0
NT   CT2  CT2   67.700    110.0
CA   CA   OCE   45.200    120.0
CT1  NT   CT2   50.000    113.0
CT1  NT   CT3   50.000    113.0
CT2  NT   CT3   50.000    112.0
NT   CT3  HA    45.000    107.50   35.00   2.10100
NT   CT2  HA    45.000    107.50   35.00   2.10100
NT   CT1  HA    45.000    107.50   35.00   2.10100
HC   NT   CT1   30.000    109.50   20.00   2.07400
HC   NT   CT2   30.000    109.50   20.00   2.07400
HC   NT   CT3   30.000    109.50   20.00   2.07400
CA   OCE  CT3   95.000    118.71
OCE  CT3  HA    60.00     109.5
CT2  CT2  CT0   58.350    113.50   11.16   2.56100
CT2  CT1  CT0   53.350    111.0     8.00   2.56100
CT1  CT1  CT0   53.350    111.0     8.00   2.56100
HA   CT2  CT0   33.430    110.10   22.53   2.17900
CT2  CT0  CT1   53.350    109.0     8.00   2.56100
CT2  CT0  CT2   53.350    110.0     8.00   2.56100
CT2  CT0  CA    53.350    109.5     8.00   2.56100
CT1  CT0  CA    53.350    109.0     8.00   2.56100
CT0  CA   CA    45.800    120.60
CT0  CT1  HA    34.500    110.10   22.53   2.17900
N3   CT3  HA    35.000    109.50   50.00   2.14000
N3   CT2  HA    35.000    109.50   50.00   2.14000
N3   CT1  HA    35.000    109.50   50.00   2.14000
CT3  N3   CT1   53.000    110.90
CT2  N3   CT1   53.000    110.90
CT2  N3   CT3   53.000    110.90
N3   CT1  CT1   67.700    110.90
N3   CT1  CT2   67.700    110.0
N3   CT2  CT2   67.700    110.0

DIHEDRALS
!
!V(dihedral) = Kchi(1 + cos(n(chi) - delta))
!
!Kchi: kcal/mole
!n: multiplicity
!delta: degrees
!
!atom types             Kchi     n    delta
!
CT0  CA   CA   CA       3.1000   2    180.00
```

```
CT2  CA   CA   CT0      4.2000   2    180.00
HP   CA   CA   CT0      4.2000   2    180.00
HP   CA   CA   OCE      1.256    2    180.00
OCE  CA   CA   CA       1.0000   2    180.00
CA   CA   OCE  CT3      1.4170   2    180.00
CA   OCE  CT3  HA       0.5760   3      0.00
CA   CT0  CT1  CT2      0.0400   3      0.00
CA   CT0  CT1  CT1      0.0400   3      0.00
CA   CT0  CT1  HA       0.0400   3      0.00
CA   CT0  CT2  CT2      0.5402   3      0.00
HA   CT2  CT0  CA       0.0400   3      0.00
CT2  CT0  CT1  CT2      0.1500   1      0.00
CT2  CT0  CT1  CT1      0.1500   1      0.00
CT2  CT0  CT1  HA       0.4435   3      0.00
CT2  CT0  CA   CA       0.2300   2    180.00
CT1  CT0  CA   CA       0.2300   2    180.00
CT2  CT0  CT2  CT2      0.2000   3      0.00
CT2  CT0  CT2  HA       0.2000   3      0.00
CT1  CT0  CT2  CT2      0.2000   3      0.00
CT1  CT0  CT2  HA       0.2000   3      0.00
CT1  CT1  NT   CT2      0.1000   3      0.00
CT1  CT1  NT   CT3      0.1000   3      0.00
CT1  CT1  NT   HC       0.1000   3      0.00
CT2  CT1  NT   CT2      0.1000   3      0.00
CT2  CT1  NT   CT3      0.1000   3      0.00
CT2  CT1  NT   HC       0.1000   3      0.00
HA   CT1  NT   CT2      0.1000   3      0.00
HA   CT1  NT   CT3      0.1000   3      0.00
HA   CT1  NT   HC       0.1000   3      0.00
CT1  NT   CT2  CT2      0.1000   3      0.00
CT1  NT   CT2  HA       0.1000   3      0.00
CT3  NT   CT2  CT2      0.1000   3      0.00
CT3  NT   CT2  HA       0.1000   3      0.00
HC   NT   CT2  CT2      0.1000   3      0.00
HC   NT   CT2  HA       0.1000   3      0.00
CT1  NT   CT3  HA       0.1000   3    251.15
CT2  NT   CT3  HA       0.1000   3      0.00
HC   NT   CT3  HA       0.1000   3      0.00 ! from the amine
stream file
!HNA3 CNT3 N3  CNT3     0.3150   3      0.00 !fitting to exptl
data
HA CT3 N3  CT1     0.3150   3     0.00    !fitting to exptl data
HA CT3 N3  CT2     0.3150   3     0.00    !fitting to exptl data
HA CT1 N3  CT2     0.3150   3     0.00    !fitting to exptl data
HA CT1 N3  CT3     0.3150   3     0.00    !fitting to exptl data
HA CT2 N3  CT1     0.3150   3     0.00    !fitting to exptl data
HA CT2 N3  CT3     0.3150   3     0.00    !fitting to exptl data
X  CT1 N3  X       0.3150   3     0.00    !from HS CT1 N3 CT2
X  CT2 N3  X       0.3150   3     0.00    !from HS CT1 N3 CT2

IMPROPER
!
!V(improper) = Kpsi(psi - psi0)**2
!
!Kpsi: kcal/mole/rad**2
!psi0: degrees
!note that the second column of numbers (0) is ignored
!
```

```
!atom types             Kpsi        0  psi0
!
CA  CA  CA  HP        20.000   0 0.000   ! from HA CPB C C (heme)
CA  CA  CA  CT2       96.000   0 0.000   ! from CC X X CT1
CA  CA  CA  CT0       96.000   0 0.000   ! from CC X X CT1
CA  OCE CA  CA        96.000   0 0.000   ! from CC X X CT1
CT1 N3  CT2 CT3    15.6000     0 120.0000

NONBONDED nbxmod  5 atom cdiel shift vatom vdistance vswitch -
cutnb 14.0 ctofnb 12.0 ctonnb 10.0 eps 1.0 e14fac 1.0 wmin 1.5
                !adm jr., 5/08/91, suggested cutoff scheme
!
!V(Lennard-Jones) = Eps(i,j)*[(Rmin(i,j)/r(i,j))**12 -
2(Rmin(i,j)/r(i,j))**6]
!
!epsilon [kcal/mole]: Eps(i,j) = sqrt(eps(i) * eps(j))
!Rmin/2  [A]:         Rmin(i,j) = Rmin/2(i) + Rmin/2(j)
!
!atom  ignored   epsilon     Rmin/2  ignored   eps,1-4
Rmin/2,1-4
!

NT   0.0     -0.2000     1.8500    !
OCE  0.0     -0.1521     1.7700    !
CT0  0.0     -0.0200     2.275 0.0 -0.01 1.9 ! from CT, from CT1x
N3   0.0     -0.0350     2.000
END
```

Part B Absolute energies (in atomic units) for all computed species. All QM and QM/MM energies were calculated at the B3LYP/6-31G* level of theory (with LACVP for Fe).

QM energy of triplet oxygen atom	$E_{QM}O$	=	-75.0573242
QM energy of relaxed Fe(III) porphyrin	$E_{QM}(Fe)$	=	-1510.614765
QM energy of unrelaxed Fe(III) porphyrin	$E_{QM}(Fe^*)$	=	-1510.653854
Relaxation energy =	$E_{QM}(Fe) - E_{QM}(Fe^*)$	=	0.039089017

Table S1 Absolute QM/MM energies for Compound I ($E_{QM/MM}$(FeO)) and unrelaxed Fe(III) resting state ($E_{QM/MM}$(Fe*)) in the **2C9_apo** simulation

Snapshot [ps]	**$E_{QM/MM}$(FeO)**	**$E_{QM/MM}$(Fe*)**
0	-1636.907377	-1561.707872
200	-1636.82625	-1561.633356
400	-1636.893422	-1561.711793
600	-1636.391303	-1561.208728
800	-1637.596848	-1562.403147
1000	-1638.148509	-1562.949302
1200	-1637.611517	-1562.402052
1400	-1637.516744	-1562.329535
1600	-1637.603194	-1562.410317
1800	-1638.217694	-1563.026913
2000	-1639.996712	-1564.80418
2200	-1637.638259	-1562.454109
2400	-1637.005229	-1561.812395
2600	-1637.836285	-1562.632844
2800	-1637.469693	-1562.281352
3000	-1638.186007	*
3200	-1638.078274	-1562.891212
3400	-1639.977814	-1564.792337
3600	-1637.425406	-1562.236322
3800	-1637.476232	-1562.287394
4000	-1638.673403	-1563.488725
4200	-1638.593623	-1563.401051
4400	-1638.94762	-1563.749573
4600	-1638.566883	-1563.378925
4800	-1638.035674	-1562.831822
5000	-1638.341865	-1563.13747

Table S2 Absolute QM/MM energies for Compound I ($E_{QM/MM}$(FeO)) and unrelaxed Fe(III) resting state ($E_{QM/MM}$(Fe*)) in the **2C9_prox** simulation

Snapshot [ps]	**$E_{QM/MM}$(FeO)**	**$E_{QM/MM}$(Fe*)**
0	-2211.369373	-2136.19929
200	-2209.898663	-2134.720503
400	-2210.080927	-2134.897184
600	-2209.552079	-2134.373783
800	-2209.923604	-2134.748977
1000	-2209.444388	-2134.260259
1200	-2211.348313	-2136.163837
1400	-2210.501299	-2135.318172
1600	-2210.842599	-2135.659211
1800	-2210.212184	-2135.031005
2000	-2209.649563	-2134.465454
2200	-2210.259975	-2135.078412
2400	-2210.459221	-2135.281036
2600	-2209.848896	-2134.66971
2800	-2209.5128	-2134.330237
3000	-2210.541031	-2135.360884
3200	-2210.939025	-2135.760973
3400	-2209.922657	-2134.740267
3600	-2210.533676	-2135.355504
3800	-2210.276736	-2135.086851
4000	-2210.579494	-2135.381345
4200	-2210.478699	-2135.274207
4400	-2210.141375	-2134.944585
4600	-2211.045436	-2135.845662
4800	-2211.201947	-2135.98314
5000	-2210.643981	-2135.449476

Table S3 Absolute QM/MM energies for Compound I ($E_{QM/MM}$(FeO)) and unrelaxed Fe(III) resting state ($E_{QM/MM}$(Fe*)) in the **2C9_dist** simulation

Snapshot [ps]	**$E_{QM/MM}$(FeO)**	**$E_{QM/MM}$(Fe*)**
0	-2209.801979	-2134.623378
200	-2209.849037	-2134.67259
400	-2209.814915	-2134.637421
600	-2210.838288	-2135.666213
800	-2209.295205	-2134.108396
1000	-2209.962773	-2134.773681
1200	-2208.770515	-2133.590192
1400	-2209.306404	-2134.126617
1600	-2209.772847	-2134.589697
1800	-2210.299001	-2135.122875
2000	-2210.818539	-2135.631277
2200	-2209.441458	-2134.25566
2400	-2210.480465	-2135.295543
2600	-2210.516308	-2135.326721
2800	-2212.854697	-2137.670703
3000	-2210.14149	-2134.944658
3200	-2210.047482	-2134.864727
3400	-2210.024975	-2134.832673
3600	-2210.470527	-2135.279824
3800	-2210.9494	-2135.765246
4000	-2211.733565	
4200	-2208.860542	-2133.677887
4400	-2209.814868	-2134.619075
4600	-2211.07056	-2135.88986
4800	-2210.790471	-2135.609404
5000	-2210.544899	-2135.35977

Table S4 Absolute QM/MM energies for Compound I ($E_{QM/MM}$(FeO)) and unrelaxed Fe(III) resting state ($E_{QM/MM}$(Fe*)) in the **2C9_2warf** simulation

Snapshot [ps]	**$E_{QM/MM}$(FeO)**	**$E_{QM/MM}$(Fe*)**
0	-2209.090584	-2133.919761
200	-2208.484447	-2133.311804
400	*	*
600	*	*
800	-2210.109172	-2134.929779
1000	-2209.987435	-2134.812278
1200	-2209.290539	-2134.1096
1400	-2210.158613	-2134.977607
1600	-2209.419077	-2134.242999
1800	-2209.445886	-2134.271231
2000	-2210.011443	-2134.834679
2200	-2211.247532	-2136.075983
2400	-2209.993419	-2134.816796
2600	-2210.454279	-2135.285223
2800	-2210.26779	-2135.093347
3000	-2209.859789	-2134.68529
3200	-2209.702458	-2134.530128
3400	-2209.092298	-2133.920762
3600	-2211.543866	-2136.367615
3800	-2209.690391	-2134.514031
4000	-2209.813105	-2134.622426
4200	-2210.039606	-2134.86509
4400	-2210.745014	-2135.5627
4600	-2210.909464	-2135.727775
4800	-2210.765019	-2135.584155
5000	-2210.214085	-2135.03753

Table S5 Absolute QM/MM energies for Compound I ($E_{QM/MM}$(FeO)) and unrelaxed Fe(III) resting state ($E_{QM/MM}$(Fe*)) in the **2D6_apo** simulation

Snapshot [ps]	**$E_{QM/MM}$(FeO)**	**$E_{QM/MM}$(Fe*)**
0	-1638.014747	-1562.844551
200	-1640.779478	-1565.602414
400	-1641.209776	-1566.034947
600	-1641.211843	-1566.035982
800	-1641.658926	-1566.485364
1000	-1641.600708	-1566.41687
1200	-1641.587276	-1566.409671
1400	-1641.338209	-1566.166141
1600	-1641.999665	-1566.823241
1800	-1641.519998	-1566.339204
2000	-1641.475185	-1566.297585
2200	-1641.621403	-1566.444089
2400	-1641.859497	-1566.681695
2600	-1642.389482	-1567.209481
2800	-1641.713168	-1566.533457
3000	-1641.891379	-1566.697581
3200	-1642.161189	-1566.971878
3400	-1642.218429	-1567.018099
3600	-1642.479438	-1567.288124
3800	-1642.623911	-1567.430351
4000	-1642.28249	-1567.089023
4200	-1642.103164	-1566.910081
4400	-1642.479087	-1567.275286
4600	-1641.991913	-1566.789938
4800	-1642.333912	-1567.147974
5000	-1642.261348	-1567.070494

Table S6 Absolute QM/MM energies for Compound I ($E_{QM/MM}$(FeO)) and unrelaxed Fe(III) resting state ($E_{QM/MM}$(Fe*)) in the **2D6_dex** simulation

Snapshot [ps]	**$E_{QM/MM}$(FeO)**	**$E_{QM/MM}$(Fe*)**
0	-1987.259326	-1912.080665
200	-1987.456249	-1912.284676
400	-1988.092333	-1912.92082
600	-1987.445434	-1912.274539
800	-1988.469274	-1913.298814
1000	-1987.699525	-1912.52847
1200	-1988.433186	-1913.257741
1400	-1987.716698	-1912.54414
1600	-1988.618842	-1913.447775
1800	-1987.931326	-1912.760063
2000	-1988.108817	-1912.93762
2200	-1988.065904	-1912.893367
2400	-1988.36517	-1913.191774
2600	-1988.744976	-1913.574956
2800	-1988.503928	-1913.330982
3000	-1988.570046	-1913.386814
3200	-1988.304542	-1913.129719
3400	-1988.524511	-1913.345364
3600	-1988.072428	-1912.892492
3800	-1988.144973	-1912.966853
4000	-1988.506091	-1913.330629
4200	-1988.309299	-1913.128781
4400	-1988.059865	-1912.882908
4600	-1988.551285	-1913.369875
4800	-1988.850023	-1913.67086
5000	-1988.250416	-1913.075667

Table S7 Absolute QM/MM energies for Compound I ($E_{QM/MM}$(FeO)) and unrelaxed Fe(III) resting state ($E_{QM/MM}$(Fe*)) in the **3A4_apo** simulation

Snapshot [ps]	**$E_{QM/MM}$(FeO)**	**$E_{QM/MM}$(Fe*)**
0	-1637.836979	-1562.659449
200	-1637.93327	-1562.743602
400	-1638.374702	-1563.197103
600	-1637.976058	-1562.795303
800	-1637.575963	-1562.389738
1000	-1639.020723	-1563.838428
1200	-1637.42385	-1562.234942
1400	-1638.374484	-1563.187701
1600	-1638.322488	-1563.140894
1800	-1638.041727	-1562.85689
2000	-1638.353595	-1563.168274
2200	-1638.763795	-1563.579384
2400	-1638.386076	-1563.198847
2600	-1638.184974	-1563.000893
2800	-1637.498243	-1562.296645
3000	-1637.496843	-1562.312704
3200	-1639.06221	-1563.874851
3400	-1638.910872	-1563.727767
3600	-1637.693371	-1562.504458
3800	-1638.696138	-1563.513448
4000	-1637.164234	-1561.984612
4200	-1639.37596	-1564.199479
4400	-1638.953997	-1563.769435
4600	-1638.740077	-1563.559743
4800	-1638.912378	-1563.731206
5000	-1637.61744	-1562.44117

Table S8 Absolute QM/MM energies for Compound I ($E_{QM/MM}$(FeO)) and unrelaxed Fe(III) resting state ($E_{QM/MM}$(Fe*)) in the **3A4_dex** simulation

Snapshot [ps]	**$E_{QM/MM}$(FeO)**	**$E_{QM/MM}$(Fe*)**
0	-1637.196334	-1562.015364
200	-1637.593503	-1562.411155
400	-1639.365531	-1564.177474
600	-1637.807129	-1562.624513
800	-1638.476493	-1563.291296
1000	-1638.366614	-1563.182127
1200	-1637.023858	-1561.840734
1400	-1637.907142	-1562.727748
1600	-1637.560466	-1562.385689
1800	-1638.511888	-1563.327051
2000	-1638.035538	-1562.851033
2200	-1637.997945	-1562.815032
2400	-1637.848372	-1562.658468
2600	-1638.816799	-1563.638855
2800	-1637.56859	-1562.390537
3000	-1637.22953	-1562.04586
3200	-1638.270617	-1563.082057
3400	-1638.555299	-1563.374452
3600	-1639.133401	-1563.947407
3800	-1637.936961	-1562.755451
4000	-1638.482263	-1563.299429
4200	-1637.98119	-1562.793872
4400	-1637.761715	-1562.582114
4600	-1638.718599	-1563.530535
4800	-1638.870809	-1563.677533
5000	-1638.097815	-1562.909308

Table S9 Absolute QM/MM energies for Compound I ($E_{QM/MM}$(FeO)) and unrelaxed Fe(III) resting state ($E_{QM/MM}$(Fe*)) in the **P450$_{cam}$_apo** simulation

Snapshot [ps]	**$E_{QM/MM}$(FeO)**	**$E_{QM/MM}$(Fe*)**
0	-1639.111762	-1563.928181
200	-1638.121693	-1562.939536
400	-1639.970799	-1564.794782
600	-1638.688537	-1563.511184
800	-1641.986597	-1566.807714
1000	-1642.923284	-1567.735062
1200	-1639.618909	-1564.432681
1400	-1637.536004	-1562.351091
1600	-1637.813228	-1562.635077
1800	-1636.459957	-1561.281569
2000	-1637.588059	-1562.412389
2200	-1639.216279	-1564.03621
2400	-1640.84631	-1565.663678
2600	-1638.335671	-1563.152518
2800	-1636.16733	-1560.967914
3000	-1637.127584	-1561.941452
3200	-1638.533717	-1563.354941
3400	-1639.121007	-1563.930711
3600	-1637.465421	-1562.282986
3800	-1637.248251	-1562.05867
4000	-1638.61852	-1563.420791
4200	-1636.126764	-1560.930846
4400	-1639.226436	-1564.043224
4600	-1638.006777	-1562.824499
4800	-1639.93946	-1564.756512
5000	-1637.883969	-1562.707619

Table S10 Absolute QM/MM energies for Compound I ($E_{QM/MM}$(FeO)) and unrelaxed Fe(III) resting state ($E_{QM/MM}$(Fe*)) in the **P450$_{cam}$_prop** simulation

Snapshot [ps]	**$E_{QM/MM}$(FeO)**	**$E_{QM/MM}$(Fe*)**
0	-1756.239667	-1681.060061
200	-1755.550799	-1680.372462
400	-1755.507125	-1680.331318
600	-1754.774692	-1679.59858
800	-1759.568876	-1684.39224
1000	-1758.434443	-1683.254936
1200	-1755.504909	-1680.324459
1400	-1755.512597	-1680.334612
1600	-1757.118153	-1681.938263
1800	-1756.039641	-1680.860267
2000	-1759.37413	-1684.191072
2200	-1755.816508	-1680.635724
2400	-1758.065581	-1682.888317
2600	-1756.02191	*
2800	-1754.992015	-1679.813666
3000	-1755.652733	-1680.474375
3200	-1757.093883	-1681.912133
3400	-1756.667105	-1681.487211
3600	-1755.315922	-1680.130683
3800	-1754.883525	-1679.701953
4000	-1761.734157	-1686.552884
4200	-1754.662712	-1679.471868
4400	-1755.470241	-1680.297057
4600	-1756.204112	-1681.022579
4800	-1755.411861	-1680.232131
5000	-1753.828087	-1678.648963

Part C Mulliken spin densities for QM/MM optimized snapshots of Compound I

Table S11 Mulliken spin densities for individual fragments in QM/MM optimized snapshots of Compound I taken from the **2C9_apo** MD simulation.

Snapshot [ps]	ρ(Fe)	ρ(O)	ρ(S)	ρ(porphyrin)
0	1.16458	0.7704	0.46444	0.57491
200	1.15865	0.77894	0.46042	0.57611
400	1.15712	0.79073	0.34752	0.68449
600	1.15017	0.79744	0.40028	0.62838
800	1.16	0.77848	0.43152	0.60536
1000	*	*	*	*
1200	1.19339	0.73095	0.54593	0.50152
1400	1.14964	0.79372	0.3892	0.64502
1600	1.15576	0.7825	0.43665	0.60299
1800	1.15864	0.78327	0.4134	0.62062
2000	1.15539	0.78359	0.41858	0.6168
2200	1.1557	0.79144	0.35176	0.6821
2400	1.22756	0.71554	0.31268	0.72794
2600	1.22697	0.70616	0.45915	0.58054
2800	1.15007	0.79276	0.41494	0.6185
3000	1.16713	0.77768	0.35994	0.67524
3200	1.15998	0.78368	0.36214	0.67344
3400	1.15496	0.78729	0.40598	0.62966
3600	1.17838	0.76608	0.38792	0.64642
3800	1.16397	0.77651	0.41938	0.61547
4000	1.14767	0.795	0.32154	0.71791
4200	1.1641	0.77307	0.46269	0.57499
4400	1.16529	0.76628	0.54878	0.4898
4600	1.14955	0.79129	0.4609	0.57219
4800	1.19952	0.72865	0.54413	0.49767
5000	1.21418	0.71439	0.56547	0.47556

Table S12 Mulliken spin densities for individual fragments in QM/MM optimized snapshots of Compound I taken from the **2C9_prox** MD simulation.

Snapshot [ps]	ρ(Fe)	ρ(O)	ρ(S)	ρ(porphyrin)
0	1.1419	0.81784	0.41677	0.59695
200	1.14638	0.80393	0.52507	0.4956
400	1.1987	0.74574	0.46223	0.56682
600	1.191	0.76186	0.40521	0.61589
800	1.17584	0.77905	0.36049	0.65705
1000	1.19392	0.74885	0.47251	0.55455
1200	1.18681	0.75875	0.48864	0.53745
1400	1.20156	0.74013	0.45879	0.56989
1600	1.20576	0.73815	0.48517	0.53865
1800	1.20366	0.74154	0.47209	0.55214
2000	1.20589	0.7386	0.40525	0.62305
2200	1.21548	0.73126	0.40906	0.6181
2400	1.21561	0.73741	0.3774	0.64177
2600	1.20287	0.7493	0.41731	0.60194
2800	1.15606	0.78984	0.51649	0.50777
3000	1.14809	0.79489	0.50637	0.52087
3200	1.15752	0.78	0.56587	0.45641
3400	1.17254	0.76316	0.56323	0.46104
3600	1.15583	0.78378	0.5512	0.47071
3800	1.17745	0.75426	0.60567	0.42489
4000	1.18138	0.74661	0.7367	0.29064
4200	1.17918	0.74694	0.72577	0.30794
4400	1.18429	0.74624	0.64493	0.38731
4600	1.17466	0.75399	0.68184	0.35327
4800	1.20869	0.70331	0.8112	0.22731
5000	1.14728	0.79474	0.45989	0.56817

Table S13 Mulliken spin densities for individual fragments in QM/MM optimized snapshots of Compound I taken from the **2C9_dist** MD simulation.

Snapshot [ps]	ρ(Fe)	ρ(O)	ρ(S)	ρ(porphyrin)
0	1.1418	0.81121	0.32868	0.69943
200	1.14622	0.80949	0.35303	0.6705
400	1.13152	0.81949	0.42969	0.59374
600	1.11956	0.8342	0.41153	0.61109
800	1.1638	0.78084	0.47999	0.54852
1000	1.16592	0.77453	0.49357	0.53777
1200	1.14742	0.80471	0.44512	0.5778
1400	1.1588	0.79499	0.42368	0.59922
1600	1.17591	0.77634	0.42859	0.5954
1800	1.13482	0.82092	0.3785	0.644
2000	1.16062	0.78187	0.48587	0.54482
2200	1.15949	0.78407	0.42842	0.60387
2400	1.16646	0.77746	0.45885	0.57235
2600	1.18926	0.75254	0.53387	0.4946
2800	1.14811	0.79684	0.48111	0.54666
3000	1.16947	0.76633	0.54825	0.48636
3200	1.14971	0.79632	0.46141	0.56709
3400	1.16082	0.7786	0.47446	0.56045
3600	1.16726	0.77445	0.51473	0.51484
3800	1.16081	0.78652	0.49044	0.53386
4000	1.17577	0.76356	0.53235	0.4988
4200	1.16818	0.77988	0.44824	0.57864
4400	1.23419	0.70656	0.50821	0.52122
4600	1.18653	0.76493	0.45592	0.56576
4800	1.16562	0.78934	0.36219	0.66237
5000	1.16978	0.77901	0.46856	0.55692

Table S14 Mulliken spin densities for individual fragments in QM/MM optimized snapshots of Compound I taken from the **2C9_2warf** MD simulation.

Snapshot [ps]	ρ(Fe)	ρ(O)	ρ(S)	ρ(porphyrin)
0	1.1004	0.85087	0.40789	0.61346
200	1.1362	0.81208	0.41492	0.60971
400	1.11955	0.8383	0.34379	0.67498
600	1.11792	0.83417	0.38987	0.63253
800	1.13661	0.80731	0.46816	0.56016
1000	1.13425	0.81392	0.4153	0.61113
1200	1.14701	0.79636	0.42769	0.60345
1400	1.1443	0.79926	0.45974	0.56855
1600	1.14865	0.79897	0.43155	0.59006
1800	1.12366	0.82299	0.44662	0.57689
2000	1.15342	0.79387	0.40787	0.61966
2200	1.13761	0.81172	0.3743	0.64715
2400	1.13908	0.81016	0.39248	0.63126
2600	1.10761	0.84517	0.33439	0.68767
2800	1.12564	0.82042	0.45487	0.56555
3000	1.13021	0.82089	0.47228	0.54274
3200	1.13142	0.8204	0.32648	0.69729
3400	1.12339	0.82821	0.37613	0.64257
3600	1.13783	0.81639	0.38016	0.64068
3800	1.14384	0.80901	0.39449	0.62427
4000	1.15519	0.78367	0.50362	0.52938
4200	1.12901	0.82294	0.39102	0.63251
4400	1.17871	0.77872	0.34673	0.67664
4600	1.1373	0.81091	0.431	0.59024
4800	1.18166	0.76628	0.44405	0.57787
5000	1.17686	0.77857	0.31924	0.7049

Table S15 Mulliken spin densities for individual fragments in QM/MM optimized snapshots of Compound I taken from the **2D6_apo** MD simulation.

Snapshot [ps]	ρ(Fe)	ρ(O)	ρ(S)	ρ(porphyrin)
0	1.11818	0.83633	0.32575	0.69981
200	1.12532	0.82258	0.38369	0.64593
400	1.13135	0.81873	0.39784	0.62735
600	1.1238	0.82527	0.37681	0.65101
800	1.13335	0.81949	0.38451	0.63862
1000	1.16801	0.77827	0.37614	0.65434
1200	1.13456	0.81369	0.36371	0.66514
1400	1.119	0.83498	0.35165	0.67238
1600	1.13065	0.81642	0.37684	0.65308
1800	1.13659	0.80847	0.40948	0.62041
2000	1.13715	0.81063	0.39852	0.63054
2200	1.12222	0.82573	0.35521	0.6753
2400	1.13741	0.80965	0.41692	0.61088
2600	1.12736	0.81839	0.38225	0.64879
2800	1.13656	0.81006	0.35444	0.67711
3000	1.16476	0.77158	0.43838	0.59917
3200	1.18932	0.7533	0.38255	0.65132
3400	1.17703	0.75624	0.43243	0.60721
3600	1.15619	0.78812	0.35786	0.67638
3800	1.15935	0.78197	0.40577	0.62819
4000	1.17009	0.7699	0.3868	0.65008
4200	1.17955	0.75699	0.4223	0.61543
4400	1.19174	0.73845	0.46729	0.57456
4600	1.20069	0.73181	0.46854	0.57205
4800	1.17422	0.77147	0.3702	0.66183
5000	1.18635	0.75509	0.41889	0.6145

Table S16 Mulliken spin densities for individual fragments in QM/MM optimized snapshots of Compound I taken from the **2D6_dex** MD simulation.

Snapshot [ps]	ρ(Fe)	ρ(O)	ρ(S)	ρ(porphyrin)
0	1.18094	0.76855	0.31245	0.71599
200	1.13824	0.81286	0.33646	0.68415
400	1.1429	0.8032	0.30722	0.71807
600	1.12692	0.8289	0.34525	0.67712
800	1.12204	0.83079	0.32249	0.70369
1000	1.12698	0.82572	0.33975	0.68587
1200	1.14238	0.80802	0.44811	0.57479
1400	1.12532	0.82209	0.36722	0.66182
1600	1.12195	0.82861	0.36436	0.66154
1800	1.13036	0.82146	0.33331	0.69361
2000	1.13359	0.82046	0.37346	0.64907
2200	1.12245	0.82569	0.32972	0.69863
2400	1.12839	0.82149	0.37749	0.64746
2600	1.1245	0.82665	0.36158	0.66302
2800	1.11987	0.82826	0.37331	0.65385
3000	1.15505	0.782	0.46458	0.56876
3200	1.13102	0.81813	0.34826	0.68142
3400	1.14505	0.7987	0.42114	0.60894
3600	1.15107	0.79167	0.45014	0.5786
3800	1.14946	0.79549	0.41051	0.621
4000	1.14064	0.80577	0.34421	0.68928
4200	1.1626	0.7811	0.42216	0.60647
4400	1.15052	0.79186	0.35232	0.59676
4600	1.14267	0.80024	0.43485	0.6775
4800	1.14976	0.79429	0.36963	0.66276
5000	1.14267	0.80024	0.35312	0.6775

Table S17 Mulliken spin densities for individual fragments in QM/MM optimized snapshots of Compound I taken from the **3A4_apo** MD simulation.

Snapshot [ps]	ρ(Fe)	ρ(O)	ρ(S)	ρ(porphyrin)
0	1.14961	0.80345	0.41994	0.60257
200	1.15923	0.78353	0.59377	0.42889
400	1.15082	0.80172	0.41374	0.60846
600	1.15442	0.79271	0.45973	0.56563
800	1.16941	0.77449	0.44058	0.58812
1000	1.15707	0.78885	0.45494	0.57244
1200	1.1731	0.77019	0.49435	0.53454
1400	1.1694	0.77427	0.55137	0.47215
1600	1.17799	0.76991	0.42118	0.60511
1800	1.17909	0.76843	0.46633	0.55871
2000	1.14869	0.79432	0.45038	0.57984
2200	1.17317	0.77116	0.45014	0.57872
2400	1.16314	0.7795	0.50505	0.52133
2600	1.14249	0.80244	0.49577	0.52885
2800	1.24724	0.68696	0.52595	0.50963
3000	1.17028	0.77374	0.46172	0.56639
3200	1.18593	0.75669	0.51115	0.51525
3400	1.13653	0.80868	0.50088	0.52365
3600	1.19545	0.74781	0.5241	0.50252
3800	1.16863	0.77846	0.44766	0.57801
4000	1.13985	0.80624	0.45942	0.56704
4200	1.13355	0.81936	0.4289	0.59157
4400	1.14236	0.80089	0.44181	0.58933
4600	1.16568	0.78473	0.41218	0.61216
4800	1.15211	0.7966	0.42974	0.59572
5000	1.14072	0.81377	0.41096	0.60962

Table S18 Mulliken spin densities for individual fragments in QM/MM optimized snapshots of Compound I taken from the **3A4_dex** MD simulation.

Snapshot [ps]	ρ(Fe)	ρ(O)	ρ(S)	ρ(porphyrin)
0	1.14629	0.80234	0.46285	0.55982
200	1.15663	0.78972	0.50919	0.51457
400	1.15637	0.78678	0.48523	0.54402
600	1.15025	0.79751	0.54301	0.47794
800	1.139	0.80457	0.54134	0.48434
1000	1.15435	0.79282	0.54504	0.47613
1200	1.17228	0.77648	0.46697	0.55664
1400	1.11631	0.83044	0.49163	0.53297
1600	1.09405	0.85622	0.47047	0.55122
1800	1.13043	0.81381	0.45957	0.57065
2000	1.14606	0.79941	0.50309	0.52131
2200	1.18543	0.76362	0.43834	0.58721
2400	1.23228	0.71364	0.31938	0.71536
2600	1.11938	0.83062	0.39835	0.62674
2800	1.12857	0.82441	0.35617	0.66875
3000	1.16657	0.77731	0.47053	0.55689
3200	1.21545	0.72995	0.34127	0.69327
3400	1.12094	0.82645	0.42873	0.59826
3600	1.16336	0.78437	0.38109	0.64729
3800	1.13312	0.81414	0.37475	0.65589
4000	1.13503	0.81311	0.39872	0.62857
4200	1.16655	0.77758	0.44805	0.58048
4400	1.12315	0.82725	0.41642	0.60811
4600	1.17109	0.77307	0.43748	0.59229
4800	1.20377	0.73684	0.40737	0.62806
5000	1.19012	0.75405	0.38914	0.64435

Table S19 Mulliken spin densities for individual fragments in QM/MM optimized snapshots of Compound I taken from the **$P450_{cam}$_apo** MD simulation.

Snapshot [ps]	ρ(Fe)	ρ(O)	ρ(S)	ρ(porphyrin)
0	1.15479	0.79202	0.31235	0.72117
200	1.15797	0.7865	0.35496	0.67892
400	1.11078	0.84029	0.24124	0.79297
600	1.11142	0.83858	0.30587	0.72622
800	1.13104	0.81932	0.32498	0.70819
1000	1.14568	0.79552	0.41482	0.6202
1200	1.17315	0.77169	0.26007	0.78213
1400	1.1619	0.78473	0.33222	0.70367
1600	1.11041	0.84069	0.29488	0.73757
1800	1.12151	0.82783	0.39445	0.63453
2000	1.1196	0.83433	0.24161	0.79132
2200	1.13692	0.81467	0.33717	0.694
2400	1.1265	0.81986	0.32644	0.70967
2600	1.1701	0.77692	0.33465	0.69906
2800	1.23461	0.70194	0.39419	0.64737
3000	1.21627	0.73001	0.29922	0.73957
3200	1.11918	0.82888	0.34686	0.68427
3400	1.18622	0.75767	0.34164	0.69525
3600	1.1252	0.82213	0.32784	0.70648
3800	1.14088	0.79952	0.4472	0.58725
4000	1.23782	0.70234	0.36271	0.67709
4200	1.18776	0.74749	0.46117	0.57882
4400	1.12786	0.81909	0.36274	0.67072
4600	1.13731	0.81019	0.36497	0.66806
4800	1.14328	0.80213	0.33224	0.70332
5000	1.12557	0.82679	0.32016	0.71095

Table S20 Mulliken spin densities for individual fragments in QM/MM optimized snapshots of Compound I taken from the **P450$_{cam}$_prop** MD simulation.

Snapshot [ps]	ρ(Fe)	ρ(O)	ρ(S)	ρ(porphyrin)
0	1.14589	0.80186	0.27685	0.75303
200	1.14144	0.80471	0.30175	0.72765
400	1.11803	0.83006	0.17405	0.84453
600	1.14078	0.8076	0.25815	0.77252
800	1.13412	0.81603	0.26217	0.76571
1000	1.12172	0.82425	0.25761	0.77202
1200	1.14878	0.79685	0.21995	0.79103
1400	1.15751	0.7841	0.22541	0.80455
1600	1.13989	0.8035	0.21677	0.80803
1800	1.13235	0.81332	0.19768	0.84317
2000	1.16662	0.77629	0.3421	0.69484
2200	1.1449	0.79791	0.25061	0.72981
2400	1.11569	0.83082	0.33637	0.68886
2600	1.1004	0.85295	0.37857	0.64117
2800	1.12464	0.82411	0.22867	0.80452
3000	1.13759	0.80754	0.25551	0.77955
3200	1.18447	0.75801	0.2316	0.80394
3400	1.133	0.81385	0.27753	0.75574
3600	1.18305	0.75691	0.35443	0.68141
3800	1.14215	0.80302	0.27325	0.76297
4000	1.13588	0.80618	0.27444	0.75875
4200	1.17712	0.75755	0.46636	0.56387
4400	1.12129	0.82299	0.30159	0.72203
4600	1.17283	0.77356	0.25203	0.78671
4800	1.12897	0.81789	0.31174	0.72061
5000	1.13741	0.81112	0.24013	0.79644

Part D **Mulliken charges for QM/MM optimized snapshots of Compound I**

Table S21 Mulliken charges for individual fragments in QM/MM optimized snapshots of Compound I taken from the **2C9_apo** MD simulation.

Snapshot [ps]	Q(Fe)	Q(O)	Q(S)	Q(porphyrin)
0	0.58543	-0.4349	-0.17025	0.11138
200	0.5543	-0.44139	-0.11942	0.09522
400	0.49001	-0.43969	-0.12844	0.17635
600	0.50247	-0.44415	-0.10526	0.12572
800	0.56028	-0.44284	-0.16243	0.13491
1000	0.5447	-0.46286	-0.11467	0.10642
1200	0.59781	-0.45244	-0.17255	0.09952
1400	0.52238	-0.44095	-0.14961	0.15503
1600	0.56108	-0.43368	-0.16944	0.12491
1800	0.53429	-0.43985	-0.14446	0.14103
2000	0.53886	-0.44472	-0.13294	0.13397
2200	0.5142	-0.44162	-0.17303	0.19097
2400	0.49207	-0.51964	-0.15131	0.26474
2600	0.54894	-0.50886	-0.1077	0.14177
2800	0.54741	-0.44048	-0.13168	0.11908
3000	0.53036	-0.45274	-0.16761	0.18254
3200	0.55265	-0.43597	-0.20268	0.18119
3400	0.53143	-0.43775	-0.1384	0.13601
3600	0.53172	-0.45609	-0.15474	0.16282
3800	0.52813	-0.45255	-0.13027	0.13653
4000	0.5343	-0.44107	-0.19449	0.2082
4200	0.56178	-0.44082	-0.15097	0.11095
4400	0.57582	-0.4414	-0.0785	0.02364
4600	0.53501	-0.44152	-0.09301	0.08189
4800	0.59129	-0.4462	-0.14957	0.07576
5000	0.56609	-0.45443	-0.10042	0.05843

Table S22 Mulliken charges for individual fragments in QM/MM optimized snapshots of Compound I taken from the **2C9_prox** MD simulation.

Snapshot [ps]	Q(Fe)	Q(O)	Q(S)	Q(porphyrin)
0	0.47332	-0.39046	-0.11996	0.09064
200	0.48429	-0.39371	-0.06207	0.01358
400	0.48447	-0.44736	-0.11432	0.11271
600	0.48847	-0.4537	-0.14324	0.15422
800	0.4618	-0.46546	-0.10123	0.16942
1000	0.50699	-0.46439	-0.11409	0.1021
1200	0.49559	-0.46373	-0.06894	0.08316
1400	0.49471	-0.47987	-0.08442	0.10692
1600	0.50556	-0.47019	-0.09723	0.09207
1800	0.4954	-0.4778	-0.07981	0.10138
2000	0.52327	-0.48438	-0.15729	0.16799
2200	0.48655	-0.47177	-0.1309	0.15655
2400	0.46974	-0.48477	-0.11396	0.18119
2600	0.48245	-0.46442	-0.11333	0.13973
2800	0.53329	-0.39661	-0.12043	0.02937
3000	0.51876	-0.39701	-0.11451	0.03136
3200	0.48877	-0.41577	-0.00131	-0.0078
3400	0.51267	-0.42371	-0.01824	-0.01163
3600	0.49788	-0.41465	-0.00924	-0.01147
3800	0.54126	-0.42431	-0.03046	-0.02821
4000	0.61571	-0.41121	0.0062	-0.14134
4200	0.60515	-0.40359	-0.02697	-0.11477
4400	0.57431	-0.41783	-0.04124	-0.05654
4600	0.59833	-0.39873	-0.04772	-0.07676
4800	0.66867	-0.42996	-0.01807	-0.16312
5000	0.50624	-0.40756	-0.09731	0.06727

Table S23 Mulliken charges for individual fragments in QM/MM optimized snapshots of Compound I taken from the **2C9_dist** MD simulation.

Snapshot [ps]	Q(Fe)	Q(O)	Q(S)	Q(porphyrin)
0	0.48227	-0.4511	-0.16032	0.18155
200	0.49407	-0.4445	-0.13931	0.15206
400	0.48956	-0.43174	-0.08548	0.0731
600	0.48584	-0.37944	-0.13798	0.08653
800	0.5076	-0.45954	-0.08581	0.07863
1000	0.4981	-0.44805	-0.07379	0.06487
1200	0.4755	-0.45101	-0.06098	0.08177
1400	0.49389	-0.4455	-0.09169	0.10365
1600	0.51452	-0.44402	-0.13656	0.10866
1800	0.47193	-0.44147	-0.10268	0.12424
2000	0.51658	-0.4516	-0.10784	0.08276
2200	0.50993	-0.47439	-0.10925	0.12152
2400	0.50931	-0.46216	-0.10646	0.10371
2600	0.53377	-0.43974	-0.09373	0.03289
2800	0.51629	-0.43081	-0.09606	0.05797
3000	0.55233	-0.44639	-0.07958	0.01879
3200	0.52678	-0.43794	-0.11429	0.07565
3400	0.54484	-0.44165	-0.1261	0.07908
3600	0.52211	-0.45047	-0.07896	0.05244
3800	0.50584	-0.45596	-0.05108	0.05177
4000	0.53221	-0.45871	-0.07005	0.04574
4200	0.50594	-0.44114	-0.09428	0.08772
4400	0.51659	-0.5127	-0.04447	0.07981
4600	0.49662	-0.44502	-0.0904	0.08627
4800	0.48552	-0.45346	-0.13942	0.16598
5000	0.53863	-0.44635	-0.11565	0.07672

Table S24 Mulliken charges for individual fragments in QM/MM optimized snapshots of Compound I taken from the **2C9_2warf** MD simulation.

Snapshot [ps]	Q(Fe)	Q(O)	Q(S)	Q(porphyrin)
0	0.49698	-0.36264	-0.16353	0.08608
200	0.51371	-0.39445	-0.16514	0.09981
400	0.47597	-0.38049	-0.16806	0.14061
600	0.49304	-0.37951	-0.16064	0.09597
800	0.51056	-0.3936	-0.1287	0.05461
1000	0.50117	-0.39203	-0.16363	0.10734
1200	0.52261	-0.40215	-0.17108	0.10461
1400	0.49834	-0.40324	-0.1302	0.07047
1600	0.49218	-0.40888	-0.11997	0.08956
1800	0.48016	-0.38185	-0.13663	0.07671
2000	0.49988	-0.41094	-0.15373	0.12814
2200	0.48638	-0.39665	-0.17992	0.13707
2400	0.49088	-0.40288	-0.15062	0.11576
2600	0.46076	-0.37741	-0.16838	0.14634
2800	0.49399	-0.38383	-0.11563	0.05119
3000	0.50095	-0.38181	-0.10773	0.02981
3200	0.47995	-0.39868	-0.19146	0.17227
3400	0.47501	-0.39076	-0.15592	0.11375
3600	0.4948	-0.39731	-0.16794	0.1149
3800	0.47114	-0.40186	-0.13468	0.11228
4000	0.55451	-0.38575	-0.19841	0.07286
4200	0.47108	-0.3865	-0.14794	0.1099
4400	0.47506	-0.46148	-0.1627	0.18678
4600	0.48824	-0.43681	-0.11665	0.1095
4800	0.48581	-0.4512	-0.09298	0.09501
5000	0.45853	-0.46348	-0.14488	0.20631

Table S25 Mulliken charges for individual fragments in QM/MM optimized snapshots of Compound I taken from the **2D6_apo** MD simulation.

Snapshot [ps]	Q(Fe)	Q(O)	Q(S)	Q(porphyrin)
0	0.47352	-0.39067	-0.14899	0.16648
200	0.51394	-0.3871	-0.15731	0.12998
400	0.49673	-0.39559	-0.12145	0.12148
600	0.50851	-0.3888	-0.15999	0.14273
800	0.48874	-0.39761	-0.11979	0.13086
1000	0.50744	-0.46191	-0.12387	0.17717
1200	0.50533	-0.39888	-0.16603	0.16548
1400	0.49872	-0.38888	-0.14193	0.14587
1600	0.52852	-0.3809	-0.18213	0.14737
1800	0.5416	-0.38417	-0.19609	0.12765
2000	0.53314	-0.39197	-0.1737	0.13613
2200	0.52395	-0.38248	-0.19738	0.16608
2400	0.51502	-0.39172	-0.15087	0.11393
2600	0.5267	-0.38824	-0.19563	0.14381
2800	0.52808	-0.39486	-0.20263	0.17417
3000	0.56289	-0.43099	-0.17999	0.13755
3200	0.531	-0.46384	-0.16003	0.18805
3400	0.55975	-0.4852	-0.13244	0.15744
3600	0.55377	-0.47296	-0.17661	0.20282
3800	0.55582	-0.46304	-0.16568	0.15664
4000	0.56263	-0.4603	-0.17574	0.17542
4200	0.5576	-0.46678	-0.14353	0.1494
4400	0.60607	-0.48404	-0.17439	0.14064
4600	0.57828	-0.48619	-0.13402	0.13233
4800	0.53206	-0.45467	-0.15118	0.1813
5000	0.52536	-0.46591	-0.12591	0.1478

Table S26 Mulliken charges for individual fragments in QM/MM optimized snapshots of Compound I taken from the **2D6_dex** MD simulation.

Snapshot [ps]	Q(Fe)	Q(O)	Q(S)	Q(porphyrin)
0	0.4477	-0.4419	-0.14312	0.23641
200	0.45991	-0.41121	-0.11841	0.16611
400	0.47704	-0.4177	-0.16672	0.20502
600	0.47518	-0.39344	-0.16903	0.17313
800	0.47146	-0.39421	-0.19163	0.20247
1000	0.4828	-0.39623	-0.17932	0.18436
1200	0.48791	-0.40168	-0.10921	0.08888
1400	0.48198	-0.39911	-0.17033	0.1659
1600	0.46152	-0.39668	-0.14514	0.16396
1800	0.45735	-0.40428	-0.1662	0.19708
2000	0.46937	-0.3962	-0.17624	0.16508
2200	0.46531	-0.39936	-0.1901	0.19912
2400	0.47899	-0.39533	-0.15492	0.16545
2600	0.48267	-0.39491	-0.17534	0.15675
2800	0.47039	-0.39421	-0.14988	0.15341
3000	0.51132	-0.41551	-0.1207	0.09822
3200	0.49169	-0.39183	-0.19658	0.17305
3400	0.4917	-0.4088	-0.14439	0.12511
3600	0.47836	-0.41783	-0.0927	0.09352
3800	0.47926	-0.41289	-0.14211	0.14517
4000	0.46075	-0.41363	-0.15759	0.19143
4200	0.50766	-0.42428	-0.14053	0.12124
4400	0.47395	-0.41874	-0.16856	0.17449
4600	0.48769	-0.41434	-0.1178	0.12548
4800	0.49456	-0.41605	-0.17202	0.16878
5000	0.47741	-0.41944	-0.1611	0.16943

Table S27 Mulliken charges for individual fragments in QM/MM optimized snapshots of Compound I taken from the **3A4_apo** MD simulation.

Snapshot [ps]	Q(Fe)	Q(O)	Q(S)	Q(porphyrin)
0	0.49002	-0.4487	-0.06554	0.08565
200	0.53828	-0.44926	-0.00876	-0.04949
400	0.4807	-0.4667	-0.06399	0.10463
600	0.51438	-0.42254	-0.09474	0.06909
800	0.52464	-0.45961	-0.10847	0.1096
1000	0.50948	-0.44358	-0.07872	0.07663
1200	0.53352	-0.45889	-0.07603	0.06482
1400	0.52061	-0.45368	-0.02219	0.00123
1600	0.48924	-0.44152	-0.08971	0.10955
1800	0.50774	-0.44797	-0.07303	0.07675
2000	0.52925	-0.43568	-0.11029	0.07669
2200	0.50859	-0.4527	-0.08416	0.08905
2400	0.52665	-0.44318	-0.05719	0.03558
2600	0.51276	-0.44349	-0.04881	0.02816
2800	0.50999	-0.50712	-0.02955	0.08444
3000	0.51965	-0.43892	-0.08521	0.06884
3200	0.51107	-0.44863	-0.05122	0.03887
3400	0.52462	-0.43593	-0.05529	0.02537
3600	0.53093	-0.45199	-0.04333	0.03932
3800	0.51213	-0.44362	-0.09008	0.08322
4000	0.5214	-0.41888	-0.09558	0.05656
4200	0.49984	-0.44154	-0.08567	0.07587
4400	0.51784	-0.44476	-0.10326	0.08989
4600	0.49159	-0.44258	-0.09375	0.11026
4800	0.51231	-0.45187	-0.08371	0.08932
5000	0.48293	-0.44975	-0.05349	0.09647

Table S28 Mulliken charges for individual fragments in QM/MM optimized snapshots of Compound I taken from the **3A4_dex** MD simulation.

Snapshot [ps]	Q(Fe)	Q(O)	Q(S)	Q(porphyrin)
0	0.50219	-0.45127	-0.05418	0.05825
200	0.52298	-0.44378	-0.05296	0.02409
400	0.53728	-0.45313	-0.09296	0.06029
600	0.51604	-0.44955	-0.02133	-0.00798
800	0.52887	-0.43827	-0.05227	-0.00639
1000	0.53069	-0.44533	-0.03852	-0.00723
1200	0.51452	-0.44814	-0.08233	0.06893
1400	0.53341	-0.414	-0.08543	0.01581
1600	0.51249	-0.39273	-0.07419	0.00159
1800	0.54103	-0.43234	-0.10793	0.05983
2000	0.53467	-0.43683	-0.07297	0.01913
2200	0.48793	-0.47186	-0.06317	0.09374
2400	0.49299	-0.51581	-0.13811	0.22645
2600	0.52405	-0.43852	-0.11547	0.09044
2800	0.49404	-0.45452	-0.11535	0.1352
3000	0.51022	-0.42955	-0.09117	0.05929
3200	0.47083	-0.51431	-0.11506	0.21694
3400	0.51975	-0.43404	-0.11288	0.07601
3600	0.50952	-0.47844	-0.12445	0.14126
3800	0.50549	-0.45019	-0.1264	0.13094
4000	0.5131	-0.44964	-0.11089	0.10679
4200	0.49507	-0.47994	-0.04642	0.08714
4400	0.525	-0.44163	-0.10337	0.08663
4600	0.50984	-0.47784	-0.08505	0.09773
4800	0.49143	-0.51297	-0.07315	0.14584
5000	0.49553	-0.48451	-0.13169	0.16459

Table S29 Mulliken charges for individual fragments in QM/MM optimized snapshots of Compound I taken from the **$P450_{cam}$_apo** MD simulation.

Snapshot [ps]	Q(Fe)	Q(O)	Q(S)	Q(porphyrin)
0	0.52828	-0.45817	-0.18372	0.2162
200	0.52042	-0.44589	-0.16132	0.17277
400	0.5183	-0.43379	-0.23685	0.24447
600	0.5247	-0.42316	-0.20889	0.19066
800	0.53442	-0.43593	-0.18535	0.18496
1000	0.55236	-0.4431	-0.1535	0.12439
1200	0.52741	-0.45041	-0.24597	0.27689
1400	0.54048	-0.42724	-0.20258	0.19534
1600	0.54302	-0.42377	-0.21408	0.19938
1800	0.52856	-0.42307	-0.14489	0.12249
2000	0.51139	-0.4321	-0.22498	0.24494
2200	0.52158	-0.43794	-0.17771	0.17426
2400	0.53756	-0.42671	-0.19584	0.19238
2600	0.51336	-0.44255	-0.17777	0.19864
2800	0.55217	-0.49644	-0.16948	0.20195
3000	0.51146	-0.4781	-0.19346	0.2575
3200	0.54826	-0.42451	-0.2009	0.16393
3400	0.50624	-0.46762	-0.16599	0.21917
3600	0.54941	-0.4343	-0.20652	0.18964
3800	0.58472	-0.42179	-0.18346	0.10647
4000	0.53131	-0.49622	-0.17966	0.21897
4200	0.58627	-0.43123	-0.17612	0.11485
4400	0.55477	-0.42371	-0.1794	0.15221
4600	0.54422	-0.43099	-0.17988	0.15229
4800	0.55551	-0.42985	-0.21891	0.19185
5000	0.50829	-0.43473	-0.16943	0.18267

Table S30 Mulliken charges for individual fragments in QM/MM optimized snapshots of Compound I taken from the **P450$_{cam}$_prop** MD simulation.

Snapshot [ps]	Q(Fe)	Q(O)	Q(S)	Q(porphyrin)
0	0.48426	-0.42561	-0.22807	0.23858
200	0.47991	-0.42166	-0.21832	0.2146
400	0.48373	-0.43223	-0.27344	0.29852
600	0.48767	-0.43336	-0.23297	0.24716
800	0.47328	-0.43651	-0.20624	0.2358
1000	0.49331	-0.42158	-0.24862	0.24349
1200	0.50934	-0.44741	-0.24427	0.25855
1400	0.49873	-0.45937	-0.23625	0.27983
1600	0.51337	-0.45074	-0.27231	0.27706
1800	0.50433	-0.42256	-0.31258	0.29973
2000	0.50862	-0.439	-0.17368	0.19585
2200	0.5152	-0.45092	-0.2072	0.19539
2400	0.46374	-0.41897	-0.13853	0.15653
2600	0.48917	-0.36474	-0.1545	0.09519
2800	0.49655	-0.43917	-0.21531	0.26158
3000	0.48502	-0.4409	-0.19134	0.24881
3200	0.50623	-0.47596	-0.19757	0.27501
3400	0.49107	-0.4361	-0.20009	0.21892
3600	0.52381	-0.4593	-0.16871	0.18681
3800	0.4941	-0.44212	-0.17589	0.2354
4000	0.50896	-0.44001	-0.20854	0.22535
4200	0.58208	-0.48147	-0.08363	0.07782
4400	0.49817	-0.4015	-0.17398	0.1815
4600	0.46935	-0.44594	-0.20203	0.28003
4800	0.47621	-0.44197	-0.13529	0.20123
5000	0.48214	-0.45039	-0.18593	0.27591

Part E Key bond lengths and hydrogen bond distances

Table S31 Distances [in Å], between the heme iron and Cys435 sulfur, heme iron and ferryl oxygen, Cys435 sulfur and the backbone nitrogen atoms of Val436, Gly437 and Glu438 in the QM/MM optimized snapshots from the **2C9_apo** simulation.

Snapshot [ps]	d(Fe–S)	d(Fe–O)	d(S–Val436)	d(S–Gly437)	d(S–Glu438)
0	2.77984	1.61488	3.31776	2.32686	3.47932
200	2.67446	1.61826	3.39141	2.36771	3.41419
400	2.56206	1.62288	3.2112	2.41874	3.42235
600	2.57893	1.62014	3.29596	2.3496	3.57655
800	2.70439	1.61817	3.19405	2.29746	3.38096
1000	2.70766	1.61719	3.23435	2.26208	3.46235
1200	2.88243	1.61439	3.07147	2.21397	3.61365
1400	2.61673	1.62312	3.12328	2.41222	3.29346
1600	2.72544	1.61849	3.37019	2.39243	3.2794
1800	2.66767	1.61981	3.32001	2.29854	3.45354
2000	2.65047	1.62104	3.18175	2.26728	3.39207
2200	2.61385	1.62119	3.25106	2.26454	3.54927
2400	2.56638	1.6272	3.12316	2.27817	3.43631
2600	2.67321	1.62236	3.29426	2.31892	3.55777
2800	2.65971	1.61954	3.36428	2.32332	3.77502
3000	2.63418	1.61971	3.24441	2.26553	3.41537
3200	2.67076	1.61687	2.78732	2.2777	3.42221
3400	2.62353	1.62146	3.29985	2.3061	3.63222
3600	2.64818	1.62065	2.99	2.2646	3.574
3800	2.61668	1.6202	3.32289	2.32301	3.33275
4000	2.6145	1.62266	3.23869	2.25001	3.60284
4200	2.71022	1.61561	3.24027	2.25211	3.57293
4400	2.72864	1.61739	3.20553	2.50124	3.93607
4600	2.63486	1.61818	3.58957	2.37818	3.51961
4800	2.81916	1.6095	3.28931	2.28351	3.27236
5000	2.78146	1.61537	3.03701	2.3617	3.7115

Table S32 Distances [in Å], between the heme iron and Cys435 sulfur, heme iron and ferryl oxygen, Cys435 sulfur and the backbone nitrogen atoms of Val436, Gly437 and Glu438 in the QM/MM optimized snapshots from the **2C9_prox** simulation.

Snapshot [ps]	d(Fe–S)	d(Fe–O)	d(S–Val436)	d(S–Gly437)	d(S–Glu438)
0	2.62792	1.61964	3.26053	2.46248	3.56521
200	2.64668	1.61814	3.19536	2.55341	3.65963
400	2.61001	1.61857	3.33809	2.28099	3.46768
600	2.62345	1.61941	3.13009	2.26732	3.5494
800	2.55855	1.62595	3.32603	2.52627	3.52832
1000	2.61652	1.61952	3.42603	2.336	3.24168
1200	2.60956	1.62058	3.17366	2.5911	3.65928
1400	2.57118	1.62195	3.14763	2.34604	3.40921
1600	2.61572	1.61975	3.28428	2.42006	3.38235
1800	2.58686	1.62045	3.2748	2.44035	3.5874
2000	2.61873	1.6219	3.14318	2.40971	3.19751
2200	2.59962	1.6217	3.06453	2.3124	3.86068
2400	2.56699	1.6225	3.36355	2.28588	3.55914
2600	2.6234	1.62013	3.45146	2.38699	3.62052
2800	2.71616	1.61564	2.97324	2.44718	3.66927
3000	2.64382	1.61538	3.134	2.27144	3.31443
3200	2.64067	1.61847	3.62377	4.18154	3.06029
3400	2.65189	1.61911	3.38164	4.19436	3.04256
3600	2.623	1.62228	3.78012	4.45076	3.12401
3800	2.72698	1.61594	3.4006	4.18632	3.17671
4000	2.88982	1.61252	3.73696	5.08974	3.60525
4200	2.94193	1.61041	3.58033	4.48109	3.18757
4400	2.81914	1.61386	3.59279	4.6289	3.13005
4600	2.90536	1.61018	3.68846	4.5584	3.22345
4800	3.16717	1.61138	3.39394	5.05818	3.81201
5000	2.61807	1.61745	3.05706	4.35654	2.70921

Table S33 Distances [in Å], between the heme iron and Cys435 sulfur, heme iron and ferryl oxygen, Cys435 sulfur and the backbone nitrogen atoms of Val436, Gly437 and Glu438 in the QM/MM optimized snapshots from the **2C9_dist** simulation.

Snapshot [ps]	d(Fe–S)	d(Fe–O)	d(S–Val436)	d(S–Gly437)	d(S–Glu438)
0	2.54704	1.62578	3.28194	2.46948	3.31352
200	2.5754	1.6225	3.37709	2.46482	3.55044
400	2.54798	1.62429	3.28189	2.38342	3.60804
600	2.58604	1.62092	3.34743	2.35855	3.54075
800	2.60737	1.6227	3.66642	2.47128	3.49943
1000	2.59792	1.62413	3.55487	2.64526	3.22014
1200	2.54801	1.62415	3.46724	2.57563	3.56532
1400	2.58486	1.62629	3.26315	2.59252	4.01358
1600	2.63922	1.61878	3.29235	2.30364	3.58111
1800	2.5341	1.62586	3.46633	2.36391	3.50752
2000	2.62083	1.61856	3.62647	2.39087	3.32125
2200	2.55915	1.6225	3.59881	2.37629	3.34787
2400	2.58817	1.62216	3.62891	2.42589	3.49093
2600	2.66695	1.61678	3.56385	2.34441	3.54289
2800	2.59812	1.62011	3.4211	2.43245	3.54969
3000	2.68672	1.6201	3.43584	2.43704	3.62966
3200	2.60881	1.62019	3.4326	2.42766	3.46375
3400	2.66863	1.61916	3.33684	2.32112	3.5617
3600	2.64655	1.61976	3.29241	2.42765	3.64094
3800	2.58898	1.62126	3.38915	2.75468	3.67338
4000	2.66061	1.6161	3.15577	2.52828	3.76819
4200	2.58992	1.62133	3.09151	2.5355	3.71231
4400	2.58726	1.62396	3.47272	2.49044	3.87887
4600	2.58725	1.61968	3.55538	2.47028	3.52296
4800	2.57945	1.62588	2.91674	2.37823	3.63516
5000	2.6558	1.61792	3.08313	2.31247	3.97602

Table S34 Distances [in Å], between the heme iron and Cys435 sulfur, heme iron and ferryl oxygen, Cys435 sulfur and the backbone nitrogen atoms of Val436, Gly437 and Glu438 in the QM/MM optimized snapshots from the **2C9_2warf** simulation.

Snapshot [ps]	d(Fe–S)	d(Fe–O)	d(S–Val436)	d(S–Gly437)	d(S–Glu438)
0	2.59809	1.61896	3.27265	2.29955	3.40715
200	2.61504	1.61892	3.23935	2.36327	3.44195
400	2.5959	1.62102	3.25932	2.38322	3.42764
600	2.58384	1.61973	3.41683	2.37598	3.24985
800	2.63182	1.6178	3.32325	2.25759	3.87655
1000	2.61399	1.61821	3.08668	2.27252	3.61312
1200	2.64939	1.61729	3.02154	2.221	3.50065
1400	2.60604	1.61802	3.21679	2.26604	3.35655
1600	2.59898	1.62036	3.13973	2.37981	3.75301
1800	2.5825	1.62023	3.27	2.25119	3.77244
2000	2.61649	1.62006	2.9285	2.34805	3.51487
2200	2.59536	1.61964	2.83598	2.20873	3.52809
2400	2.60891	1.62216	3.00176	2.25666	4.13609
2600	2.56283	1.62077	2.93198	2.26348	3.85535
2800	2.63306	1.61722	3.18377	2.31568	3.50049
3000	2.65155	1.61767	3.25307	2.34028	3.96453
3200	2.56994	1.62198	2.70007	2.21185	3.58988
3400	2.58769	1.6216	3.27673	2.3268	3.22176
3600	2.63713	1.62023	3.25052	2.43599	3.12734
3800	2.64754	1.61902	3.27323	2.38919	3.47872
4000	2.86436	1.61384	3.28125	2.31917	3.99774
4200	2.60734	1.6206	3.01422	2.38007	3.30387
4400	2.63608	1.62021	2.8973	2.33562	3.61224
4600	2.58581	1.62169	3.06449	2.26743	3.6374
4800	2.59165	1.61692	3.12778	2.42518	4.00107
5000	2.55301	1.62465	3.26924	2.29367	3.42748

Table S35 Distances [in Å], between the heme iron and Cys435 sulfur, heme iron and ferryl oxygen, Cys435 sulfur and the backbone nitrogen atoms of Leu231, Gly232 and Glu233 in the QM/MM optimized snapshots from the **2D6_apo** simulation.

Snapshot [ps]	d(Fe–S)	d(Fe–O)	d(S–Leu231)	d(S–Gly232)	d(S–Glu233)
0	2.5517	1.62119	3.33462	2.41898	2.41898
200	2.65183	1.61607	3.36153	2.46744	2.46744
400	2.60261	1.6189	3.38863	2.43906	2.43906
600	2.62462	1.61735	3.16814	2.51229	2.51229
800	2.60793	1.62079	3.24407	2.65953	2.65953
1000	2.59699	1.62152	3.5083	2.56662	2.56662
1200	2.60634	1.62007	3.2825	2.3986	2.3986
1400	2.59684	1.61971	3.20034	2.60621	2.60621
1600	2.68605	1.61534	3.65205	2.46294	2.46294
1800	2.70494	1.61464	3.49221	2.31274	2.31274
2000	2.69456	1.61738	3.49415	2.36745	2.36745
2200	2.6628	1.61727	3.611	2.38071	2.38071
2400	2.64427	1.6166	3.75287	2.37353	2.37353
2600	2.65165	1.61737	3.57289	2.34524	2.34524
2800	2.65012	1.61789	3.61253	2.35651	2.35651
3000	2.74895	1.61886	3.82427	2.41707	2.41707
3200	2.64015	1.61964	3.27829	2.30305	2.30305
3400	2.70028	1.62738	3.01739	2.44369	2.44369
3600	2.69057	1.62684	3.10586	2.60952	2.60952
3800	2.69636	1.62672	2.97109	2.2928	2.2928
4000	2.68771	1.62267	3.20189	2.3023	2.3023
4200	2.691	1.62383	3.31937	2.32626	2.32626
4400	2.78258	1.61884	3.19099	2.28815	2.28815
4600	2.75616	1.62298	3.50578	2.41385	2.41385
4800	2.63758	1.61962	3.45819	2.38868	2.38868
5000	2.63356	1.62232	3.43312	2.32808	2.32808

Table S36 Distances [in Å], between the heme iron and Cys435 sulfur, heme iron and ferryl oxygen, Cys435 sulfur and the backbone nitrogen atoms of Val436, Gly437 and Glu438 in the QM/MM optimized snapshots from the **2D6_dex** simulation.

Snapshot [ps]	d(Fe–S)	d(Fe–O)	d(S–Val436)	d(S–Gly437)	d(S–Glu438)
0	2.56172	1.62691	3.12794	2.36478	3.98708
200	2.54171	1.62561	3.24152	2.47921	3.61618
400	2.55798	1.62362	3.21544	2.30421	3.15807
600	2.5977	1.62207	3.27797	2.38437	3.30023
800	2.58144	1.62198	3.24545	2.32542	3.3352
1000	2.61286	1.62125	3.3767	2.40861	3.28494
1200	2.63366	1.61857	3.86877	2.44147	3.23768
1400	2.59547	1.62066	3.33286	2.22766	3.47152
1600	2.57124	1.62194	3.53327	2.4034	3.26208
1800	2.56412	1.62312	3.48287	2.32821	3.47447
2000	2.60515	1.6207	3.48651	2.34127	3.21922
2200	2.55706	1.62345	3.44664	2.25261	2.94158
2400	2.61521	1.62002	3.41586	2.41835	3.43735
2600	2.60118	1.61976	3.40756	2.31109	3.40795
2800	2.57544	1.62089	3.6776	2.33757	3.08154
3000	2.65011	1.61972	3.74154	2.28264	3.2786
3200	2.63713	1.61879	3.56	2.32201	3.05852
3400	2.60784	1.62049	3.62416	2.36953	3.1993
3600	2.59789	1.62173	3.98175	2.58766	3.09273
3800	2.60979	1.62285	3.54975	2.41454	3.83071
4000	2.55376	1.62471	3.46486	2.27264	3.22146
4200	2.65457	1.62109	2.99175	2.26352	4.34017
4400	2.54583	1.62564	3.31587	2.18211	3.88177
4600	2.60275	1.62163	3.64398	2.35901	3.45967
4800	2.62027	1.6221	3.41091	2.34232	3.35471
5000	2.55858	1.62355	3.5737	2.33696	3.05052

Table S37 Distances [in Å], between the heme iron and Cys435 sulfur, heme iron and ferryl oxygen, Cys435 sulfur and the backbone nitrogen atoms of Ile443, Gly444 and Met445 in the QM/MM optimized snapshots from the **3A4_apo** simulation.

Snapshot [ps]	d(Fe–S)	d(Fe–O)	d(S–Ile443)	d(S–Gly444)	d(S–Met445)
0	2.54948	1.62425	3.57787	2.47925	3.57892
200	2.65542	1.61959	3.71568	2.75166	3.36163
400	2.52809	1.62339	3.62655	2.47182	3.38699
600	2.6104	1.62169	3.45592	2.49764	3.50858
800	2.60937	1.62062	3.4085	2.38463	3.49413
1000	2.59176	1.62263	3.39424	2.52522	3.79959
1200	2.66236	1.62146	3.55362	2.51125	3.4857
1400	2.59033	1.61792	3.3245	2.45426	3.7097
1600	2.56327	1.62326	3.18677	2.42727	3.48701
1800	2.62387	1.62405	3.18684	2.41638	3.95541
2000	2.61608	1.622	3.28161	2.32087	3.61306
2200	2.57867	1.62082	3.32718	2.36258	3.55952
2400	2.62378	1.62151	3.64123	2.46826	3.58075
2600	2.57554	1.62417	3.37042	2.37146	3.74436
2800	2.6368	1.6282	3.56697	2.49823	3.48246
3000	2.60135	1.62042	3.43016	2.46732	3.53767
3200	2.59016	1.62085	3.44674	2.43555	3.46625
3400	2.59821	1.62015	3.2628	2.44198	3.75605
3600	2.6877	1.61893	2.96565	3.217	4.0255
3800	2.59411	1.62082	3.38041	2.45898	3.39734
4000	2.58755	1.61847	3.17663	2.34012	3.44116
4200	2.54853	1.62062	3.27672	2.33742	3.43549
4400	2.60142	1.62428	3.27643	2.42086	3.43139
4600	2.57599	1.62532	3.33483	2.34263	3.64294
4800	2.5641	1.62258	3.24631	2.38233	3.6952
5000	2.55198	1.62378	2.80286	2.87831	3.93779

Table S38 Distances [in Å], between the heme iron and Cys435 sulfur, heme iron and ferryl oxygen, Cys435 sulfur and the backbone nitrogen atoms of Ile443, Gly444 and Met445 in the QM/MM optimized snapshots from the **3A4_dex** simulation.

Snapshot [ps]	d(Fe–S)	d(Fe–O)	d(S–Ile443)	d(S–Gly444)	d(S–Met445)
0	2.57156	1.62312	3.50036	2.55537	3.47199
200	2.60573	1.62026	3.41812	2.5851	3.42451
400	2.64463	1.61837	3.4289	2.34525	3.21903
600	2.60038	1.62051	3.57741	2.66213	3.49044
800	2.60053	1.61903	3.58565	2.46803	3.17569
1000	2.65973	1.61935	3.58472	2.72298	3.7921
1200	2.63405	1.6191	3.1274	2.43298	3.8081
1400	2.60111	1.6191	3.47612	2.41952	3.13885
1600	2.57066	1.62091	3.59078	2.48356	3.20564
1800	2.61311	1.62139	3.33409	2.42019	3.13834
2000	2.63327	1.61907	3.82036	2.58403	3.13351
2200	2.56301	1.62504	3.1611	2.48063	3.33685
2400	2.54517	1.62893	3.09647	2.34776	3.2793
2600	2.56666	1.62336	3.48055	2.60381	3.09331
2800	2.53479	1.6258	3.2146	2.43801	3.19202
3000	2.59263	1.62108	3.32546	2.45919	3.10902
3200	2.53714	1.62901	3.2448	2.42473	3.27916
3400	2.58162	1.62487	3.30375	2.41087	3.11531
3600	2.56629	1.62761	3.24922	2.47287	3.00457
3800	2.54878	1.62445	3.036	2.27485	3.25651
4000	2.57435	1.62668	3.10801	2.46336	3.26362
4200	2.55148	1.62777	3.33863	2.54678	3.40789
4400	2.58106	1.62339	3.20649	2.56911	3.42629
4600	2.56825	1.6246	3.49163	2.48929	3.21795
4800	2.54254	1.63152	3.4238	2.46579	3.34019
5000	2.5741	1.62824	2.96693	2.32234	3.2092

Table S39 Distances [in Å], between the heme iron and Cys435 sulfur, heme iron and ferryl oxygen, Cys435 sulfur and the backbone nitrogen atoms of Leu358, Gly359 and Gln360 in the QM/MM optimized snapshots from the **$P450_{cam}$_apo** simulation.

Snapshot [ps]	d(Fe–S)	d(Fe–O)	d(S–Leu358)	d(S–Gly359)	d(S–Glu360)
0	2.58441	1.62225	3.3539	2.49144	3.20664
200	2.57702	1.62086	3.59579	2.46691	3.07238
400	2.54508	1.62452	3.09282	2.18901	3.25571
600	2.57258	1.62334	3.33024	2.29819	2.77933
800	2.60923	1.61684	3.33265	2.32239	3.93951
1000	2.66457	1.61755	3.13482	2.26707	4.21688
1200	2.61835	1.62333	3.10566	2.22525	3.33671
1400	2.65534	1.61895	3.06539	2.17597	3.89262
1600	2.60171	1.62022	3.24797	2.22675	3.25898
1800	2.59521	1.61717	3.48437	2.32446	3.56742
2000	2.56429	1.62247	3.18492	2.19521	3.27362
2200	2.59203	1.62094	3.32706	2.23016	3.52423
2400	2.62197	1.61906	3.10512	2.19662	3.6625
2600	2.58987	1.62088	3.35666	2.21635	3.45889
2800	2.69206	1.62223	3.33231	2.28583	3.93691
3000	2.5894	1.62367	3.41707	2.18107	3.50681
3200	2.61844	1.61874	3.20236	2.23647	3.2654
3400	2.60134	1.62673	3.34336	2.23629	3.78851
3600	2.62518	1.61979	3.07917	2.16815	3.58588
3800	2.74567	1.61236	3.12861	2.15271	3.83288
4000	2.65491	1.62613	3.4862	2.23243	3.51808
4200	2.79157	1.61688	3.39661	2.30285	3.78807
4400	2.67098	1.61937	3.44906	2.24855	3.65051
4600	2.64935	1.618	3.3385	2.24726	3.77022
4800	2.65589	1.6176	3.00056	2.17869	3.53183
5000	2.56399	1.62029	3.33678	2.22803	3.94871

Table S40 Distances [in Å], between the heme iron and Cys435 sulfur, heme iron and ferryl oxygen, Cys435 sulfur and the backbone nitrogen atoms of Leu358, Gly359 and Glu360 in the QM/MM optimized snapshots from the **$P450_{cam}$_prop** simulation.

Snapshot [ps]	d(Fe–S)	d(Fe–O)	d(S–Leu358)	d(S–Gly359)	d(S–Glu360)
0	2.59327	1.62497	3.43013	2.4338	2.80913
200	2.57574	1.62632	3.33553	2.36145	2.91568
400	2.55939	1.62583	3.13577	2.37845	2.66767
600	2.59933	1.6257	3.37723	2.47677	3.12338
800	2.55454	1.62593	3.12432	2.34927	3.12344
1000	2.61251	1.6238	2.99158	2.32562	3.2824
1200	2.58295	1.62558	3.0789	2.35892	3.30834
1400	2.55243	1.62751	3.27636	2.37267	2.82634
1600	2.60402	1.62626	3.12073	2.27852	2.82024
1800	2.60962	1.62434	3.08298	2.26633	2.62332
2000	2.62775	1.62003	3.4914	2.46214	3.80849
2200	2.59403	1.6266	3.36034	2.26581	3.65158
2400	2.57118	1.62483	3.52656	2.48967	3.63594
2600	2.60358	1.61762	3.36898	2.31313	3.83907
2800	2.58086	1.62637	3.31236	3.92331	2.50206
3000	2.58966	1.62366	2.97097	4.38875	2.82808
3200	2.57741	1.62882	3.26317	4.05405	2.60739
3400	2.60879	1.62592	3.2397	3.96641	2.48779
3600	2.63197	1.62237	3.46319	3.55102	2.4783
3800	2.60967	1.62526	3.25683	4.36917	2.7542
4000	2.62745	1.62506	3.22151	3.97257	2.53851
4200	2.70086	1.61948	3.72022	5.13102	2.88738
4400	2.61125	1.62378	3.17462	4.35443	2.86593
4600	2.60599	1.62635	3.36837	4.00431	2.7249
4800	2.58707	1.62549	3.11928	4.42946	2.91666
5000	2.5893	1.62606	3.18237	4.00909	2.62153

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