Understanding the determinants of selectivity in drug metabolism through modeling of dextromethorphan oxidation by cytochrome P450

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SUPPORTING INFORMATION

I. Dextromethorphan topology file and most important parameters

II. Cartesian coordinates of the located stationary points in the QM only calculations

III. Cartesian coordinates of the atoms in the QM region in the QM/MM transition states and starting structures

IV. Fig. S1. Dextromethorphan docked into the active site of P450 2D6. The two stereoisomers of the protonated Dextromethorphan can interact either with Glu216 or with Asp301.

Fig.S2. Distances measured in the MD simulations of P450 2D6 with dextromethorphan docked into the active site. The OH distances were measured between the ferryl-oxygen atom and the alpha-hydrogen atoms (the three colors in the diagrams correspond to the three alpha-hydrogen atoms) A: The protonated amino-group of dextromethorphan interacts with Glu216. B: protonated amino-group of dextromethorphan interacts with Asp301.

Fig.S3. Distances measured in the MD simulations of P450 2D6 with dextromethorphan docked into the active site. The OC distances were measured between the ferryl-oxygen atom and the *ortho* carbon atoms. red: simulation in which hydrogen bond exists between Glu216 and dextromethorphan blue: simulation in which hydrogen bond exists between Asp301 and dextromethorphan

Fig.S4. QM/MM adiabatic energy scan profiles for A. hydrogen-abstraction B. aromatic carbon oxidation.

V. Table S1. Selected geometrical parameters of QM only transition states (at the B3LYP/LACVP** level) and QM/MM optimized starting structures and transition states.

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I. Dextromethorphan topology file and most important parameters

Non standard atom types:

```
MASS   210 OCE   15.99900 O ! aromatic ether oxygen
MASS   211 NT    14.00700 N ! tertiary protonated amine nitrogen
MASS   212 CT0   12.01100 C ! aliphatic sp3 C bonded to 4 carbon atoms,
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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     Ca from the paper
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
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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

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

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   110.0000 ! ALLOW   ALI POL
NT   CT1  CT2    67.700   110.0000 ! ALLOW   ALI POL
NT   CT2  CT2    67.700   110.0000 ! ALLOW   ALI POL
CA   CA   OCE      45.20    120.0   ! from OH1  CA   CA
CT1  NT   CT2     50.000    113.00  ! force const. from CT2  NH1  C
CT1  NT   CT3     50.000    113.00  ! force const. from CT2  NH1  C
CT2  NT   CT3     50.000    112.00  ! force const. from CT2  NH1  C
NT   CT3  HA    45.000    107.50   35.00   2.10100 ! ALLOW   ALI POL
NT   CT2  HA    45.000    107.50   35.00   2.10100 ! ALLOW   ALI POL
NT   CT1  HA    45.000    107.50   35.00   2.10100 ! ALLOW   ALI POL
HC   NT   CT1   30.000    109.50   20.00   2.07400 ! ALLOW   POL ALI
HC   NT   CT2   30.000    109.50   20.00   2.07400 ! ALLOW   POL ALI
HC   NT   CT3   30.000    109.50   20.00   2.07400 ! ALLOW   POL ALI
CA   OCE   CT3     95.000    118.71   ! from ether article cit. see above, but equilibrium value from
QM
OCE   CT3  HA       60.00     109.5   ! from ether article cit. see above
CT2  CT2  CT0   58.350    113.50   11.16   2.56100 ! ALLOW   ALI
CT2  CT1  CT0   53.350    111.00    8.00   2.56100 ! ALLOW   ALI
CT1  CT1  CT0   53.350    111.00    8.00   2.56100 ! ALLOW ALI
HA   CT2  CT0   33.430    110.10   22.53   2.17900 ! ALLOW   ALI
CT2  CT0  CT1   53.350    109.     8.00   2.56100 ! ALLOW   ALI
CT2  CT0  CT2   53.350    110.     8.00   2.56100 ! ALLOW   ALI
CT2  CT0  CA    53.350    109.5    8.00   2.56100 ! ALLOW   ALI
CT1  CT0  CA      53.350     109.0    8.00   2.56100 ! ALLOW   ALI
CT0  CA   CA       45.800   120.6000 ! ALLOW   ALI ARO
CT0  CT1  HA       34.500    110.10   22.53   2.17900 ! ALLOW   ALI

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: needs work
END
```

II. Cartesian coordinates of the located stationary points in the QM only calculations

anisole
B3LYP/lacvp**

Total energy	-346.7766		
C1	-5.9001	4.1158	-0.9640
C2	-6.8994	3.4786	-1.6947
C3	-4.6300	3.5327	-0.8923
C4	-4.3659	2.3321	-1.5405
C5	-5.3768	1.6948	-2.2755
C6	-6.6502	2.2699	-2.3531
O7	-5.0173	0.5207	-2.8753
C8	-5.9950	-0.1713	-3.6333
H9	-6.8521	-0.4698	-3.0153
H10	-6.3563	0.4310	-4.4772
H11	-5.5020	-1.0660	-4.0173
H12	-7.4447	1.7939	-2.9155
H13	-3.8398	4.0177	-0.3255
H14	-3.3873	1.8652	-1.4955
H15	-6.1034	5.0539	-0.4567
H16	-7.8906	3.9193	-1.7594

Compound I (doublet)
B3LYP/lacvp**

Total energy	-1585.81392		
N1	1.4132	1.3895	0.0722
C2	2.7773	1.1986	0.0760
C3	1.2257	2.7528	0.0891
C4	3.4587	2.4695	0.0619
H5	4.5340	2.5902	0.0508
C6	2.4981	3.4314	0.0729
H7	2.6205	4.5065	0.0712
N8	1.4124	-1.4551	0.1326
C9	2.7682	-1.2684	0.1381
C10	1.2200	-2.8122	0.1574
C11	2.4881	-3.4990	0.1695
H12	2.6062	-4.5743	0.1829
C13	3.4518	-2.5387	0.1586
H14	4.5269	-2.6605	0.1613
N15	-1.4360	-1.4505	0.1410
C16	-1.2483	-2.8064	0.1550
C17	-2.7900	-1.2596	0.1242
C18	-2.5184	-3.4906	0.1457
H19	-2.6394	-4.5656	0.1498
C20	-3.4788	-2.5274	0.1257
H21	-4.5543	-2.6452	0.1104
N22	-1.4303	1.3953	0.1057
C23	-1.2388	2.7522	0.1217
C24	-2.7903	1.2081	0.0971
C25	-3.4718	2.4797	0.0949
H26	-4.5468	2.6024	0.0804
C27	-2.5081	3.4385	0.1152
H28	-2.6255	4.5138	0.1186
C29	3.4085	-0.0333	0.1110
C30	-0.0042	3.3884	0.1282
C31	-3.4262	-0.0234	0.0998
C32	-0.0150	-3.4452	0.1631
H33	4.4940	-0.0360	0.1181
H34	-0.0033	4.4737	0.1475
H35	-4.5118	-0.0230	0.0879
H36	-0.0173	-4.5308	0.1755
Fe37	-0.0128	-0.0346	0.2616
O38	0.0124	0.0022	1.8853
S39	0.0751	0.2628	-2.2997
H40	1.3416	-0.1650	-2.4815

Compound I (quartet)
B3LYP/lacvp**

Total energy	-1585.81393		
N1	1.4124	1.3907	0.0776
C2	2.7772	1.1999	0.0766
C3	1.2253	2.7546	0.0901
C4	3.4582	2.4706	0.0574
H5	4.5334	2.5913	0.0431
C6	2.4975	3.4324	0.0688
H7	2.6197	4.5072	0.0640
N8	1.4148	-1.4518	0.1329
C9	2.7704	-1.2664	0.1410
C10	1.2212	-2.8091	0.1552
C11	2.4890	-3.4967	0.1696
H12	2.6064	-4.5720	0.1822
C13	3.4534	-2.5371	0.1621
H14	4.5285	-2.6594	0.1670
N15	-1.4358	-1.4483	0.1358
C16	-1.2476	-2.8036	0.1510
C17	-2.7893	-1.2577	0.1228
C18	-2.5175	-3.4885	0.1464
H19	-2.6382	-4.5636	0.1528
C20	-3.4781	-2.5256	0.1280
H21	-4.5536	-2.6436	0.1165
N22	-1.4284	1.3990	0.1094
C23	-1.2385	2.7559	0.1247
C24	-2.7887	1.2105	0.0974
C25	-3.4709	2.4818	0.0942
H26	-4.5459	2.6036	0.0777
C27	-2.5080	3.4414	0.1164
H28	-2.6262	4.5166	0.1194
C29	3.4098	-0.0309	0.1137
C30	-0.0035	3.3916	0.1313
C31	-3.4247	-0.0209	0.0986
C32	-0.0137	-3.4419	0.1577
H33	4.4954	-0.0321	0.1207
H34	-0.0015	4.4769	0.1497
H35	-4.5103	-0.0198	0.0862
H36	-0.0158	-4.5275	0.1687
Fe37	-0.0100	-0.0285	0.2600
O38	-0.0053	-0.0302	1.8864
S39	0.0748	0.2629	-2.2912
H40	1.3364	-0.1777	-2.4766

H-abstraction TS state (quartet)
B3LYP/lacvp**

Total energy	-1932.5661		
H1	2.8484	0.6010	-0.2950
S2	2.3318	-0.5772	0.1099

O5	-1.6447	0.4082	-0.1292
Fe6	0.0348	0.0467	0.0807
N7	0.2923	-0.0265	-1.9561
N8	-0.2786	-1.9455	0.0878
N9	-0.1653	0.1043	2.0569
N10	0.5492	1.9871	0.0566
C11	0.5663	1.0269	-2.7857
C12	0.6524	0.5743	-4.1541
C13	0.4410	-0.7691	-4.1357
C14	0.2156	-1.1363	-2.7575
C15	-0.2944	-2.7887	-0.9973
C16	-0.6344	-4.1253	-0.5770
C17	-0.8377	-4.0759	0.7678
C18	-0.6164	-2.7098	1.1720
C19	-0.5164	-0.9365	2.8799
C20	-0.5781	-0.4872	4.2512
C21	-0.2419	0.8293	4.2490
C22	0.0183	1.1907	2.8753
C23	0.6313	2.8238	1.1375
C24	0.9439	4.1640	0.7080
C25	1.0237	4.1319	-0.6497
C26	0.7727	2.7701	-1.0514
C27	0.7724	2.3357	-2.3693
H28	0.9689	3.0787	-3.1359
C29	-0.0586	-2.4228	-2.3156
H30	-0.1006	-3.2086	-3.0630
C31	-0.7351	-2.2439	2.4757
H32	-1.0054	-2.9648	3.2408
C33	0.4029	2.4542	2.4573
H34	0.5104	3.2221	3.2170
C35	-4.1089	5.2227	-1.8720
C36	-3.9560	4.2246	-0.9093
C37	-3.8238	4.9380	-3.2109
C38	-3.3985	3.6669	-3.5840
C39	-3.2562	2.6730	-2.6085
C40	-3.5267	2.9437	-1.2631
O41	-2.8257	1.4506	-3.0666
C42	-2.9885	0.3319	-2.2711
H43	-2.1735	0.3482	-1.1977
H44	-3.9781	0.2602	-1.8060
H45	-2.6933	-0.5481	-2.8405
H46	-3.3591	2.1880	-0.5035
H47	-3.9368	5.7087	-3.9691
H48	-3.1773	3.4210	-4.6180
H50	0.8555	1.2140	-5.0029
H51	0.4337	-1.4622	-4.9664
H52	-0.7107	-4.9773	-1.2398
H53	-1.1136	-4.8786	1.4385
H54	-0.8358	-1.1170	5.0927
H55	-0.1681	1.5091	5.0878
H56	1.0683	5.0093	1.3715
H57	1.2296	4.9448	-1.3330
H58	-4.4413	6.2156	-1.5827
H59	-4.1615	4.4408	0.1357

H-abstraction TS state (doublet)
B3LYP/lacvp**
Total energy -1932.56722

H1	2.8029	0.7039	0.4439
S2	2.3082	-0.5462	0.3526
O5	-1.6257	0.4014	-0.0139
Fe6	0.0532	0.0307	-0.0036
N7	0.2721	-0.0375	-1.9897
N8	-0.2687	-1.9552	0.0324
N9	-0.1577	0.1009	2.0207
N10	0.5581	1.9815	-0.0077
C11	0.5849	1.0119	-2.8207
C12	0.6849	0.5503	-4.1819
C13	0.4561	-0.7904	-4.1625
C14	0.2071	-1.1538	-2.7904
C15	-0.2888	-2.8071	-1.0406
C16	-0.6255	-4.1395	-0.6072
C17	-0.8233	-4.0762	0.7379
C18	-0.6010	-2.7078	1.1316
C19	-0.5130	-0.9362	2.8386
C20	-0.6064	-0.4771	4.2050
C21	-0.2918	0.8455	4.1964
C22	-0.0123	1.1983	2.8240
C23	0.6056	2.8200	1.0786
C24	0.9193	4.1601	0.6500
C25	1.0353	4.1252	-0.7054
C26	0.8008	2.7619	-1.1083
C27	0.8137	2.3185	-2.4227
H28	1.0328	3.0472	-3.1958
C29	-0.0569	-2.4437	-2.3600
H30	-0.0888	-3.2268	-3.1101
C31	-0.7242	-2.2445	2.4328
H32	-0.9979	-2.9672	3.1946
C33	0.3549	2.4643	2.3954
H34	0.4360	3.2438	3.1458
C35	-4.1108	5.2474	-1.8316
C36	-3.9199	4.2815	-0.8440
C37	-3.8617	4.9260	-3.1690
C38	-3.4363	3.6482	-3.5171
C39	-3.2607	2.6864	-2.5166
C40	-3.4914	2.9940	-1.1723
O41	-2.8386	1.4507	-2.9500
C42	-3.0021	0.3572	-2.1254
H43	-2.2130	0.3820	-1.1453
H44	-3.9858	0.3113	-1.6450
H45	-2.7370	-0.5420	-2.6805
H46	-3.2954	2.2630	-0.3956
H47	-4.0025	5.6733	-3.9451
H48	-3.2410	3.3731	-4.5492
H50	0.9131	1.1844	-5.0286
H51	0.4563	-1.4873	-4.9901
H52	-0.7051	-4.9974	-1.2619
H53	-1.0972	-4.8719	1.4178
H54	-0.8713	-1.1033	5.0469
H55	-0.2460	1.5349	5.0290
H56	1.0204	5.0080	1.3144
H57	1.2527	4.9374	-1.3861
H58	-4.4432	6.2456	-1.5625
H59	-4.0945	4.5289	0.1999

Aromatic carbon oxidation TS state (quartet)
B3LYP/lacvp**
Total energy -1932.56361

H1	0.3855	-1.1708	-0.3736
S2	0.4214	0.0330	0.2334
O5	-3.4909	1.0890	-0.4028
Fe6	-1.8817	0.5907	-0.0689

N7	-1.4556	0.3872	-2.0578
N8	-2.4090	-1.3376	0.0061
N9	-2.1896	0.7715	1.8948
N10	-1.1796	2.4957	-0.1357
C11	-0.9128	1.3379	-2.8860
C12	-0.7941	0.8144	-4.2258
C13	-1.2731	-0.4592	-4.1938
C14	-1.6787	-0.7177	-2.8329
C15	-2.5166	-2.2053	-1.0540
C16	-3.0000	-3.4851	-0.5946
C17	-3.1805	-3.3795	0.7495
C18	-2.8174	-2.0316	1.1142
C19	-2.6195	-0.2068	2.7521
C20	-2.7494	0.3252	4.0884
C21	-2.3945	1.6354	4.0258
C22	-2.0379	1.9059	2.6526
C23	-1.1663	3.3944	0.8940
C24	-0.6471	4.6622	0.4409
C25	-0.3448	4.5130	-0.8778
C26	-0.6847	3.1556	-1.2322
C27	-0.5551	2.6248	-2.5084
H28	-0.1450	3.2727	-3.2764
C29	-2.1903	-1.9249	-2.3723
H30	-2.3220	-2.7213	-3.0981
C31	-2.9033	-1.5172	2.4003
H32	-3.2387	-2.1861	3.1864
C33	-1.5748	3.1286	2.1957
H34	-1.5047	3.9371	2.9161
C35	-5.5595	3.7870	-0.9105
C36	-6.7133	2.9842	-0.8464
C37	-4.3932	3.2787	-1.4452
C38	-4.3151	1.9102	-1.8548
C39	-5.5425	1.1550	-1.8900
C40	-6.7110	1.6755	-1.3435
O41	-5.4228	-0.0649	-2.4595
C42	-6.5393	-0.9441	-2.4221
H43	-6.8428	-1.1543	-1.3897
H44	-7.3924	-0.5323	-2.9761
H45	-6.2092	-1.8678	-2.8987
H46	-7.6232	1.0912	-1.3164
H47	-3.4982	3.8873	-1.5127
H48	-3.5419	1.6055	-2.5494
H50	-0.3946	1.3641	-5.0682
H51	-1.3457	-1.1725	-5.0040
H52	-3.1661	-4.3433	-1.2324
H53	-3.5302	-4.1307	1.4452
H54	-3.0722	-0.2468	4.9481
H55	-2.3611	2.3652	4.8244
H56	-0.5299	5.5381	1.0652
H57	0.0697	5.2418	-1.5617
H58	-5.5968	4.8127	-0.5554
H59	-7.6295	3.3875	-0.4242

Aromatic carbon oxidation TS state (doublet)
B3LYP/lacvp**
Total energy -1932.56653

H1	0.5135	-0.9766	-0.5152
S2	0.3413	-0.1021	0.4969
O5	-3.5103	0.9850	-0.3491
Fe6	-1.8677	0.6156	-0.1383
N7	-1.3992	0.3982	-2.0678
N8	-2.3939	-1.3394	-0.0447
N9	-2.1835	0.7866	1.8573
N10	-1.2163	2.5159	-0.1913
C11	-0.8224	1.3366	-2.8929
C12	-0.6777	0.8012	-4.2219
C13	-1.1795	-0.4645	-4.1950
C14	-1.6196	-0.7142	-2.8466
C15	-2.5013	-2.2056	-1.0968
C16	-2.9924	-3.4848	-0.6383
C17	-3.1730	-3.3746	0.7046
C18	-2.8043	-2.0253	1.0663
C19	-2.6173	-0.1969	2.7048
C20	-2.7943	0.3394	4.0344
C21	-2.4756	1.6593	3.9711
C22	-2.0923	1.9281	2.6044
C23	-1.2438	3.4204	0.8397
C24	-0.7159	4.6882	0.3985
C25	-0.3498	4.5318	-0.9028
C26	-0.6665	3.1712	-1.2628
C27	-0.4699	2.6258	-2.5229
H28	-0.0242	3.2607	-3.2815
C29	-2.1537	-1.9175	-2.4087
H30	-2.2770	-2.7047	-3.1453
C31	-2.8928	-1.5088	2.3501
H32	-3.2331	-2.1770	3.1349
C33	-1.6682	3.1625	2.1349
H34	-1.6347	3.9834	2.8438
C35	-5.4670	3.7829	-0.8353
C36	-6.6438	3.0196	-0.7577
C37	-4.3334	3.2383	-1.4083
C38	-4.3288	1.8882	-1.8579
C39	-5.5684	1.1658	-1.8548
C40	-6.7047	1.7200	-1.2675
O41	-5.5083	-0.0514	-2.4295
C42	-6.6401	-0.9090	-2.3322
H43	-6.8985	-1.1019	-1.2849
H44	-7.5081	-0.4855	-2.8523
H45	-6.3487	-1.8429	-2.8132
H46	-7.6342	1.1661	-1.2145
H47	-3.4157	3.8104	-1.4821
H48	-3.5532	1.5364	-2.5271
H50	-0.2506	1.3398	-5.0578
H51	-1.2451	-1.1803	-5.0037
H52	-3.1590	-4.3442	-1.2745
H53	-3.5246	-4.1228	1.4027
H54	-3.1263	-0.2352	4.8889
H55	-2.4860	2.3960	4.7639
H56	-0.6288	5.5675	1.0230
H57	0.0947	5.2572	-1.5712
H58	-5.4557	4.7990	-0.4537
H59	-7.5337	3.4484	-0.3053

Dextromethorphan stereoisomer A
B3LYP/6-31G*
Total energy -831.340769

C1	-0.6418	2.3642	0.1102
C2	-0.6921	0.8139	0.1818
C3	-1.7449	0.2974	-0.8475
C4	-3.1247	0.9796	-0.7456
C5	-2.9903	2.5045	-0.8670
C6	-2.0164	3.0517	0.1835

C7	-1.8035	-1.2345	-0.7934	O18	4.1692	0.8428	0.5394
C8	-0.4753	-1.8370	-1.2482	C19	5.4682	0.2833	0.3535
C9	0.7541	-1.0929	-0.7523	C20	-3.5532	-1.7181	1.1070
C10	0.6750	0.1717	-0.1280	H21	6.1634	1.0016	0.7892
C11	2.0093	-1.6734	-0.9543	H22	5.5653	-0.6786	0.8718
C12	3.1867	-1.0478	-0.5555	H23	5.6969	0.1533	-0.7111
C13	3.1098	0.2026	0.0704	H24	1.8659	1.7387	0.7948
C14	1.8560	0.7937	0.2793	H25	-1.3698	0.5351	-1.8363
N15	-2.2181	-1.6668	0.6350	H26	-2.6922	-1.5660	-1.3055
C16	-1.2797	-1.1564	1.7168	H27	-4.1360	-2.1727	0.3043
C17	-1.1120	0.3563	1.6098	H28	-3.9008	-0.7047	1.2893
O18	4.1714	0.9168	0.5147	H29	-3.6488	-2.3123	2.0177
C19	5.4810	0.3809	0.3363	H30	-0.2348	-1.5014	1.6702
C20	-2.4819	-3.1363	0.7698	H31	-1.6387	-1.3325	2.7438
H21	6.1618	1.1191	0.7615	H32	-2.0768	0.9437	1.8804
H22	5.5972	-0.5715	0.8682	H33	-0.3871	0.8212	2.3366
H23	5.7123	0.2403	-0.7264	H34	-0.4882	-2.8573	-1.0435
H24	1.8476	1.7597	0.7713	H35	-0.6003	-1.7194	-2.3581
H25	-1.3560	0.5306	-1.8482	H36	1.9956	-2.6448	-1.4662
H26	-2.6207	-1.6154	-1.4159	H37	4.0851	-1.5895	-0.7382
H27	-1.5391	-3.6785	0.7090	H38	-3.6230	0.9635	0.1891
H28	-3.1508	-3.4554	-0.0315	H39	-3.7816	0.6953	-1.5405
H29	-2.9476	-3.3200	1.7400	H40	-2.4969	2.7863	-1.9877
H30	-0.3349	-1.6848	1.5786	H41	-3.8646	3.1316	-0.9353
H31	-1.7155	-1.4559	2.6743	H42	-2.3976	3.0931	1.0665
H32	-2.0387	0.8501	1.9247	H43	-1.7520	4.2284	-0.1006
H33	-0.3429	0.6528	2.3312	H44	-0.0735	2.6472	-0.8927
H34	-0.4109	-2.9051	-1.0063	H45	0.0511	2.8123	0.8498
H35	-0.5096	-1.8045	-2.3467	H46	-1.8150	-2.6769	0.6764
H36	2.0735	-2.6452	-1.4401				
H37	4.1395	-1.5330	-0.7311				
H38	-3.6272	0.7510	0.2088				
H39	-3.7767	0.5885	-1.5376				
H40	-2.6251	2.7500	-1.8739				
H41	-3.9736	2.9766	-0.7668				
H42	-2.4529	2.9352	1.1853				
H43	-1.8780	4.1294	0.0426				
H44	-0.1528	2.6404	-0.8326				
H45	-0.0052	2.7521	0.9127				
H46	-3.1144	-1.1923	0.7893				

Dextromethorphan stereoisomer B
B3LYP/6-31G*
Total energy -831.33474

C1	-0.5874	2.4214	0.0502
C2	-0.6911	0.8764	0.1727
C3	-1.7663	0.3549	-0.8266
C4	-3.1131	1.1045	-0.7718
C5	-2.9024	2.6099	-0.9816
C6	-1.9349	3.1620	0.0718
C7	-1.8430	-1.1764	-0.7360
C8	-0.5382	-1.7794	-1.2624
C9	0.7110	-1.0685	-0.7674
C10	0.6591	0.1929	-0.1308
C11	1.9528	-1.6768	-0.9708
C12	3.1435	-1.0837	-0.5607
C13	3.0936	0.1600	0.0808
C14	1.8531	0.7784	0.2918
N15	-2.1031	-1.6946	0.7090
C16	-1.2187	-1.0431	1.7771
C17	-1.1276	0.4693	1.6094

III. Cartesian coordinates of the atoms in the QM region in the QM/MM transition states and starting structures

Snapshot 1 TS

&zmat **Aromatic carbon oxidation**

C1	2.592	-0.748	-0.456
S2	1.567	-0.243	0.977
H3	3.172	-1.635	-0.173
H4	1.929	-1.034	-1.278
O5	-2.739	0.889	0.141
Fe6	-1.060	0.351	0.298
N7	-0.712	0.056	-1.653
N8	-1.310	-1.692	0.498
N9	-0.976	0.498	2.307
N10	-0.406	2.224	0.142
C11	-0.459	1.034	-2.587
C12	-0.617	0.514	-3.919
C13	-0.887	-0.815	-3.785
C14	-0.960	-1.086	-2.373
C15	-1.428	-2.623	-0.503
C16	-1.646	-3.949	0.046
C17	-1.614	-3.816	1.405
C18	-1.371	-2.408	1.658
C19	-1.004	-0.524	3.214
C20	-0.876	-0.025	4.562
C21	-0.833	1.336	4.473
C22	-0.849	1.644	3.050
C23	-0.493	3.175	1.130
C24	-0.230	4.483	0.574
C25	0.100	4.300	-0.740
C26	-0.066	2.895	-1.010
C27	-0.093	2.340	-2.285
H28	0.109	2.999	-3.123
C29	-1.273	-2.338	-1.850
H30	-1.369	-3.153	-2.563
C31	-1.191	-1.867	2.925
H32	-1.250	-2.534	3.777
C33	-0.698	2.907	2.484
H34	-0.695	3.758	3.156
C35	-5.152	3.903	-0.573
C36	-6.135	3.117	-1.214
C37	-3.842	3.437	-0.480
C38	-3.408	2.173	-1.026
C39	-4.405	1.499	-1.812
C40	-5.733	1.924	-1.848
O41	-3.920	0.471	-2.559
C42	-4.636	0.088	-3.719
H43	-4.826	0.955	-4.367
H44	-4.003	-0.633	-4.239
H45	-5.592	-0.382	-3.470
H46	-6.443	1.352	-2.434
H47	-3.083	4.073	-0.031
H48	-2.423	2.178	-1.466
H49	3.294	0.006	-0.855
H50	-0.665	1.108	-4.817
H51	-1.058	-1.566	-4.549
H52	-1.808	-4.831	-0.572
H53	-1.774	-4.516	2.237
H54	-0.761	-0.713	5.396
H55	-0.825	2.109	5.243
H56	-0.386	5.417	1.102
H57	0.456	5.011	-1.476
H58	-5.397	4.933	-0.209
H59	-7.198	3.470	-1.257

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Snapshot 1 minimum

&zmat **Aromatic carbon oxidation**

C1	2.703	-0.757	-0.468
S2	1.714	-0.259	0.983
H3	3.323	-1.621	-0.202
H4	2.032	-1.059	-1.278
O5	-2.313	0.445	0.249
Fe6	-0.715	0.178	0.385
N7	-0.460	-0.055	-1.609
N8	-0.972	-1.814	0.559
N9	-0.716	0.395	2.370
N10	-0.253	2.147	0.207
C11	-0.302	0.948	-2.529
C12	-0.531	0.462	-3.865
C13	-0.779	-0.873	-3.747
C14	-0.750	-1.179	-2.339
C15	-1.170	-2.716	-0.448
C16	-1.514	-4.014	0.091
C17	-1.503	-3.886	1.452
C18	-1.147	-2.507	1.718
C19	-0.806	-0.612	3.283
C20	-0.785	-0.090	4.629
C21	-0.754	1.271	4.522
C22	-0.692	1.557	3.097
C23	-0.401	3.104	1.177
C24	-0.207	4.424	0.610
C25	0.131	4.245	-0.701
C26	0.036	2.827	-0.953
C27	0.009	2.268	-2.223
H28	0.147	2.941	-3.063
C29	-1.048	-2.428	-1.804
H30	-1.213	-3.234	-2.513
C31	-1.016	-1.956	2.991
H32	-1.176	-2.605	3.844
C33	-0.609	2.826	2.528
H34	-0.689	3.676	3.195
C35	-5.273	4.089	-0.727
C36	-6.223	3.259	-1.332
C37	-3.921	3.739	-0.769
C38	-3.505	2.600	-1.436
C39	-4.438	1.808	-2.108
C40	-5.797	2.120	-2.043
O41	-3.899	0.764	-2.816
C42	-4.700	0.111	-3.775
H43	-5.105	0.816	-4.518
H44	-4.049	-0.610	-4.275
H45	-5.537	-0.424	-3.312
H46	-6.510	1.500	-2.577
H47	-3.180	4.382	-0.299
H48	-2.466	2.323	-1.490
H49	3.359	0.025	-0.866
H50	-0.618	1.079	-4.752
H51	-1.012	-1.590	-4.526
H52	-1.760	-4.857	-0.554
H53	-1.731	-4.568	2.276

H54	-0.752	-0.767	5.473
H55	-0.788	2.069	5.269
H56	-0.371	5.370	1.121
H57	0.468	4.971	-1.439
H58	-5.525	5.048	-0.249
H59	-7.291	3.552	-1.322

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Snapshot 2 TS

&zmat **Aromatic carbon oxidation**

C1	2.663	-0.578	-0.482
S2	1.610	-0.083	0.934
H3	3.260	-1.449	-0.181
H4	2.014	-0.890	-1.308
O5	-2.793	1.039	-0.133
Fe6	-1.117	0.440	0.106
N7	-0.681	0.114	-1.831
N8	-1.317	-1.622	0.327
N9	-1.071	0.584	2.126
N10	-0.412	2.285	-0.040
C11	-0.405	1.081	-2.770
C12	-0.495	0.533	-4.099
C13	-0.728	-0.803	-3.949
C14	-0.866	-1.047	-2.539
C15	-1.382	-2.565	-0.668
C16	-1.593	-3.889	-0.118
C17	-1.601	-3.749	1.240
C18	-1.406	-2.331	1.492
C19	-1.133	-0.433	3.043
C20	-1.021	0.076	4.391
C21	-0.937	1.434	4.292
C22	-0.928	1.731	2.866
C23	-0.500	3.240	0.945
C24	-0.196	4.539	0.391
C25	0.162	4.344	-0.913
C26	-0.032	2.943	-1.187
C27	-0.036	2.386	-2.462
H28	0.208	3.040	-3.294
C29	-1.175	-2.297	-2.010
H30	-1.215	-3.128	-2.708
C31	-1.299	-1.779	2.762
H32	-1.392	-2.443	3.614
C33	-0.733	2.985	2.296
H34	-0.714	3.839	2.964
C35	-5.153	4.003	-0.992
C36	-6.120	3.174	-1.615
C37	-3.843	3.558	-0.851
C38	-3.374	2.260	-1.326
C39	-4.362	1.551	-2.114
C40	-5.692	1.959	-2.189
O41	-3.850	0.521	-2.822
C42	-4.594	0.004	-3.910
H43	-4.957	0.811	-4.562
H44	-3.897	-0.632	-4.454
H45	-5.447	-0.596	-3.573
H46	-6.388	1.354	-2.760
H47	-3.101	4.230	-0.428
H48	-2.397	2.293	-1.787
H49	3.348	0.190	-0.885
H50	-0.512	1.100	-5.017
H51	-0.786	-1.583	-4.702
H52	-1.728	-4.773	-0.740
H53	-1.747	-4.457	2.065
H54	-0.959	-0.602	5.241
H55	-0.902	2.217	5.053
H56	-0.352	5.479	0.910
H57	0.569	5.035	-1.638
H58	-5.430	5.044	-0.666
H59	-7.182	3.513	-1.713

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Snapshot 2 minimum

&zmat **Aromatic carbon oxidation**

C1	2.794	-0.610	-0.491
S2	1.770	-0.140	0.949
H3	3.433	-1.456	-0.208
H4	2.141	-0.939	-1.306
O5	-2.271	0.491	0.057
Fe6	-0.675	0.236	0.237
N7	-0.367	-0.008	-1.758
N8	-0.911	-1.762	0.418
N9	-0.736	0.459	2.220
N10	-0.220	2.196	0.049
C11	-0.210	0.987	-2.687
C12	-0.389	0.480	-4.024
C13	-0.592	-0.863	-3.896
C14	-0.604	-1.148	-2.483
C15	-1.073	-2.669	-0.591
C16	-1.438	-3.963	-0.061
C17	-1.471	-3.832	1.299
C18	-1.134	-2.448	1.574
C19	-0.872	-0.539	3.140
C20	-0.894	0.001	4.480
C21	-0.832	1.360	4.359
C22	-0.724	1.628	2.935
C23	-0.384	3.160	1.009
C24	-0.166	4.475	0.441
C25	0.208	4.285	-0.857
C26	0.101	2.867	-1.107
C27	0.091	2.310	-2.379
H28	0.251	2.984	-3.215
C29	-0.904	-2.393	-1.944
H30	-1.041	-3.207	-2.648
C31	-1.072	-1.886	2.848
H32	-1.279	-2.532	3.694
C33	-0.623	2.892	2.357
H34	-0.714	3.750	3.012
C35	-5.283	4.200	-1.122
C36	-6.207	3.322	-1.701
C37	-3.923	3.878	-1.131
C38	-3.471	2.718	-1.738
C39	-4.382	1.869	-2.370
C40	-5.747	2.158	-2.343
O41	-3.821	0.807	-3.029
C42	-4.621	0.071	-3.929
H43	-5.095	0.718	-4.682
H44	-3.940	-0.625	-4.422
H45	-5.404	-0.504	-3.417
H46	-6.439	1.493	-2.848
H47	-3.206	4.567	-0.692
H48	-2.422	2.469	-1.781
H49	3.432	0.186	-0.896
H50	-0.456	1.076	-4.931
H51	-0.726	-1.607	-4.673

H52	-1.672	-4.803	-0.713
H53	-1.702	-4.527	2.107
H54	-0.922	-0.655	5.342
H55	-0.860	2.171	5.095
H56	-0.348	5.426	0.938
H57	0.588	4.992	-1.590
H58	-5.566	5.172	-0.685
H59	-7.278	3.598	-1.750

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Snapshot 3 TS

&zmat **Aromatic carbon oxidation**

C1	2.107	-0.718	-0.931
S2	1.063	-0.237	0.497
H3	2.662	-1.627	-0.667
H4	1.460	-0.956	-1.782
O5	-3.139	1.129	-0.365
Fe6	-1.473	0.491	-0.232
N7	-1.168	0.187	-2.192
N8	-1.793	-1.549	-0.031
N9	-1.400	0.623	1.777
N10	-0.746	2.321	-0.387
C11	-0.831	1.142	-3.123
C12	-0.973	0.624	-4.457
C13	-1.334	-0.684	-4.325
C14	-1.466	-0.942	-2.914
C15	-1.960	-2.463	-1.035
C16	-2.148	-3.795	-0.499
C17	-2.022	-3.695	0.858
C18	-1.794	-2.284	1.121
C19	-1.431	-0.404	2.680
C20	-1.283	0.088	4.028
C21	-1.212	1.449	3.944
C22	-1.240	1.764	2.521
C23	-0.812	3.277	0.597
C24	-0.485	4.572	0.041
C25	-0.133	4.368	-1.264
C26	-0.358	2.972	-1.534
C27	-0.392	2.422	-2.810
H28	-0.130	3.066	-3.643
C29	-1.834	-2.176	-2.386
H30	-1.960	-2.994	-3.089
C31	-1.600	-1.750	2.388
H32	-1.639	-2.425	3.235
C33	-1.047	3.021	1.951
H34	-1.017	3.875	2.619
C35	-5.454	4.201	-1.014
C36	-6.472	3.457	-1.650
C37	-4.151	3.706	-0.964
C38	-3.764	2.419	-1.508
C39	-4.817	1.753	-2.238
C40	-6.124	2.237	-2.268
O41	-4.387	0.663	-2.912
C42	-5.300	-0.082	-3.690
H43	-6.146	-0.426	-3.086
H44	-5.680	0.503	-4.538
H45	-4.742	-0.943	-4.063
H46	-6.864	1.678	-2.828
H47	-3.369	4.322	-0.532
H48	-2.794	2.393	-1.985
H49	2.831	0.039	-1.277
H50	-0.889	1.192	-5.371
H51	-1.476	-1.430	-5.098
H52	-2.364	-4.641	-1.146
H53	-2.094	-4.422	1.682
H54	-1.180	-0.613	4.855
H55	-1.163	2.218	4.716
H56	-0.630	5.508	0.570
H57	0.260	5.047	-2.014
H58	-5.680	5.206	-0.572
H59	-7.519	3.869	-1.703

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Snapshot 3 minimum

&zmat **Aromatic carbon oxidation**

C1	2.245	-0.781	-0.956
S2	1.243	-0.356	0.508
H3	2.851	-1.666	-0.727
H4	1.584	-1.028	-1.793
O5	-2.719	0.621	-0.258
Fe6	-1.133	0.285	-0.144
N7	-0.895	0.055	-2.146
N8	-1.471	-1.684	0.025
N9	-1.130	0.496	1.836
N10	-0.576	2.226	-0.323
C11	-0.654	1.042	-3.064
C12	-0.878	0.568	-4.406
C13	-1.218	-0.747	-4.291
C14	-1.244	-1.049	-2.881
C15	-1.709	-2.568	-0.986
C16	-2.023	-3.874	-0.455
C17	-1.925	-3.781	0.906
C18	-1.585	-2.398	1.179
C19	-1.228	-0.511	2.748
C20	-1.186	0.012	4.091
C21	-1.127	1.372	3.986
C22	-1.074	1.660	2.560
C23	-0.712	3.192	0.639
C24	-0.461	4.504	0.073
C25	-0.093	4.305	-1.228
C26	-0.236	2.891	-1.476
C27	-0.266	2.340	-2.750
H28	-0.075	3.005	-3.587
C29	-1.606	-2.280	-2.342
H30	-1.804	-3.084	-3.043
C31	-1.428	-1.857	2.454
H32	-1.550	-2.518	3.302
C33	-0.955	2.925	1.989
H34	-1.015	3.781	2.652
C35	-5.536	4.383	-1.142
C36	-6.524	3.590	-1.733
C37	-4.192	4.012	-1.240
C38	-3.826	2.862	-1.916
C39	-4.804	2.056	-2.503
C40	-6.150	2.421	-2.421
O41	-4.326	0.949	-3.151
C42	-5.245	0.045	-3.723
H43	-6.000	-0.283	-2.996
H44	-5.757	0.477	-4.595
H45	-4.661	-0.818	-4.048
H46	-6.892	1.799	-2.909
H47	-3.423	4.635	-0.792
H48	-2.793	2.555	-1.995
H49	2.912	0.018	-1.293

H50	-0.838	1.165	-5.311
H51	-1.427	-1.457	-5.080
H52	-2.311	-4.680	-1.121
H53	-2.059	-4.492	1.725
H54	-1.157	-0.668	4.935
H55	-1.121	2.167	4.736
H56	-0.621	5.451	0.585
H57	0.276	5.004	-1.980
H58	-5.758	5.316	-0.604
H59	-7.575	3.942	-1.741

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Snapshot 1 TS

&zmat **Hydrogen abstraction**

C1	2.918	-0.999	-0.725
S2	1.917	-0.428	0.708
H3	3.521	-1.867	-0.434
H4	2.255	-1.306	-1.538
O5	-2.133	0.355	-0.233
Fe6	-0.443	0.065	0.034
N7	-0.137	-0.238	-1.945
N8	-0.694	-1.918	0.293
N9	-0.556	0.351	2.019
N10	-0.028	2.023	-0.218
C11	0.056	0.722	-2.904
C12	-0.050	0.152	-4.222
C13	-0.264	-1.184	-4.046
C14	-0.328	-1.410	-2.626
C15	-0.801	-2.873	-0.685
C16	-1.088	-4.163	-0.100
C17	-1.119	-3.983	1.253
C18	-0.860	-2.572	1.474
C19	-0.590	-0.622	2.984
C20	-0.459	-0.036	4.303
C21	-0.401	1.315	4.130
C22	-0.457	1.538	2.696
C23	-0.200	3.005	0.716
C24	-0.041	4.312	0.118
C25	0.301	4.105	-1.186
C26	0.245	2.676	-1.398
C27	0.285	2.071	-2.645
H28	0.441	2.714	-3.506
C29	-0.617	-2.643	-2.040
H30	-0.708	-3.488	-2.714
C31	-0.776	-1.975	2.733
H32	-0.910	-2.616	3.595
C33	-0.382	2.781	2.080
H34	-0.427	3.660	2.712
C35	-5.564	4.436	-0.743
C36	-6.581	3.597	-1.240
C37	-4.223	4.092	-0.898
C38	-3.856	2.875	-1.460
C39	-4.860	2.004	-1.878
C40	-6.210	2.378	-1.818
O41	-4.600	0.740	-2.351
C42	-3.272	0.345	-2.504
H43	-2.691	1.025	-3.139
H44	-2.631	0.328	-1.333
H45	-3.275	-0.683	-2.871
H46	-6.936	1.675	-2.218
H47	-3.450	4.765	-0.535
H48	-2.812	2.593	-1.507
H49	3.570	-0.208	-1.118
H50	-0.035	0.710	-5.148
H51	-0.389	-1.953	-4.795
H52	-1.270	-5.049	-0.699
H53	-1.314	-4.661	2.089
H54	-0.357	-0.610	5.217
H55	-0.310	2.145	4.838
H56	-0.233	5.250	0.630
H57	0.641	4.818	-1.929
H58	-5.777	5.344	-0.168
H59	-7.647	3.948	-1.216

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Snapshot 1 minimum

&zmat **Hydrogen abstraction**

C1	2.954	-1.081	-0.724
S2	1.984	-0.544	0.742
H3	3.576	-1.943	-0.462
H4	2.272	-1.386	-1.523
O5	-2.021	0.359	-0.127
Fe6	-0.432	0.083	0.062
N7	-0.132	-0.216	-1.918
N8	-0.655	-1.902	0.322
N9	-0.444	0.356	2.044
N10	-0.006	2.042	-0.199
C11	0.024	0.751	-2.883
C12	-0.105	0.182	-4.199
C13	-0.298	-1.158	-4.020
C14	-0.333	-1.386	-2.599
C15	-0.774	-2.854	-0.659
C16	-1.066	-4.143	-0.076
C17	-1.096	-3.967	1.277
C18	-0.825	-2.560	1.503
C19	-0.506	-0.616	3.009
C20	-0.397	-0.026	4.325
C21	-0.343	1.326	4.148
C22	-0.377	1.547	2.716
C23	-0.181	3.025	0.739
C24	-0.044	4.332	0.136
C25	0.293	4.125	-1.170
C26	0.242	2.696	-1.378
C27	0.254	2.097	-2.631
H28	0.380	2.743	-3.494
C29	-0.608	-2.621	-2.014
H30	-0.708	-3.463	-2.690
C31	-0.728	-1.966	2.761
H32	-0.887	-2.602	3.623
C33	-0.338	2.795	2.100
H34	-0.410	3.672	2.733
C35	-5.595	4.351	-0.766
C36	-6.649	3.578	-1.291
C37	-4.277	3.954	-0.984
C38	-3.973	2.789	-1.691
C39	-5.019	2.019	-2.204
C40	-6.344	2.423	-2.010
O41	-4.870	0.871	-2.931
C42	-3.555	0.405	-3.184
H43	-3.003	1.097	-3.838
H44	-2.991	0.261	-2.255
H45	-3.672	-0.553	-3.697
H46	-7.104	1.793	-2.462
H47	-3.464	4.562	-0.595

H48	-2.939	2.496	-1.830
H49	3.581	-0.270	-1.120
H50	-0.087	0.730	-5.134
H51	-0.406	-1.927	-4.773
H52	-1.265	-5.026	-0.675
H53	-1.299	-4.648	2.106
H54	-0.304	-0.600	5.240
H55	-0.276	2.161	4.852
H56	-0.249	5.273	0.636
H57	0.636	4.837	-1.912
H58	-5.787	5.264	-0.178
H59	-7.697	3.938	-1.232

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Snapshot 2 TS

&zmat **Hydrogen abstraction**

C1	2.298	-0.560	-0.702
S2	1.234	0.029	0.665
H3	2.892	-1.413	-0.348
H4	1.664	-0.902	-1.526
O5	-2.856	0.546	-0.400
Fe6	-1.167	0.305	-0.100
N7	-0.812	0.055	-2.078
N8	-1.370	-1.697	0.089
N9	-1.316	0.526	1.892
N10	-0.742	2.266	-0.260
C11	-0.639	1.055	-2.997
C12	-0.805	0.552	-4.337
C13	-1.039	-0.789	-4.216
C14	-1.051	-1.085	-2.807
C15	-1.533	-2.611	-0.919
C16	-1.847	-3.914	-0.375
C17	-1.832	-3.784	0.987
C18	-1.528	-2.392	1.248
C19	-1.307	-0.486	2.810
C20	-1.214	0.036	4.156
C21	-1.218	1.394	4.050
C22	-1.253	1.683	2.623
C23	-0.897	3.219	0.713
C24	-0.651	4.535	0.164
C25	-0.291	4.362	-1.140
C26	-0.413	2.949	-1.412
C27	-0.388	2.391	-2.680
H28	-0.229	3.068	-3.512
C29	-1.365	-2.331	-2.270
H30	-1.494	-3.149	-2.972
C31	-1.424	-1.837	2.523
H32	-1.515	-2.500	3.375
C33	-1.146	2.948	2.058
H34	-1.197	3.801	2.725
C35	-6.008	4.942	-1.401
C36	-7.073	4.116	-1.806
C37	-4.691	4.499	-1.514
C38	-4.397	3.209	-1.944
C39	-5.454	2.360	-2.272
C40	-6.777	2.826	-2.260
O41	-5.283	1.036	-2.587
C42	-3.988	0.527	-2.681
H43	-3.352	1.094	-3.369
H44	-3.351	0.548	-1.504
H45	-4.070	-0.527	-2.950
H46	-7.541	2.125	-2.587

H47	-3.878	5.150	-1.206
H48	-3.373	2.860	-1.953
H49	2.971	0.205	-1.107
H50	-0.905	1.166	-5.224
H51	-1.253	-1.509	-4.995
H52	-2.067	-4.772	-1.005
H53	-2.019	-4.482	1.811
H54	-1.090	-0.623	5.009
H55	-1.198	2.186	4.802
H56	-0.795	5.479	0.685
H57	0.090	5.099	-1.844
H58	-6.156	5.920	-0.923
H59	-8.119	4.509	-1.754

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Snapshot 2 minimum

&zmat **Hydrogen abstraction**

C1	2.335	-0.575	-0.709
S2	1.318	-0.043	0.710
H3	2.947	-1.432	-0.399
H4	1.676	-0.900	-1.520
O5	-2.730	0.543	-0.259
Fe6	-1.137	0.303	-0.059
N7	-0.805	0.060	-2.053
N8	-1.344	-1.699	0.112
N9	-1.182	0.516	1.917
N10	-0.688	2.266	-0.234
C11	-0.648	1.061	-2.975
C12	-0.825	0.560	-4.316
C13	-1.060	-0.779	-4.195
C14	-1.063	-1.077	-2.785
C15	-1.526	-2.603	-0.896
C16	-1.846	-3.908	-0.358
C17	-1.825	-3.784	1.003
C18	-1.500	-2.397	1.272
C19	-1.213	-0.495	2.831
C20	-1.158	0.033	4.174
C21	-1.166	1.392	4.065
C22	-1.163	1.680	2.641
C23	-0.853	3.222	0.732
C24	-0.639	4.540	0.175
C25	-0.284	4.365	-1.130
C26	-0.389	2.948	-1.394
C27	-0.387	2.395	-2.663
H28	-0.244	3.074	-3.496
C29	-1.378	-2.321	-2.251
H30	-1.523	-3.134	-2.955
C31	-1.372	-1.846	2.543
H32	-1.492	-2.504	3.396
C33	-1.093	2.947	2.078
H34	-1.182	3.798	2.742
C35	-6.022	4.903	-1.397
C36	-7.113	4.144	-1.859
C37	-4.733	4.392	-1.545
C38	-4.498	3.143	-2.127
C39	-5.585	2.410	-2.613
C40	-6.879	2.922	-2.484
O41	-5.520	1.200	-3.242
C42	-4.266	0.534	-3.292
H43	-3.532	1.105	-3.874
H44	-3.865	0.353	-2.286
H45	-4.456	-0.416	-3.800

H46	-7.671	2.307	-2.900
H47	-3.883	4.965	-1.179
H48	-3.488	2.754	-2.181
H49	2.988	0.203	-1.114
H50	-0.918	1.171	-5.211
H51	-1.266	-1.500	-4.981
H52	-2.068	-4.765	-0.992
H53	-2.015	-4.482	1.824
H54	-1.056	-0.625	5.026
H55	-1.171	2.188	4.809
H56	-0.791	5.485	0.690
H57	0.090	5.101	-1.839
H58	-6.158	5.893	-0.916
H59	-8.145	4.530	-1.772

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Snapshot 3 TS

&zmat **Hydrogen abstraction**

C1	2.356	-0.662	-0.783
S2	1.311	-0.126	0.623
H3	2.908	-1.563	-0.491
H4	1.720	-0.912	-1.637
O5	-2.789	0.450	-0.176
Fe6	-1.087	0.197	0.068
N7	-0.790	-0.067	-1.908
N8	-1.311	-1.796	0.279
N9	-1.184	0.439	2.064
N10	-0.670	2.161	-0.111
C11	-0.563	0.919	-2.828
C12	-0.731	0.414	-4.162
C13	-1.036	-0.911	-4.042
C14	-1.067	-1.203	-2.630
C15	-1.496	-2.718	-0.717
C16	-1.780	-4.021	-0.149
C17	-1.731	-3.875	1.209
C18	-1.431	-2.479	1.448
C19	-1.185	-0.562	2.995
C20	-1.112	-0.025	4.337
C21	-1.120	1.333	4.215
C22	-1.139	1.605	2.784
C23	-0.825	3.122	0.852
C24	-0.606	4.436	0.288
C25	-0.253	4.251	-1.018
C26	-0.350	2.833	-1.269
C27	-0.300	2.254	-2.527
H28	-0.122	2.914	-3.371
C29	-1.383	-2.443	-2.074
H30	-1.543	-3.261	-2.767
C31	-1.312	-1.914	2.716
H32	-1.401	-2.570	3.573
C33	-1.051	2.864	2.204
H34	-1.108	3.724	2.862
C35	-5.936	4.902	-1.276
C36	-6.966	4.088	-1.783
C37	-4.608	4.476	-1.333
C38	-4.279	3.199	-1.780
C39	-5.312	2.351	-2.178
C40	-6.632	2.814	-2.251
O41	-5.137	1.025	-2.479
C42	-3.852	0.500	-2.502
H43	-3.165	1.065	-3.139
H44	-3.267	0.497	-1.282
H45	-3.926	-0.553	-2.773
H46	-7.364	2.116	-2.645
H47	-3.819	5.122	-0.960
H48	-3.252	2.855	-1.737
H49	3.086	0.087	-1.124
H50	-0.722	1.017	-5.056
H51	-1.314	-1.580	-4.845
H52	-1.987	-4.903	-0.749
H53	-1.899	-4.556	2.050
H54	-1.018	-0.666	5.209
H55	-1.118	2.133	4.961
H56	-0.766	5.377	0.810
H57	0.120	4.972	-1.738
H58	-6.135	5.829	-0.722
H59	-8.020	4.463	-1.781

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Snapshot 3 minimum

&zmat **Hydrogen abstraction**

C1	2.415	-0.699	-0.786
S2	1.402	-0.245	0.664
H3	3.001	-1.593	-0.538
H4	1.763	-0.943	-1.630
O5	-2.640	0.439	-0.032
Fe6	-1.042	0.181	0.114
N7	-0.768	-0.073	-1.869
N8	-1.273	-1.808	0.313
N9	-1.021	0.413	2.103
N10	-0.592	2.146	-0.071
C11	-0.548	0.915	-2.792
C12	-0.714	0.411	-4.129
C13	-1.027	-0.913	-4.008
C14	-1.061	-1.206	-2.595
C15	-1.475	-2.721	-0.682
C16	-1.765	-4.025	-0.122
C17	-1.712	-3.887	1.237
C18	-1.391	-2.496	1.483
C19	-1.069	-0.586	3.030
C20	-1.039	-0.047	4.369
C21	-1.045	1.313	4.244
C22	-1.020	1.584	2.818
C23	-0.758	3.110	0.888
C24	-0.570	4.426	0.315
C25	-0.221	4.240	-0.992
C26	-0.300	2.819	-1.234
C27	-0.273	2.246	-2.494
H28	-0.108	2.907	-3.339
C29	-1.377	-2.442	-2.042
H30	-1.544	-3.257	-2.736
C31	-1.245	-1.936	2.748
H32	-1.369	-2.588	3.606
C33	-0.974	2.846	2.239
H34	-1.075	3.703	2.896
C35	-5.941	4.857	-1.261
C36	-6.996	4.101	-1.803
C37	-4.636	4.374	-1.360
C38	-4.352	3.136	-1.947
C39	-5.410	2.383	-2.467
C40	-6.712	2.884	-2.415
O41	-5.313	1.157	-3.055
C42	-4.074	0.469	-2.991
H43	-3.316	0.956	-3.617

H44	-3.703	0.396	-1.962
H45	-4.269	-0.531	-3.388
H46	-7.468	2.254	-2.865
H47	-3.814	4.954	-0.944
H48	-3.335	2.764	-1.968
H49	3.115	0.075	-1.122
H50	-0.700	1.010	-5.031
H51	-1.293	-1.581	-4.819
H52	-1.981	-4.900	-0.734
H53	-1.889	-4.569	2.072
H54	-0.993	-0.688	5.241
H55	-1.077	2.118	4.982
H56	-0.749	5.369	0.825
H57	0.136	4.959	-1.723
H58	-6.127	5.805	-0.718
H59	-8.037	4.472	-1.777

&

Snapshot 1 TS (doublet state)

&zmat **Hydrogen abstraction**

C1	2.919	-0.980	-0.702
S2	1.914	-0.402	0.729
H3	3.525	-1.843	-0.403
H4	2.259	-1.297	-1.513
O5	-2.147	0.359	-0.164
Fe6	-0.443	0.058	0.020
N7	-0.163	-0.236	-1.947
N8	-0.689	-1.922	0.287
N9	-0.562	0.350	2.024
N10	-0.032	2.024	-0.227
C11	0.045	0.723	-2.908
C12	-0.050	0.151	-4.226
C13	-0.268	-1.184	-4.050
C14	-0.344	-1.412	-2.631
C15	-0.801	-2.878	-0.687
C16	-1.088	-4.167	-0.101
C17	-1.121	-3.985	1.253
C18	-0.860	-2.574	1.472
C19	-0.599	-0.620	2.986
C20	-0.470	-0.036	4.307
C21	-0.411	1.316	4.133
C22	-0.466	1.536	2.698
C23	-0.199	3.004	0.713
C24	-0.038	4.311	0.117
C25	0.302	4.107	-1.188
C26	0.243	2.679	-1.402
C27	0.282	2.070	-2.650
H28	0.452	2.710	-3.512
C29	-0.626	-2.645	-2.046
H30	-0.716	-3.492	-2.718
C31	-0.781	-1.976	2.730
H32	-0.918	-2.619	3.590
C33	-0.382	2.778	2.076
H34	-0.428	3.659	2.706
C35	-5.557	4.439	-0.742
C36	-6.569	3.595	-1.240
C37	-4.215	4.092	-0.878
C38	-3.843	2.866	-1.418
C39	-4.844	1.993	-1.841
C40	-6.194	2.373	-1.804
O41	-4.583	0.724	-2.299
C42	-3.256	0.337	-2.444
H43	-2.667	1.035	-3.046
H44	-2.635	0.313	-1.267
H45	-3.240	-0.685	-2.822
H46	-6.913	1.667	-2.210
H47	-3.444	4.768	-0.514
H48	-2.800	2.580	-1.442
H49	3.569	-0.191	-1.103
H50	-0.031	0.709	-5.153
H51	-0.391	-1.956	-4.796
H52	-1.269	-5.049	-0.707
H53	-1.316	-4.660	2.092
H54	-0.363	-0.612	5.220
H55	-0.313	2.149	4.840
H56	-0.232	5.249	0.631
H57	0.640	4.822	-1.932
H58	-5.777	5.348	-0.172
H59	-7.636	3.946	-1.226

&

Snapshot 1 minimum (doublet state)

&zmat **Hydrogen abstraction**

C1	2.955	-1.080	-0.725
S2	1.986	-0.544	0.742
H3	3.577	-1.943	-0.463
H4	2.273	-1.386	-1.523
O5	-2.025	0.359	-0.128
Fe6	-0.431	0.083	0.064
N7	-0.131	-0.216	-1.918
N8	-0.655	-1.902	0.322
N9	-0.444	0.355	2.045
N10	-0.006	2.042	-0.199
C11	0.023	0.751	-2.883
C12	-0.105	0.181	-4.199
C13	-0.298	-1.157	-4.020
C14	-0.333	-1.385	-2.600
C15	-0.774	-2.854	-0.659
C16	-1.067	-4.144	-0.076
C17	-1.097	-3.967	1.277
C18	-0.825	-2.560	1.503
C19	-0.506	-0.616	3.009
C20	-0.397	-0.026	4.325
C21	-0.344	1.326	4.148
C22	-0.377	1.546	2.717
C23	-0.181	3.025	0.738
C24	-0.045	4.332	0.136
C25	0.293	4.125	-1.169
C26	0.242	2.697	-1.378
C27	0.254	2.096	-2.631
H28	0.380	2.743	-3.494
C29	-0.608	-2.620	-2.014
H30	-0.707	-3.463	-2.690
C31	-0.728	-1.966	2.761
H32	-0.887	-2.602	3.623
C33	-0.339	2.794	2.100
H34	-0.410	3.672	2.733
C35	-5.595	4.351	-0.766
C36	-6.649	3.577	-1.291
C37	-4.277	3.954	-0.984
C38	-3.973	2.789	-1.691
C39	-5.019	2.019	-2.204
C40	-6.345	2.423	-2.010
O41	-4.871	0.871	-2.931

C42	-3.554	0.404	-3.185	H54	-0.305	-0.600	5.240
H43	-3.003	1.097	-3.837	H55	-0.276	2.160	4.852
H44	-2.992	0.260	-2.256	H56	-0.249	5.273	0.636
H45	-3.671	-0.553	-3.698	H57	0.636	4.837	-1.912
H46	-7.104	1.794	-2.462	H58	-5.786	5.264	-0.179
H47	-3.463	4.562	-0.595	H59	-7.697	3.939	-1.232
H48	-2.939	2.496	-1.829	&			
H49	3.581	-0.270	-1.120				
H50	-0.087	0.730	-5.133				
H51	-0.406	-1.927	-4.773				
H52	-1.265	-5.026	-0.675				
H53	-1.299	-4.648	2.106				

IV. Figures

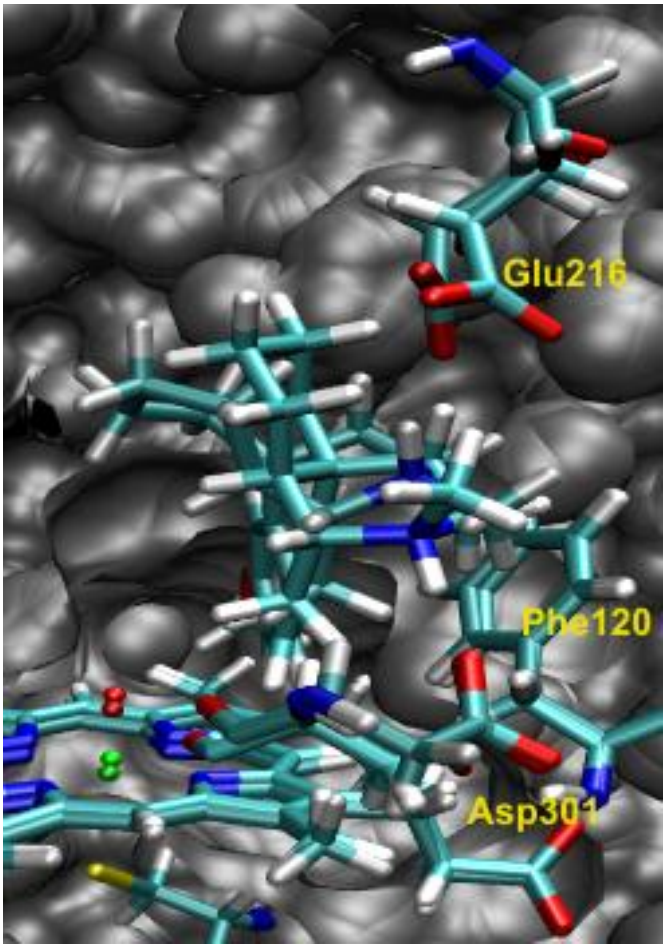
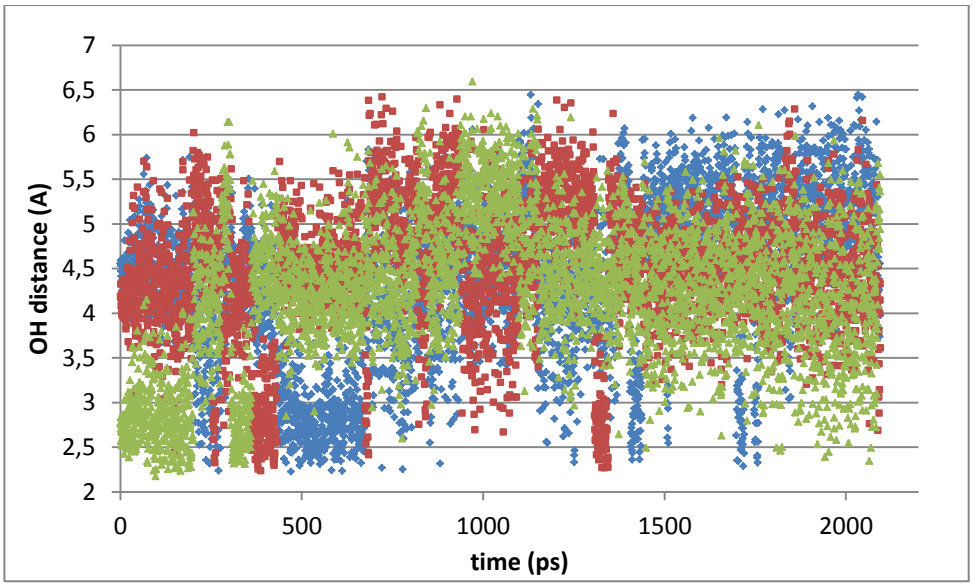


Fig. S1. Dextromethorphan docked into the active site of P450 2D6. The two stereoisomers of the protonated Dextromethorphan can interact either with Glu216 or with Asp301.

A



B

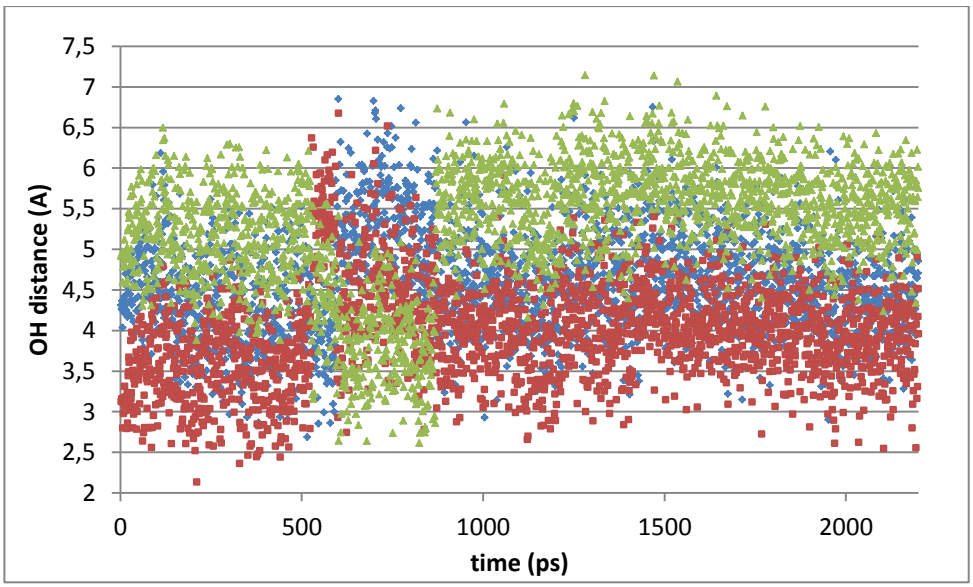


Fig.S2. Distances measured in the MD simulations of P450 2D6 with dextromethorphan docked into the active site. The OH distances were measured between the ferryl-oxygen atom and the alpha-hydrogen atoms (the three colors in the diagrams correspond to the three alpha-hydrogen atoms) A: The protonated amino-group of dextromethorphan interacts with Glu216. B: protonated amino-group of dextromethorphan interacts with Asp301.

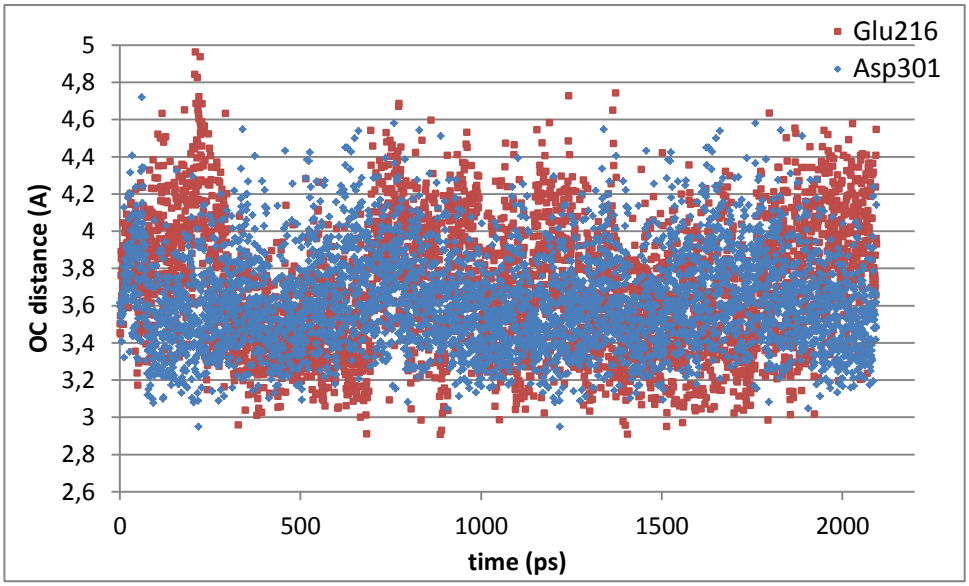
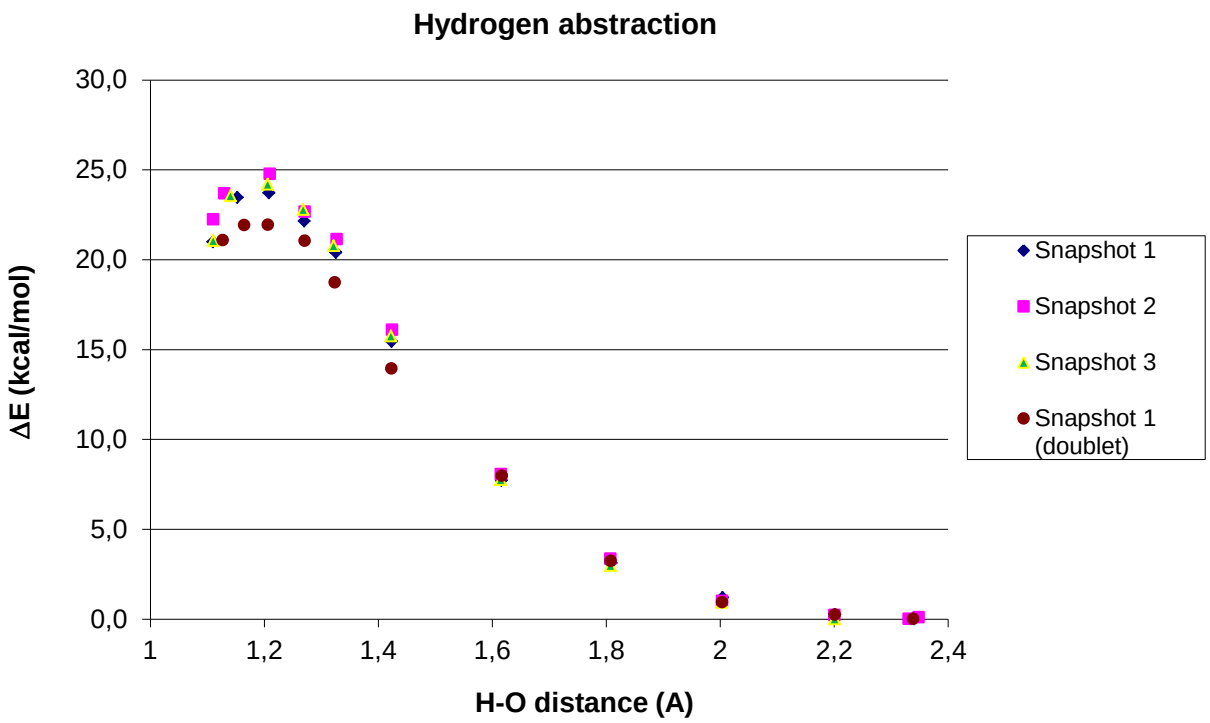


Fig.S3. Distances measured in the MD simulations of P450 2D6 with dextromethorphan docked into the active site. The OC distances were measured between the ferryl-oxygen atom and the *ortho* carbon atoms. red: simulation in which hydrogen bond exists between Glu216 and dextromethorphan blue: simulation in which hydrogen bond exists between Asp301 and dextromethorphan

A



B

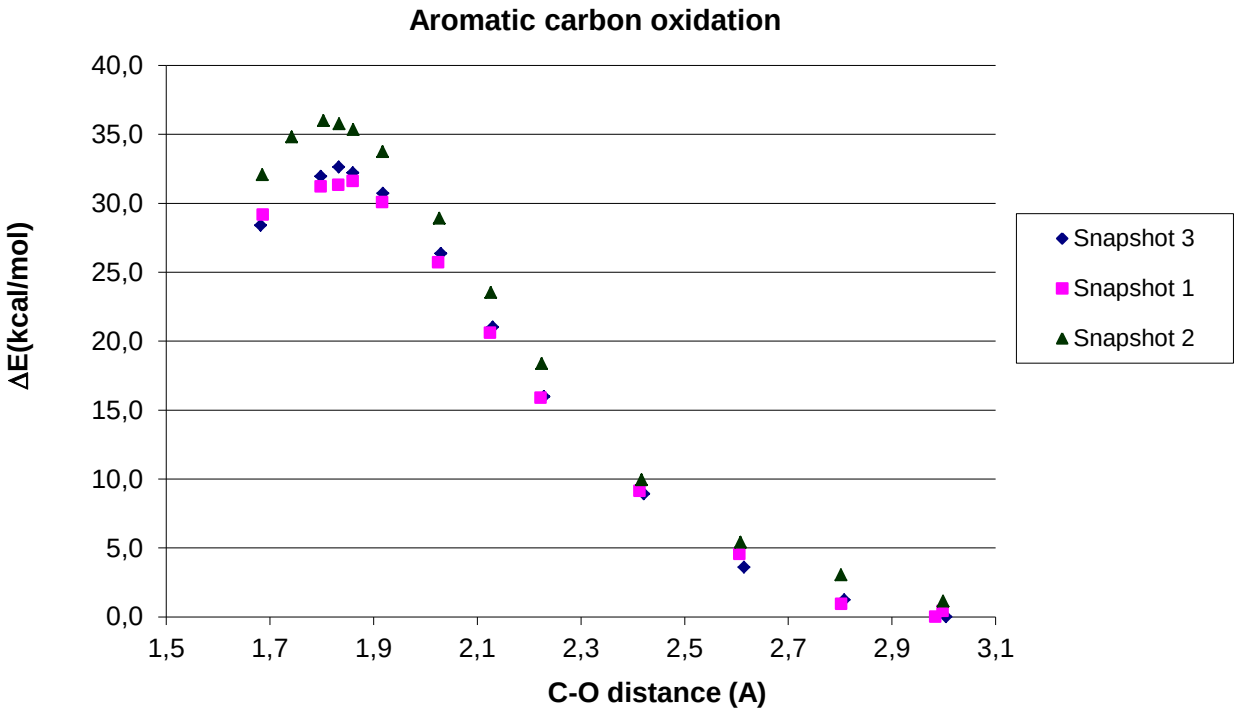


Fig.S4. QM/MM adiabatic energy scan profiles for A. hydrogen-abstraction B. aromatic carbon oxidation.

V. Table S1. Selected geometrical parameters of QM only transition states (at the B3LYP/LACVP** level) and QM/MM optimized starting structures and transition states.

			C_2-O (oxyl)	**CH**	**OH**
Aromatic carbon oxidation	QM	TS (doublet)	1.940		
		TS (quartet)	1.861		
	Snapshot 1	TS	1.860		
		minimum	2.984		
	Snapshot 2	TS	1.803		
		minimum	3.102		
	Snapshot 3	TS	1.833		
		minimum	2.999		
Hydrogen abstraction	QM	TS (doublet)		1.258	1.275
		TS (quartet)		1.348	1.194
	Snapshot 1	TS		1.335	1.209
		minimum		1.097	2.340
	Snapshot 2	TS		1.338	1.210
		minimum		1.098	2.331
	Snapshot 3	TS		1.352	1.206
		minimum		1.096	2.204
	Snapshot 1 doublet[+]	TS		1.331	1.207
		minimum		1.096	2.339

[+] this profile was started from the same geometry as Snapshot 1, and the profile was followed in the doublet state. (It is not the reoptimization of the structures obtained in the quartet energy profile).