Supporting Information for

Theoretical study of *N*-dealkylation of *N*-cyclopropyl-*N*-methylaniline catalyzed by Cytochrome P450: insight into the origin of the regioselectivity

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Table S1. Various calculated SCF energies for C_α–H hydroxylation on the *N*-substituent of *N*-cyclopropyl-*N*-methylaniline (CMA) by Cpd I, with ZPE Corrections, the bulk polarity correction and NH-S H-bond interaction incorporated. All relative values are in kcal/mol relative to the reactant $^4RC_{1A}$.

	B1 (gas-phase)		B2//B1 (gas-phase)		B2//B1 + solv.		B2//B1 + 2NH--S + solv.		B2//B1 + 2NH--S + solv.+ ZPE	
	E (a.u.)	E_{rel}	E (a.u.)	E_{rel}	E (a.u.)	E_{rel}	E (a.u.)	E_{rel}	E (a.u.)	E_{rel}
Path A: C_α–H hydroxylation on the cyclopropyl group										
$^4RC_1$	-2029.389366	**0.0**	-2029.810186	**0.0**	-2029.834291	**0.0**	-2142.982023	**0.0**	-2142.485322	**0.0**
$^2RC_1$	-2029.389521	**-0.1**	-2029.810367	**-0.1**	-2029.834675	**-0.2**	-2142.982430	**-0.3**	-2142.485850	**-0.3**
$^4TS_1$	-2029.365350	**15.1**	-2029.792386	**11.2**	-2029.815057	**12.1**	-2142.959173	**14.3**	-2142.468060	**10.8**
$^2TS_1$	-2029.368787	**12.9**	-2029.795533	**9.2**	-2029.819725	**9.1**	-2142.965879	**10.1**	-2142.474532	**6.8**
$^4IM_1$	-2029.374301	**9.5**	-2029.805685	**2.8**	-2029.827701	**4.1**	-2142.973045	**5.6**	-2142.478133	**4.5**
$^4PC_1$	-2029.467744	**-49.2**	-2029.895785	**-53.7**	-2029.919785	**-53.6**	-2143.072009	**-56.5**	-2142.574653	**-56.1**
$^2PC_1$	-2029.473198	**-52.6**	-2029.898075	**-55.2**	-2029.917475	**-52.2**	-2143.061506	**-49.9**	-2142.562447	**-48.4**
Path B: C_α–H hydroxylation on the methyl group										
$^4RC_1$	-2029.387807	**1.0**	-2029.810164	**0.0**	-2029.833956	**0.2**	-2142.981917	**0.1**	-2142.485449	**-0.1**
$^2RC_1$	-2029.387851	**1.0**	-2029.810302	**-0.1**	-2029.834091	**0.1**	-2142.981999	**0.0**	-2142.485597	**-0.2**
$^4TS_1$	-2029.365451	**15.0**	-2029.792086	**11.4**	-2029.816637	**11.1**	-2142.960637	**13.4**	-2142.468880	**10.3**
$^2TS_1$	-2029.368469	**13.1**	-2029.794843	**9.6**	-2029.821916	**7.8**	-2142.969100	**8.1**	-2142.476389	**5.6**
$^4IM_1$	-2029.377156	**7.7**	-2029.809107	**0.7**	-2029.833944	**0.2**	-2142.978902	**2.0**	-2142.484309	**0.6**
$^4PC_1$	-2029.465567	**-47.8**	-2029.893771	**-52.5**	-2029.919256	**-53.3**	-2143.071222	**-56.0**	-2142.572454	**-54.7**
$^2PC_1$	-2029.474164	**-53.2**	-2029.900458	**-56.6**	-2029.921159	**-54.5**	-2143.064622	**-51.8**	-2142.563913	**-49.3**

Table S2. Various calculated SCF energies for decomposition of carbinolaniline complex in enzymatic environment. All relative values are in kcal/mol relative to the reactant $^4RC_{1A.}$

	B1 (gas-phase)		B2//B1 (gas-phase)		B2//B1 + solv.		B2//B1 + 2NH--S + solv.		B2//B1 + 2NH--S + solv.+ ZPE	
	E (a.u.)	E_{rel}	E (a.u.)	E_{rel}	E (a.u.)	E_{rel}	E (a.u.)	E_{rel}	E (a.u.)	E_{rel}
Path A										
$^4RC_2$	-2029.467744	**-49.2**	-2029.895785	**-53.7**	-2029.919785	**-53.6**	-2143.072009	**-56.5**	-2142.574653	**-56.1**
$^2RC_2$	-2029.473198	**-52.6**	-2029.898075	**-55.2**	-2029.917475	**-52.2**	-2143.061506	**-49.9**	-2142.562447	**-48.4**
$^4TS_2$	-2029.404004	**-9.2**	-2029.830815	**-12.9**	-2029.859213	**-15.6**	-2143.010937	**-18.1**	-2142.518223	**-20.6**
$^2TS_2$	-2029.417009	**-17.4**	-2029.841186	**-19.5**	-2029.864838	**-19.2**	-2143.008168	**-16.4**	-2142.513863	**-17.9**
$^4PC_2$	-2029.447996	**-36.8**	-2029.878745	**-43.0**	-2029.904607	**-44.1**	-2143.056850	**-47.0**	-2142.563590	**-49.1**
$^2PC_2$	-2029.454450	**-40.8**	-2029.882285	**-45.2**	-2029.903352	**-43.3**	-2143.047522	**-41.1**	-2142.552326	**-42.0**
Path B										
$^4RC_2$	-2029.465567	**-47.8**	-2029.893771	**-52.5**	-2029.919256	**-53.3**	-2143.071222	**-56.0**	-2142.572454	**-54.7**
$^2RC_2$	-2029.474164	**-53.2**	-2029.900458	**-56.6**	-2029.921159	**-54.5**	-2143.064622	**-51.8**	-2142.563913	**-49.3**
$^4TS_2$	-2029.399731	**-6.5**	-2029.827627	**-10.9**	-2029.856857	**-14.2**	-2143.008443	**-16.6**	-2142.514704	**-18.4**
$^2TS_2$	-2029.415291	**-16.3**	-2029.841181	**-19.4**	-2029.866020	**-19.9**	-2143.008899	**-16.9**	-2142.513154	**-17.5**
$^4PC_2$	-2029.454518	**-40.9**	-2029.885271	**-47.1**	-2029.911688	**-48.6**	-2143.063396	**-51.1**	-2142.569654	**-52.9**
$^2PC_2$	-2029.460053	**-44.4**	-2029.888088	**-48.9**	-2029.910081	**-47.6**	-2143.054324	**-45.4**	-2142.55854	**-45.9**

Table S3. Various calculated SCF energies for carbinolaniline decomposition in nonenzymatic environment.

	B1	B2//B1	B2//B1 + solv.	B2//B1 + solv.+ZPE	B1	B2//B1	B2//B1 + solv.	B2//B1 + solv.+ ZPE
Path A								
(i) direct proton-transfer					(ii) water-assisted proton-transfer			
RC_2	-518.814336	-518.938436	-518.954421	-518.742209	-595.236821	-595.390525	-595.415111	-595.177273
TS_2	-518.746073	-518.869880	-518.899607	-518.692017	-595.199422	-595.352726	-595.38779	-595.154646
PC_2	-518.797125	-518.923733	-518.940882	-518.732611	-595.224553	-595.382395	-595.406990	-595.173731
Path B								
(iii) direct proton-transfer					(iv) water-assisted proton-transfer			
RC_2	-518.813700	-518.939119	-518.956243	-518.748120	-595.232788	-595.387058	-595.411359	-595.172310
TS_2	-518.740388	-518.864537	-518.893117	-518.684994	-595.198206	-595.350945	-595.383089	-595.149556
PC_2	-518.803880	-518.930193	-518.947254	-518.738352	-595.229549	-595.387006	-595.410431	-595.176168

Table S4. Mulliken charge and spin densities of key moieties of C_α–H hydroxylation on the *N*-substituent of CMA by Cpd I in the gas-phase, respectively. All data were computed at the B1 level.

	Spin Density						Charge					
	Fe	O	SH	Por	H	CMA•	Fe	O	SH	Por	H	CMA•
Path A: C_α–H hydroxylation on the cyclopropyl group												
$^4RC_1$	1.0992	0.9178	0.5107	0.4678	-0.0014	0.0059	0.4761	-0.4054	-0.0578	-0.0213	0.2149	-0.2065
$^2RC_1$	1.2145	0.8732	-0.5601	-0.5271	-0.0012	0.0007	0.4871	-0.4083	-0.0544	-0.0367	0.2135	-0.2012
$^4TS_1$	1.4435	0.6317	0.2644	-0.0126	-0.0086	0.6817	0.4088	-0.6046	-0.0118	-0.2849	0.4059	0.0866
$^2TS_1$	1.5967	0.1811	-0.0663	-0.1169	-0.0056	-0.5391	0.4044	-0.5817	-0.0542	-0.2703	0.3704	0.1315
$^4IM_1$	1.7352	0.2968	0.1258	-0.1090	0.0275	0.9237	0.3906	-0.6879	0.0218	-0.2416	0.4559	0.0612
$^4PC_1$	2.5113	0.0043	0.4679	0.0150	-0.0007	0.0022	0.4524	-0.6094	-0.1489	-0.3986	0.4276	0.2769
$^2PC_1$	1.1122	-0.0004	-0.0218	-0.0911	0.0002	0.0009	0.2441	-0.6147	0.0356	-0.4281	0.4423	0.3207
Path B: C_α–H hydroxylation on the methyl group												
$^4RC_1$	1.1045	0.9130	0.5265	0.4483	0.0004	0.0073	0.4833	-0.4046	-0.0494	-0.0213	0.1432	-0.1512
$^2RC_1$	1.2214	0.8690	-0.5736	-0.5158	-0.0001	-0.0010	0.4923	-0.4075	-0.0461	-0.0263	0.1426	-0.1550
$^4TS_1$	1.3751	0.6860	0.2895	0.0099	-0.0108	0.6503	0.4041	-0.5739	-0.0114	-0.2881	0.3940	0.0752
$^2TS_1$	1.5633	0.2036	-0.068	-0.1851	-0.0081	-0.5058	0.4100	-0.5472	-0.0679	-0.2664	0.3529	0.1186
$^4IM_1$	1.7386	0.3081	0.1204	-0.1118	0.0285	0.9163	0.3948	-0.6755	0.0145	-0.2521	0.4529	0.0653
$^4PC_1$	2.5006	0.0088	0.4716	0.0200	-0.0018	0.0007	0.4312	-0.6007	-0.1405	-0.3781	0.4332	0.2551
$^2PC_1$	1.0608	0.0002	0.0191	-0.0791	0.0007	-0.0009	0.2237	-0.5972	0.0361	-0.4385	0.4432	0.3326

Table S5. Mulliken charge and spin densities of key moieties of decomposition of carbinolaniline complex in enzymatic environment. All data were computed at the B1 level.

	Spin Density						Charge					
	Fe	O	SH	Por	H	rest	Fe	O	SH	Por	H	rest
Path A												
$^4RC_2$	2.5113	0.0043	0.4679	0.0150	-0.0007	0.0022	0.4524	-0.6094	-0.1489	-0.3986	0.4276	0.2769
$^2RC_2$	1.1122	-0.0004	-0.0218	-0.0911	0.0002	0.0009	0.2441	-0.6147	0.0356	-0.4281	0.4423	0.3207
$^4TS_2$	2.5566	0.0332	0.4379	-0.0331	-0.0013	0.0067	0.4367	-0.6453	-0.1789	-0.4496	0.4487	0.3885
$^2TS_2$	1.0499	0.0082	0.0220	-0.0813	-0.0002	0.0014	0.2496	-0.6523	-0.0014	0.5004	0.4673	0.4371
$^4PC_2$	2.5087	0.0071	0.4689	0.0159	-0.0000	-0.0006	0.4601	-0.3620	-0.1462	-0.3983	0.3465	0.0999
$^2PC_2$	1.0817	-0.0012	0.0044	-0.0821	-0.0000	-0.0027	0.2215	-0.3511	0.0394	-0.4318	0.3465	0.1739
Path B												
$^4RC_2$	2.5006	0.0088	0.4716	0.0200	-0.0018	0.0007	0.4312	-0.6007	-0.1405	-0.3781	0.4332	0.2551
$^2RC_2$	1.0608	0.0002	0.0191	-0.0791	0.0007	-0.0009	0.2237	-0.5972	0.0361	-0.4385	0.4432	0.3326
$^4TS_2$	2.5636	0.0412	0.4281	-0.0389	-0.0006	0.0067	0.4650	-0.6239	-0.1936	-0.465	0.4342	0.3833
$^2TS_2$	1.0243	0.0146	0.0384	-0.0767	-0.0003	-0.0004	0.2913	-0.6353	-0.0207	-0.5245	0.4493	0.4399
$^4PC_2$	2.4958	0.0042	0.4733	0.0277	0.0000	-0.0009	0.4690	-0.2944	-0.1452	-0.3895	0.3564	0.0037
$^2PC_2$	1.0799	-0.0007	0.0046	-0.0815	0.0001	-0.0024	0.2414	-0.2843	0.03985	-0.4284	0.3562	0.0753

Table S6. Data for KIE calculations for hydrogen abstraction from the CMA at B1 level.

Path A: Cα–H hydroxylation on the cyclopropyl group						
non-deuterated case				deuterated case		
	Imaginary Frequency (cm^{-1})	G (a.u.)		Imaginary Frequency (cm^{-1})	G (a.u.)	
		CMA + Cpd I	TS		CMA + Cpd I	TS
HS	1454.52	-2028.985831	-2028.943625	1075.13	-2028.989287	-2028.945310
LS	822.247	-2028.985245	-2028.947275	653.348	-2028.988701	-2028.949133
Path B: Cα–H hydroxylation on the methyl group						
non-deuterated case				deuterated case		
	Imaginary Frequency (cm^{-1})	G (a.u.)		Imaginary Frequency (cm^{-1})	G (a.u.)	
		CMA + Cpd I	TS		CMA + Cpd I	TS
HS	1487.74	-2028.985831	-2028.943762	1111.22	-2028.989240	-2028.945458
LS	750.353	-2028.985245	-2028.945268	630.364	-2028.988654	-2028.947286