Supporting Information

Hybrid Quantum Mechanics/Molecular Mechanics/Coarse Grained Modeling: A Triple-Resolution Approach for Biomolecular Systems

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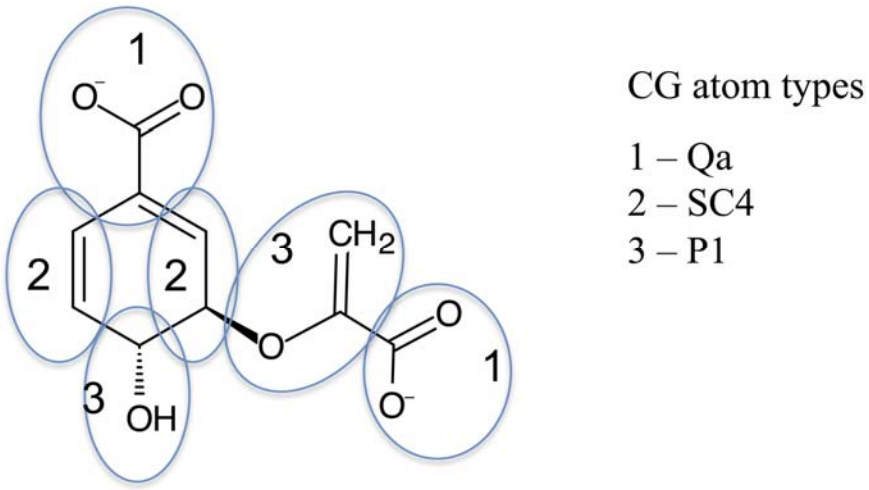

Figure S1. Mapping virtual sites in chorismate mutase. The fine-grained atoms that form a virtual site are encircled. The CG atom types of the virtual sites are also shown.

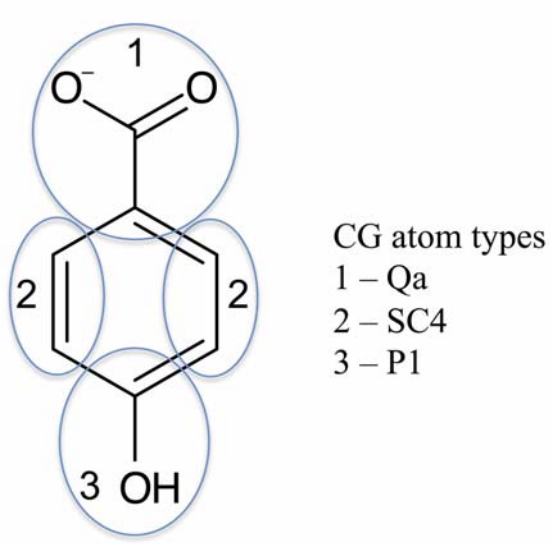

Figure S2. Mapping virtual sites in p-hydroxybenzoate. The fine-grained atoms that form a virtual site are encircled. The CG atom types of the virtual sites are also shown.

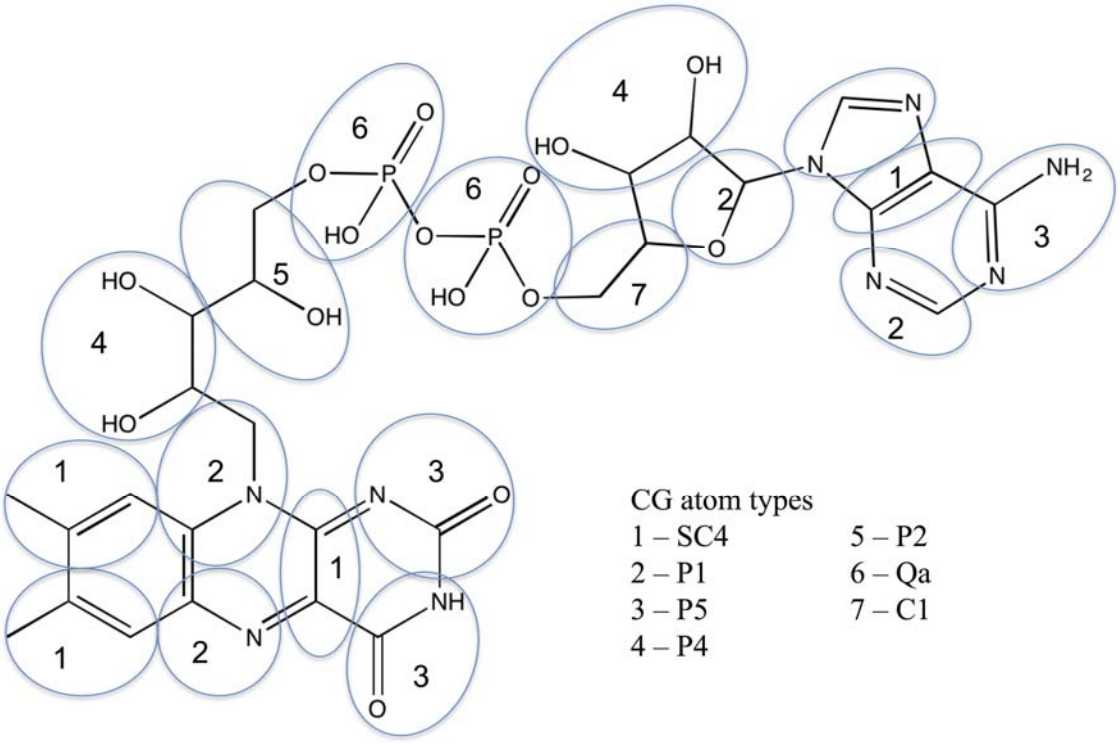

Figure S3. Mapping virtual sites in FADOOH. The fine-grained atoms that form a virtual site are encircled. The CG atom types of the virtual sites are also shown.

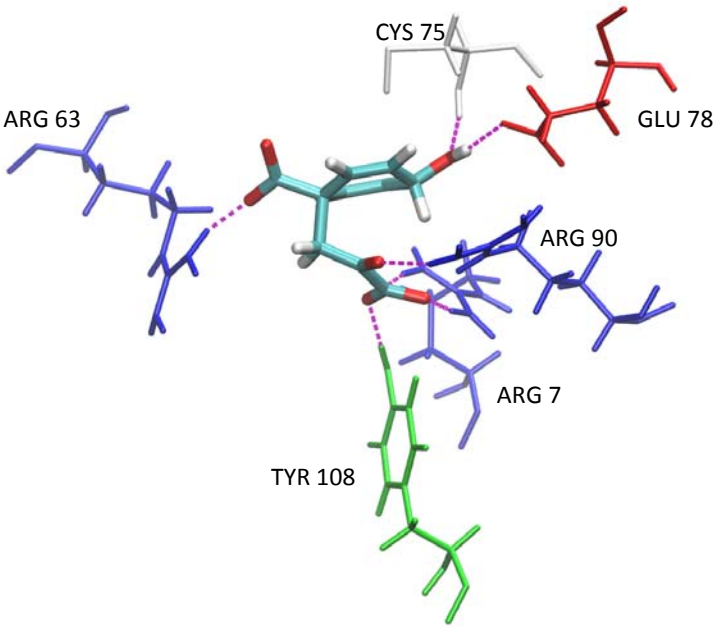

Figure S4. Hydrogen bonding between the prephenate substrate and the protein environment in a QM/MM/CG snapshot (hydrogen bond criteria: distance cutoff: 3 Å, angle cutoff: 20°)

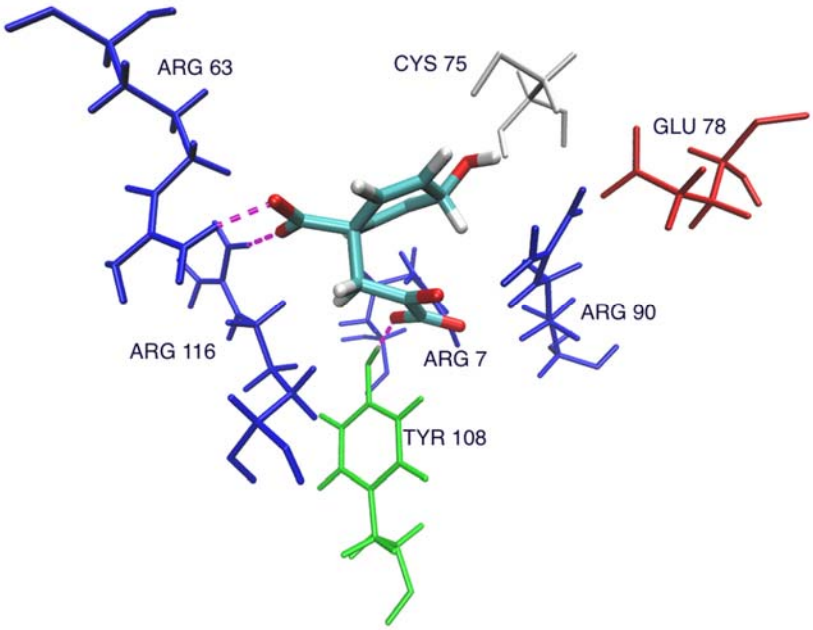

Figure S5. Hydrogen bonding between the prephenate substrate and the protein environment in a QM/MM snapshot (hydrogen bond criteria: distance cutoff: 3 Å, angle cutoff: 20°)

Table S1. Activation barriers and reaction energies from single point QM/MM/CG energy calculations at the B3LYP/6-31G* level of theory (QM region) on AM1/MM/CG geometries along the potential energy scan. $\Delta\Delta E^{\ddagger}$: activation energy, $\Delta\Delta E$: reaction energy.

Snapshot	Standard QM/MM (kcal/mol)		QM/MM/CG[a] (kcal/mol)	
	$\Delta\Delta E^{\ddagger}$	$\Delta\Delta E$	$\Delta\Delta E^{\ddagger}$	$\Delta\Delta E$
1	11.4	-17.4	13.4	-17.9
2	13.2	-15.2	12.9	-15.4
3	15.0	-16.8	-	-
4	13.4	-16.1	12.3	-20.6
5	9.6	-20.6	8.5	-21.7
6	13.8	-16.3	12.2	-15.9
7	11.0	-19.4	13.4	-16.7
8	12.2	-17.7	13.9	-17.3
9	12.7	-15.4	12.9	-14.0
10	8.9	-20.1	8.2	-20.8
Mean	12.1	-17.5	12.0	-17.8
STDEV	1.9	1.9	2.1	2.7

[a]Pol-CG water with 10 Å MM water

Table S2. Computing times for the chorismate mutase system.

System	AM1		DFT	
	t / step (s)	Savings (%)	t / step (s)	Savings (%)
QM/MM	0.36	-	195.02	-
QM/MM/CG				
0 Å TIP3P	0.18	49	137.82	29
5 Å TIP3P	0.17	52	135.45	31
10 Å TIP3P	0.20	46	157.24	19
15 Å TIP3P	0.19	47	140.56	28
19 Å TIP3P	0.24	33	149.06	24
QM/MM/pol-CG				
0 Å TIP3P	0.24	33	152.56	22
5 Å TIP3P	0.24	33	150.21	23
10 Å TIP3P	0.25	31	159.83	18
15 Å TIP3P	0.26	28	163.94	16
19 Å TIP3P	0.29	19	173.33	11

Table S3. Computing times for the PHBH system

System	AM1		DFT	
	t / step (s)	Savings (%)	t / step (s)	Savings (%)
QM/MM	1.04	-	882.5	-
QM/MM/pol-CG	0.54	48	505.3	43

Table S4. Average time for one single QM (DFT) gradient evaluation (in s) and computational savings (percent, in parenthesis) for QM/MM/CG relative to full atomistic calculations (see text) of a glycine – water system.

		Time for single QM gradient evaluation (s)			
		6-31G*	**SVP**	**6-311G(2df,2pd)**	**TZVPP**
Atomistic	BLYP	18.8	19.1	62.2	67.9
	BP86	18.5	18.6	63.2	68.1
	B3LYP	19.9	20.1	77.6	88.3
	BHLYP	20.0	26.8	91.3	92.1
15 Å CG water	BLYP	4.5 (76)	4.5 (76)	14.5 (77)	16.5 (76)
	BP86	4.5 (76)	4.5 (76)	14.8 (77)	15.8 (77)
	B3LYP	5.5 (72)	6.1 (70)	30.8 (60)	35.1 (60)
	BHLYP	5.8 (71)	5.8 (78)	30.8 (66)	34.9 (62)
15 Å pol-CG water	BLYP	7.2 (62)	7.1 (63)	23.0 (63)	25.5 (62)
	BP86	6.9 (63)	6.9 (63)	22.4 (65)	24.6 (64)
	B3LYP	8.6 (57)	8.9 (56)	39.1 (50)	44.8 (49)
	BHLYP	8.7 (56)	8.2 (69)	37.8 (59)	43.2 (53)

Table S5. Average time for one single AM1 energy and gradient evaluation (in s) and computational savings (percent, in parenthesis) for QM/MM/CG relative to full atomistic calculations (see text) of a glycine – water system.

QM method	QM/MM (s)	QM/MM/CG[a] (s)	Savings[a] (%)	QM/MM/CG[b] (s)	Savings[b] (%)
AM1	0.29	0.07	76	0.11	62

[a]GLY + 15 Å TIP3P water (inner region) + 15 Å CG water (outer region)
[b]GLY + 15 Å TIP3P water (inner region) + 15 Å pol-CG water (outer region)

Force field parameters for type D particles in pol-CG water

The charged sites of pol-CG water (type D particle) do not have LJ-interaction terms in the Martini CG force field v2.1P. However, in the CG/FG multi-scale methodology, the type D particles interact with FG charges directly. Hence, to avoid polarization catastrophe, we assigned the following LJ-parameters to type D particles:

R_{min} (van der Waals radius): 2.5 Å

E_{min} (well depth): 0.00025 kcal/mol