

Supporting Information

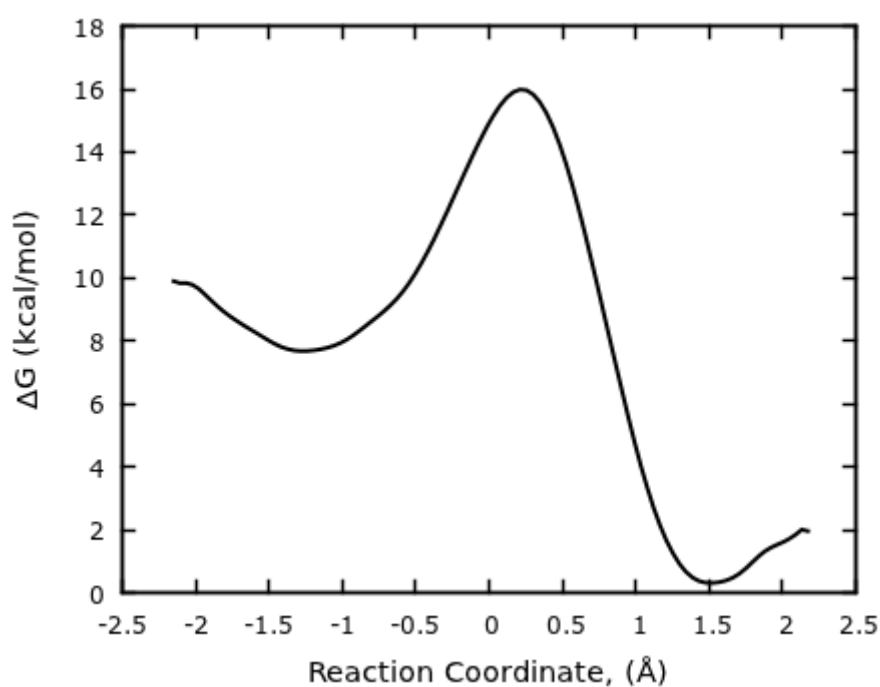
Enhancing Paradynamics for QM/MM sampling of Enzymatic Reactions

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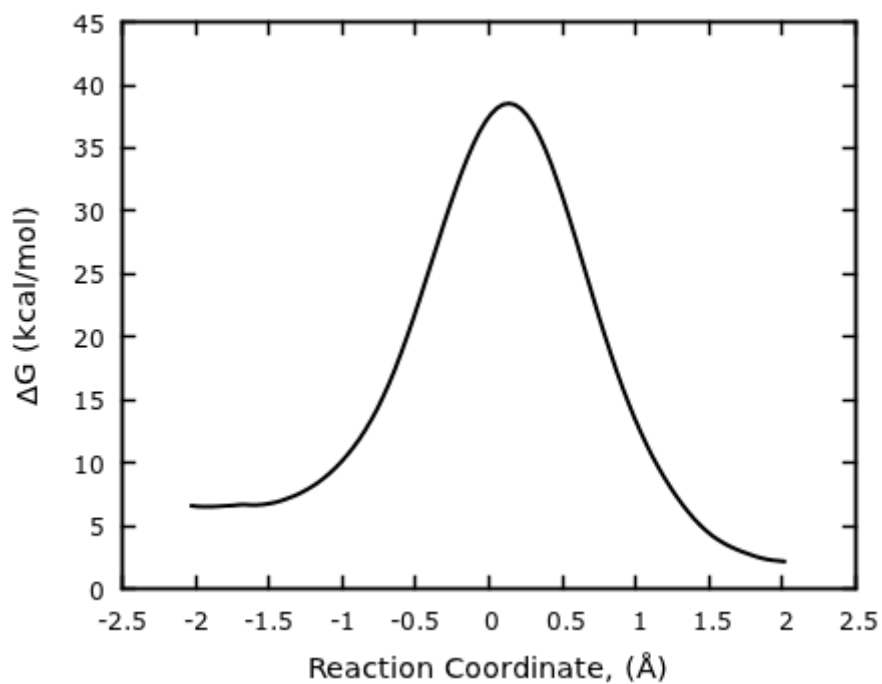
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Figure S1. The PMF obtained from sampling with PM6/MM potential for reaction catalyzed by Dh1A.^a



a) the PMF was obtained by WHAM using 41 windows of 20 ps each.

Figure S2. The PMF computed with PM3/MM potential for reaction involving trimethylsulfonium and dimethylamine.^a



a) The calculations were done using 41 windows and 20 ps of MD per window.

Figure S3. Distribution for the energy gap for $E_{PM6}-E_{EVB}$ obtained for reference and target potential during MD simulation for (a) the RS region and (b) the TS region.

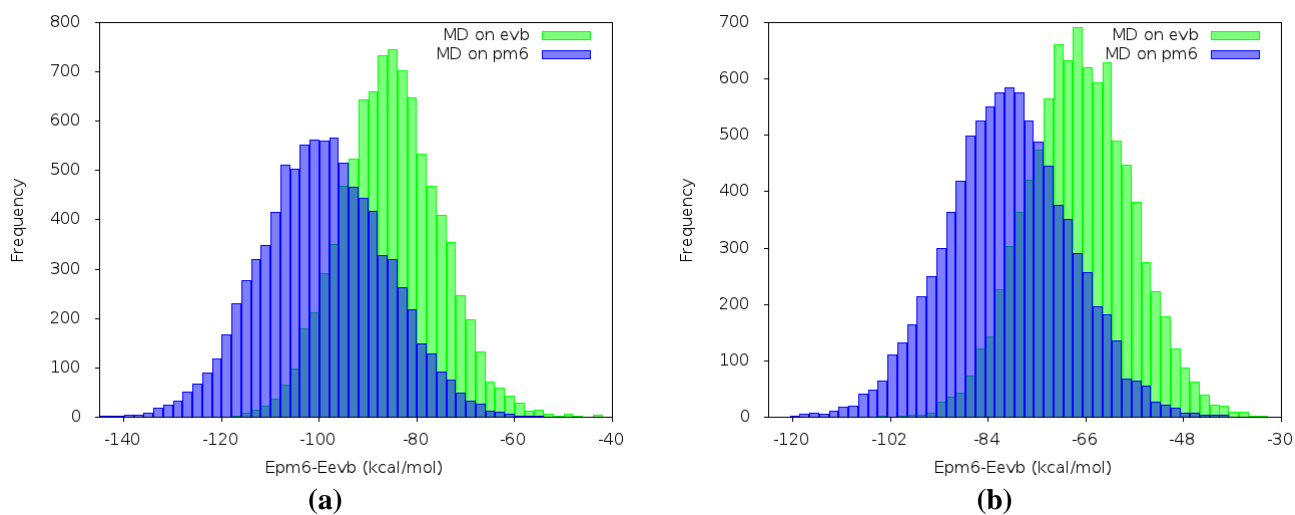
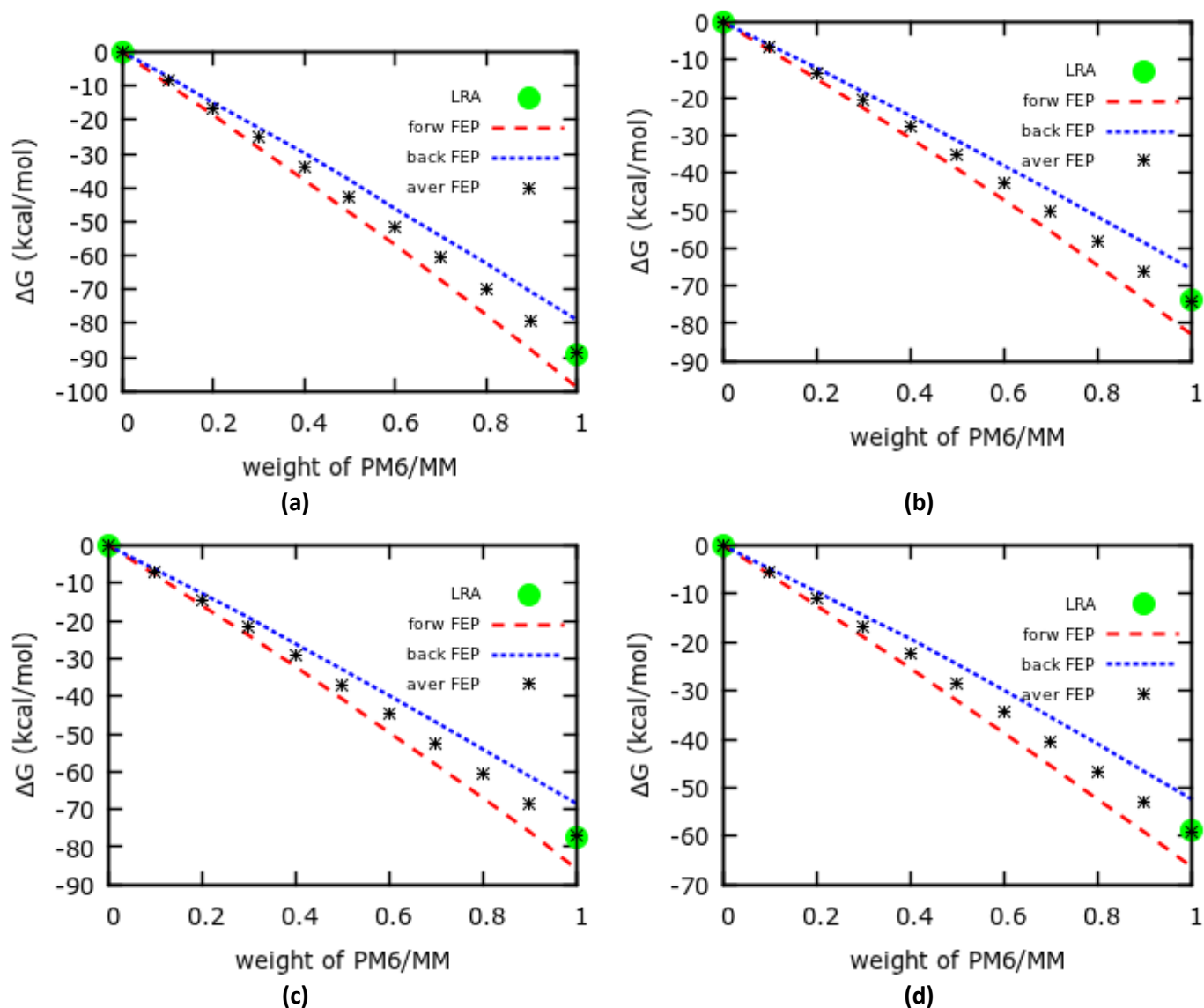
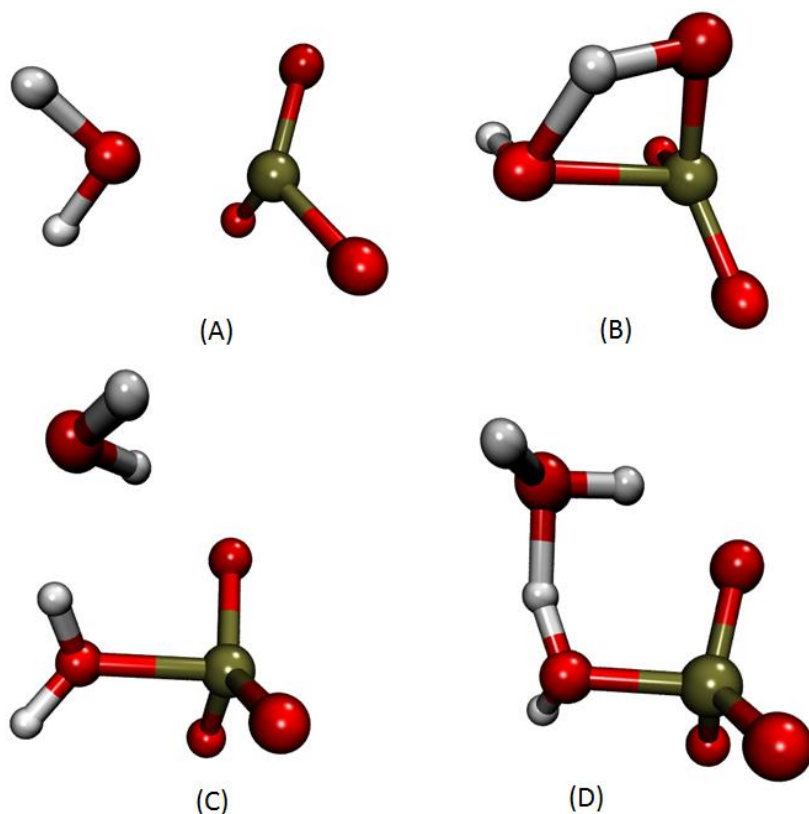


Figure S4. The forward, backward and average FEP results for moving from reference to the target potential in the Dh1A case. ^(a)



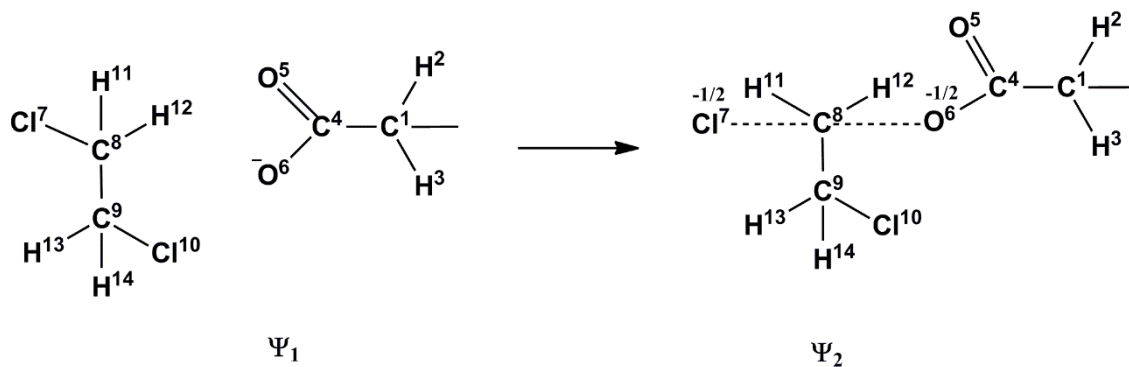
^(a)The surfaces are designate by (a) EVB1 and (b) EVB2 for reaction catalyzed by Dh1A and (c) at EVB1 and (d) EVB2 for reaction in water, where PM6/MM was used as target potential. It is important to point out that the LRA approach in some cases is found to be sufficiently accurate in accordance with the free energy perturbation evaluation while moving from RP to TP at RS and TS position.

Figure S5. The structures of the reacting fragments in the simplest model used to study the PT step in the hydrolysis of phosphate monoester in solution#.



#The structures of the 1w mechanism are described in (a) EVB1 and (b) EVB2, while the 2W water mechanism is described by (c) EVB1 and (d) EVB2.

Table S1. The EVB charges, atom types and EVB Parameters for the indicated atom types, for moving from EVB1 (Ψ_1 , Reactant State) to EVB2 (Ψ_2 , Transition State) for the S_N2 step in the catalytic reaction of haloalkene dehalogenase and water studied reaction. Energies in kcal/mol, distances are in angstroms (\AA) and angles in degrees.



Atom number	EVB1		EVB2	
	Atom Type	Charge	Atom Type	Charge
1	C0	-0.5001	C0	-0.5424
2	H0	0.1564	H0	0.2085
3	H0	0.1564	H0	0.2085
4	C+	0.8442	C+	0.7885
5	O+	-0.7861	O+	-0.6795
6	O-	-0.7861	O1	-0.6006
7	L0	-0.2230	L-	-0.5838
8	C0	-0.1217	C1	0.2074
9	C0	-0.1217	C0	-0.3096
10	L0	-0.2230	L0	-0.2254
11	H0	0.1511	H0	0.0698
12	H0	0.1511	H0	0.0698
13	H0	0.1511	H0	0.1943
14	H0	0.1511	H0	0.1943

Bonds (Morse): $\Delta M = D[1 - e^{\{-a(b-b_0)\}}]^2$

Bond Type	D	b_0	a
C0--H0	100.40	0.99	2.0
C0--L0	79.00	1.82	0.8
C1--L-	80.00	2.10	0.8
O1--C1	80.00	2.00	0.8
C0--C0	96.00	1.54	0.8
C+--O+	92.50	1.40	2.0
C1--O1	80.00	2.00	0.8

Bond Angles: $U_0 = \frac{1}{2}K_0(\theta - \theta_0)^2$

Bond Type	θ	K_θ
X-C+-Y	120.0	50.00
X-C0-Y	109.5	50.00
L--C1-H0	90.0	30.0
H0-C1-C0	120.0	30.0
O1-C1-H0	90.0	30.0
H0-C1-H0	120.0	30.0
X-O1-Y	109.0	50.00
X-O-Y	120.0	50.00
X-O+-Y	120.0	50.0

Nobonded : $U_{nb} = A_i A_j r^{-12} - B_i B_j r^{-6}$

Bond Type	A	B
H0	7.00	0.00
C0	632.00	24.00
C1	632.00	24.00
O+	774.00	24.00
O1	774.00	24.00
L0	774.00	24.00
L-	20500.00	24.00

OO	774.00	24.00
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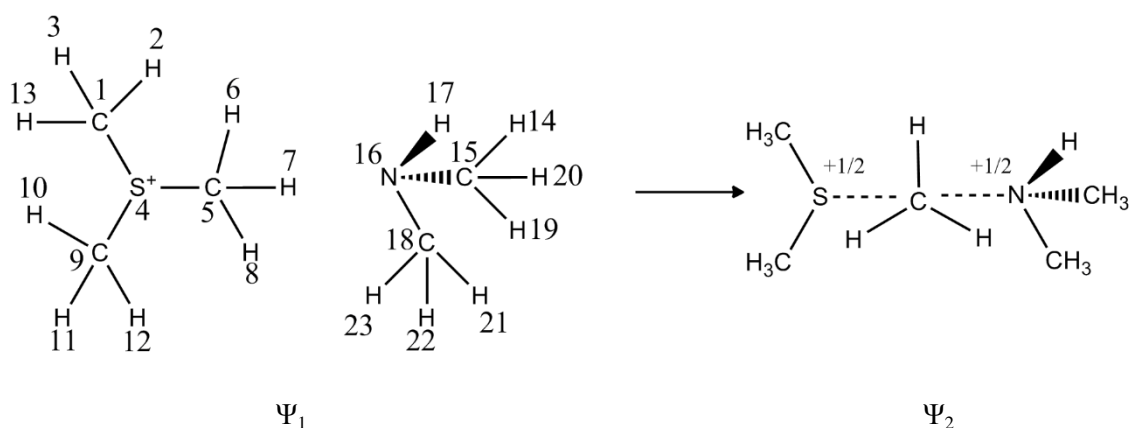
off-diagonal and shift parameters,

$$H_{12}=0.0$$

$$\alpha=0.0$$

where, the α is the gas phase shift and H_{12} is the matrix element between the two states.

Table S2. The EVB charges and atom types and EVB Parameters of the atom types for moving from EVB1 (Ψ_1) to EVB2 (Ψ_2) for the S_N2 reaction involving trimethylsulfonium and dimethylamine in solution. Energies are in kcal/mol, distances are in angstroms (Å) and angles in degrees.



Atom number	EVB1		EVB2	
	Atom Type	Charge	Atom Type	Charge
1	C0	-0.5321	C0	-0.5698
2	H0	0.2358	H0	0.2319
3	H0	0.2358	H0	0.2319
4	S+	0.4332	ST	0.1600
5	C0	-0.5321	CT	-0.4023
6	H0	0.2358	H0	0.1907
7	H0	0.2358	H0	0.1907
8	H0	0.2358	H0	0.1907
9	C0	-0.5321	C0	-0.5698
10	H0	0.2358	H0	0.2319
11	H0	0.2358	H0	0.2319
12	H0	0.2358	H0	0.2319
13	H0	0.2358	H0	0.2319
14	H0	0.0810	H0	0.1133
15	C0	-0.1469	C0	-0.2097
16	N0	-0.4774	NT	-0.1709
17	H+	0.3265	H+	0.3285
18	C0	-0.1469	C0	-0.2097
19	H0	0.0810	H0	0.1134
20	H0	0.0810	H0	0.1134
21	H0	0.0810	H0	0.1134
22	H0	0.0810	H0	0.1134

Bonds (Morse): $\Delta M = D[1 - e^{\{-a(b-b_0)\}}]^2$

Bond Type	D	b_0	a
CO--HO	100.40	0.99	2.0
CO--CO	96.00	1.54	0.8
CO--NO	93.0	1.44	2.0
CT--NT	93.0	2.00	2.0
CT--ST	93.0	2.20	2.0
CO--S+	70.0	1.80	2.0
NT--CO	93.0	1.44	2.0

Bond Angles: $U_0 = \frac{1}{2}K_0(\theta - \theta_0)^2$

Bond Type	θ	K_θ
X--CO--Y	109.5	50.00
ST--CT--HO	90.0	30.0
HO--CT--HO	120.0	30.0
ST--CT--HO	90.0	30.0
X--S+--Y	103.5	100.00
X--ST--Y	107.0	100.00
CO--NO--HO	109.5	50.0
CO--NT--HO	107.6	50.0

Nobonded : $U_{nb} = A_i A_j r^{-12} - B_i B_j r^{-6}$

Bond Type	A	B
HO	7.00	0.00
CO	632.00	24.00
CT	632.00	24.00
S+	1022.00	24.00
ST	1022.00	24.00
NO	774.00	24.00
NT	774.00	24.00

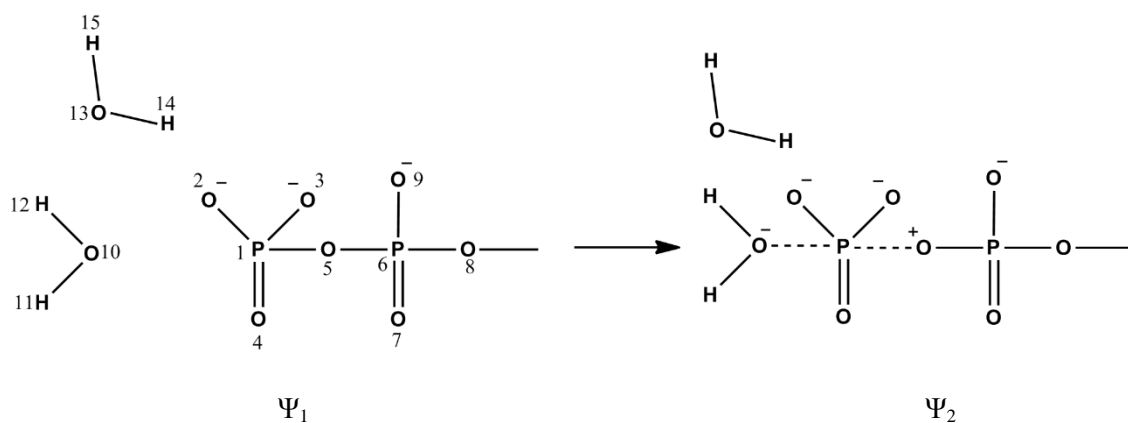
off-diagonal and shift parameters,

$$H_{12}=0.0$$

$$\alpha= 0.0$$

where, the α is the gas phase shift and H_{12} is the matrix element between the two states.

Table S3. The EVB charges, atom types and EVB Parameters of the atom types for moving from EVB1 (Ψ_1) to EVB2 (Ψ_2) for the arrival to the plateau in the hydrolysis of GTP in the Ras GAP system. Energies are in kcal/mol, distances are in angstroms (Å) and angles in degrees.



Atom number	EVB1		EVB2	
	Atom Type	Charge	Atom Type	Charge
1	P0	0.9227	P0	1.4431
2	O-	-0.7907	O-	-0.8758
3	O-	-0.7907	O-	-0.8758
4	O+	-0.7907	O+	-0.7991
5	O-	-0.5559	O1	-0.8968
6	P0	1.0178	P0	1.1471
7	O-	-0.8045	O-	-0.8968
8	O-	-0.8045	O-	-0.8968
9	O-	-0.2824	O-	-0.8968
10	O0	-0.9299	O2	-0.7025
11	H0	0.4046	H0	0.3901
12	H0	0.4046	H0	0.3901
13	O0	-0.9299	O0	-0.9299
14	H0	0.4046	H0	0.4046
15	H0	0.4046	H0	0.4046

Bonds: $\Delta M = D[1 - e^{-a(b-b_0)}]^2$

Bond Type	D	b_0	a
P0--O-	120.0	1.50	2.0
P0--O+	120.0	1.50	2.0
P0--O0	95.0	1.58	2.0
P0--O1	90.0	1.90	2.0
P0--O2	90.0	2.50	0.7
H0--O0	97.2	0.99	2.0

Bond Angles: $U_0 = \frac{1}{2}K_0(\theta - \theta_0)^2$

Bond Type	θ	K_θ
X-O1-Y	109.0	50.00
X-O-Y	120.0	50.00
X-P0-Y	109.0	100.00
X-O+-Y	120.0	50.0

Nobonded: $U_{nb} = A_i A_j r^{-12} - B_i B_j r^{-6}$

Bond Type	<i>A</i>	<i>B</i>
H0	7.00	0.00
O1	774.00	24.00
O2	774.00	24.00
P0	1250.00	24.00
O0	774.00	24.00
O-	800.00	15.00
O+	774.00	24.00

off-diagonal and shift parameters,

$$H_{12}=0.0$$

$$\alpha=0.0$$

where, the α is the gas phase shift and H_{12} is the matrix element between the two states.

Table S4. The selected ionized residues within the first solvation shells of the substrate for the RasGAP system.

Residue	Number	pKa
LYS	16	10.4
ASP	57	3.9
ARG	238	12.5
LYS	398	10.4
ASP	38	3.9
ASP	33	3.9
ARG	68	12.5
GLU	37	4.3
ARG	352	12.5

* All histidine residues were protonated automatically on ND1 by our standard MOLARIS procedure. The histidine in the first solvation shell were assumed to be neutral, leaving to further study the calculation of the pKa in the protein.

Table S5. The Free Energies for Transferring from the EVB to the PM6 moving the forward along the RC.^(a)

RC shift	$\Delta\Delta g_{\text{EVB}\rightarrow\text{PM6}}$	$\Delta\Delta g_{\text{EVB1}\rightarrow\text{EVB2}}$
0.0	-75.0	-1.0
0.1	-75.0	-1.0
0.2	-74.0	-2.0
-1.1	-89.0	-
-1.2	-90.0	-
-1.3	-91.0	-

(a) The calculations were performed by the FEP approach, for the Sn2 step in the catalytic reaction of haloalkene dehalogenase, where we have used 100 ps of MD per frame (a total of 11 frames were used per simulation).

Table S6. PD thermodynamic cycle computed by the FEP approach, for the Sn2 step in the catalytic reaction of haloalkene dehalogenase.^(a)

System	$\Delta\Delta g_{\text{EVB}\rightarrow\text{PM6}}$ (EVB1)	$\Delta\Delta g_{\text{EVB}\rightarrow\text{PM6}}$ (EVB2)	$\Delta\Delta g_{\text{EVB1}\rightarrow\text{EVB2}}$	$(\Delta\Delta g_{\text{RS}\rightarrow\text{TS}})_{\text{PD}}$	$(\Delta\Delta g_{\text{RS}\rightarrow\text{TS}})_{\text{PMF}}$
DhIA	-91.0	-74.00	-2.0	15.0	10.0

(a) Energies in kcal/mol. EVB₁ corresponds to the RS and EVB₂ corresponds to the TS for the S_{N2} step of the reaction of haloalkene dehalogenase, where we have used 100 ps of MD per frame for Evaluating the Free Energies for Transferring from the EVB to the PM6 Free-Energy Surface.