Supplementary Information

Computer simulation of reactions in β-cyclodextrin molecular reactors: transition state recognition.

Violeta Yeguas,[a,b] *Ramón López,*[a] *Alexandrine Lambert,*[b] *Gérald Monard*[b] *and Manuel F. Ruiz-López*[b*]

[a] Departamento de Química Física y Analítica, Universidad de Oviedo, C/Julián Clavería, 8, 33006 Oviedo, Spain.

[b] Equipe de Chimie et Biochimie Théoriques, SRSMC, Nancy-University, CNRS, BP 70239, 54506 Vandoeuvre-lès-Nancy, Cedex, France

Manuel.Ruiz@cbt.uhp-nancy.fr

Table of Contents

Details on computations

Details on MM force-field and MD simulations

MD simulations have been run in the constant isothermal-isobaric (NPT) ensemble at 298 K and 1 atm with an integration step of 1 fs. The chemical system was placed in a cubic box with a side length of 36.34 Å containing between 1400 and 1600 TIP3P[1] water molecules, the exact number depending on system and environment (bulk water or aqueous β-CD). The SHAKE algorithm[2] was used to keep the water molecules rigid. Periodic boundary conditions with a cutoff of 9 Å both for electrostatic and van der Waals interactions have been applied. The AMBER force field has been used to describe the β-CD and the Generalized AMBER one (GAFF) for the guest molecules[3] due to the lack of suitable parameters for the nitrogen and oxygen atoms of the ester nitro group. Atomic charges for β-CD were chosen according to Bonnet et *al*,[4] while for the guest species, they were obtained from the restrained electrostatic potential (RESP) model at the HF/6-31G(d) level of theory.[5] In the case of transition states, a flat-welled harmonic potential was used to freeze the relative positions of atoms in the six-member ring that define the reaction coordinate. The geometry defining the energy minimum of the ring was taken from calculations using the implicit model. The initial geometry of the host-guest complexes was obtained by inserting at random the B3LYP/6-31G(d) optimized guest molecules into the β-CD cavity through the PyMOL program[6] followed by MM energy minimization. The trial β-CD structure was taken from the Protein Data Bank. After an equilibration period of 500 ps, simulations have been carried out for another 500 ps saving snapshots every 1 ps. Atomic charges for guests and force constants used for TS constraints are provided as a separate file of the Supporting Information.

1. W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey and M. L. Klein, *J. Chem. Phys.*, 1983, **79**, 926.
2. S. Miyamoto and P. A. Kollman, *J. Comput. Chem.*, 1992, **13**, 952.
3. W. D. Cornell, P. Cieplak, C. I. Bayly, I. R. Gould, K. M. Merz, D. M. Ferguson, D. C. Spellmeyer, T. Fox, J. W. Caldwell and P. A. Kollman, *J. Am. Chem. Soc.*, 1995, **117**, 5179; J. Wang, R. M. Wolf, J. W. Caldwell, P. A. Kollman and D. A. Case, *J. Comput. Chem.*, 2004, **25**, 1157.
4. P. Bonnet, C. Jaime and L. Morin-Allory, *J. Org. Chem*, 2002, **67**, 8602.
5. J. Wang, P. Cieplak and P. A. Kollman, *J. Comput. Chem.*, 2000, **21**, 1049.
6. W. L. DeLano, *The PyMOL Molecular Graphics System*, Delano Scientific, San Carlos, CA, USA, 2002.

Details on QM/MM computations

Total QM/MM energies are computed as follows:

$$E = E_{QM} + E_{MM} + E_{QM/MM}$$

$$E_{QM/MM} = E_{elec} + E_{Lennard\text{-}Jones}$$

where E_{QM} and E_{MM} correspond to the QM and MM system energies, respectively, and $E_{QM/MM}$ is the interaction energy, with:

$$E_{QM} = <\psi|H^o|\psi>$$

$$E_{elec} = <\psi|V|\psi>$$

Here, ψ corresponds to the polarized wavefunction of the chemical system and H^0 and V hold, respectively, for the unperturbated Hamiltonian of the chemical system and the electrostatic potential created by the MM environment

Table 1S. B3LYP/6-31G(d) calculations of species involved in neutral ester hydrolysis mechanisms. Cartesian coordinates of optimized structures in bulk water using the implicit solvent model.

R$(H_2O)_2$

C	0.020055	-0.179639	-0.248112
C	-0.082528	-1.571929	-0.111864
C	1.067100	-2.353683	-0.056485
C	2.307904	-1.722738	-0.139207
C	2.436578	-0.340537	-0.274976
C	1.280309	0.429607	-0.329205
N	3.525171	-2.545002	-0.081607
O	3.395320	-3.763944	0.040107
C	-1.188716	0.697409	-0.311399
O	-1.119681	1.912356	-0.442084
O	4.613698	-1.973470	-0.158108
O	-2.328488	0.014149	-0.214757
C	-3.560785	0.772268	-0.273699
O	-4.073895	3.212425	2.101114
H	1.009139	-3.430928	0.048201
H	3.419179	0.112920	-0.335861
H	1.344558	1.507792	-0.434428
H	-1.057682	-2.042466	-0.049437
H	-4.352140	0.022116	-0.274960
H	-3.648355	1.426673	0.598650
H	-3.591887	1.361451	-1.194265
H	-5.011870	3.233360	1.837117
H	-3.618895	3.655043	1.346574
H	-2.193223	3.444576	-0.298905
O	-2.728599	4.244196	-0.118688
H	-2.076074	4.894033	0.207088

TS$_c$

C	-0.106564	-0.150043	0.144581
C	0.040274	-0.061535	1.532229
C	1.318913	0.107124	2.083615
C	2.437343	0.184015	1.262570
C	2.261015	0.091358	-0.121114
C	1.001352	-0.074649	-0.695748
C	-1.218693	-0.152310	2.395885
O	-0.874350	-1.230124	3.495757
N	3.433440	0.171979	-0.992108
O	3.262663	0.092586	-2.211963
O	4.541970	0.315732	-0.468546
O	-2.330280	-0.314241	1.868456
O	-1.114435	1.104675	3.367912
C	-1.699100	2.272336	2.786589
O	-1.863730	-0.049967	5.364405
H	3.431652	0.313159	1.674557
H	0.899286	-0.142004	-1.772882
H	-1.103159	-0.279726	-0.265253
H	1.434526	0.177899	3.160105
H	-2.713766	2.065074	2.431607
H	-1.722738	3.043826	3.561318
H	-1.084809	2.623156	1.948528
H	-1.631428	0.703217	4.619935
H	-1.454173	-0.810284	4.683556
H	-1.241002	0.059761	6.117825
H	-1.358226	-2.019742	3.170581

TS$_1$

C	-0.288466	0.090636	-0.147106
C	0.441391	1.202109	0.296120
C	1.829830	1.152424	0.363045
C	2.477434	-0.024381	-0.017240
C	1.773818	-1.143980	-0.462816
C	0.385691	-1.075719	-0.525365
N	3.938060	-0.084110	0.050664
O	4.545705	0.914306	0.446527
C	-1.808943	0.105110	-0.214507
O	-2.370073	-0.805971	-0.946148
O	4.496325	-1.130330	-0.290528
O	-2.236159	1.421933	-0.356227
C	-3.605690	1.594823	-0.739449
H	2.407219	2.005266	0.701114
H	2.307788	-2.041202	-0.754351
H	-0.191305	-1.924735	-0.876199
H	-0.077737	2.110522	0.582794
H	-3.746228	2.671527	-0.853069
H	-3.813362	1.084868	-1.684215
H	-4.286701	1.218953	0.033644
O	-2.202162	-0.259400	1.381101
H	-3.249477	-0.979891	1.229789
O	-4.021664	-1.595166	0.617965
H	-3.396910	-1.356738	-0.279683
H	-2.391611	0.590786	1.831158
H	-3.895769	-2.544323	0.826912

I

C	0.399657	-1.130431	-0.224953
C	-0.235376	0.108346	-0.061872
C	0.538269	1.259518	0.134024
C	1.928224	1.182295	0.161871
C	2.533675	-0.062787	-0.006275
C	1.786464	-1.226101	-0.200476
C	-1.766403	0.154775	-0.021379
O	-2.230212	-0.202542	1.274306
N	3.993994	-0.152161	0.019590
O	4.513890	-1.260357	-0.136938
O	4.639765	0.884107	0.198585
O	-2.282657	-0.776708	-0.899786
O	-2.137625	1.479759	-0.334278
C	-3.543922	1.716321	-0.430136
O	-4.624798	-1.612034	0.214548
H	2.536522	2.067465	0.308594
H	2.287410	-2.178745	-0.329490
H	-0.202439	-2.019412	-0.379893
H	0.050760	2.220117	0.257040
H	-3.653719	2.765390	-0.714271
H	-3.999366	1.080519	-1.197321
H	-4.046486	1.543969	0.528611
H	-4.347670	-1.366775	1.119169
H	-3.152305	-1.104513	-0.542809
H	-1.969830	0.512807	1.898288
H	-4.650435	-2.589948	0.235114

TS_2

C	-2.192411	-2.408734	1.684688
C	-2.085961	-1.067816	2.081204
C	-0.828271	-0.518527	2.345695
C	0.323542	-1.290746	2.211670
C	0.191166	-2.619960	1.814618

C	-1.054705	-3.194735	1.550228
C	-3.321950	-0.198665	2.239675
O	-3.190796	1.008131	2.710682
N	1.395470	-3.441335	1.671987
O	1.261084	-4.617213	1.324246
O	2.488542	-2.919666	1.905664
O	-4.355241	-0.928713	2.749558
O	-3.683001	-0.020613	0.534844
C	-5.075944	0.143530	0.267837
H	1.305138	-0.877608	2.413775
H	-1.120143	-4.232710	1.244781
H	-3.169148	-2.834655	1.479220
H	-0.754583	0.515553	2.665942
H	-5.193772	0.323274	-0.806544
H	-5.617873	-0.766536	0.540227
H	-5.501633	0.994120	0.820244
H	-5.003891	-0.287585	3.127986
H	-2.763606	1.760275	1.764403
O	-2.550125	2.087513	0.672070
H	-3.128707	2.848076	0.461145
H	-3.089613	1.109476	0.360257

P$(H_2O)_2$

C	-1.336235	0.021704	-2.247904
C	-1.314458	-0.009473	-0.858096
C	-0.096527	-0.099900	-0.170024
C	1.110080	-0.160298	-0.882066
C	1.103602	-0.129992	-2.273308
C	-0.122122	-0.038876	-2.932295
C	-0.122556	-0.126717	1.327780
O	-1.180750	-0.065985	1.952223
N	-0.135340	-0.004552	-4.401304
O	0.944600	-0.055094	-4.992201
O	1.075319	-0.220062	1.875679
O	-1.225936	0.073556	-4.969273
O	1.108510	-0.185937	4.482655
C	1.641112	1.055259	4.959660
O	-1.549702	-0.177466	4.733380
H	1.033885	-0.221983	2.898374
H	2.025685	-0.175007	-2.841304
H	-2.268667	0.091841	-2.796042
H	-2.240160	0.036611	-0.293769
H	2.051079	-0.230039	-0.347300
H	-1.581768	-0.135695	3.751641
H	-1.887527	-1.069499	4.948715
H	1.632150	1.082881	6.056121
H	2.675997	1.124821	4.613852
H	1.078174	1.916654	4.575797
H	0.147596	-0.232579	4.746926

Table 2S. B3LYP/6-31G(d) calculations of species involved in neutral ester hydrolysis mechanisms. Energetics in bulk water using the implicit solvent model. Notation and units are:

E_{sol}	Total energies (hartree)
H_{gas} and TS_{gas}	Thermal and entropy corrections, from frequency calculations in gas phase (hartree)
G and ΔG	Total and relative free energies (hartree and kcal mol^{-1}, respectively)
ΔG_{solv}	Free energies of solvation (kcal mol^{-1})

Components of the free energies of solvation, $\Delta G_{solv} = \Delta G^{\text{non-elec}}{}_{solv} + \Delta G^{\text{elec}}{}_{solv}$ (with $\Delta G^{\text{elec}}{}_{solv} = 1/2\ E_s^{el} + E_s^{pol}$)

$\Delta G^{\text{non-elec}}{}_{solv}$	non-electrostatic solvation free energy (kcal mol^{-1})
$\Delta G^{\text{elec}}{}_{solv}$	electrostatic solvation free energy (kcal mol^{-1})
$E_s^{pol} = \langle \psi_s \vert H^\circ \vert \psi_s \rangle - \langle \psi_o \vert H^\circ \vert \psi_o \rangle$	solute polarization (kcal mol^{-1})
$E_s^{el} = \langle \psi_s \vert V \vert \psi_s \rangle$	electrostatic solute-solvent interaction (kcal mol^{-1})

where ψ_o and ψ_s correspond, respectively, to the chemical system wave function in gas phase and in the continuum (with the optimized geometry in the continuum, in both cases). V represents the reaction field potential and H° the Hamiltonian for the isolated chemical system.

Species	E_{sol}	H_{gas}	TS_{gas}	G	ΔG	ΔG_{solv}	$\Delta G^{\text{non-elec}}{}_{solv}$	$\Delta G^{\text{elec}}{}_{solv}$	E_s^{pol}	E_s^{el}
R$(H_2O)_2$	-817.483198	0.214443	0.066620	-817.335375	0.0	-4.9	7.8	-12.7	1.2	-27.8
TS$_c$	-817.419869	0.206991	0.059807	-817.272685	39.3	-10.9	6.1	-17.0	2.2	-38.4
TS$_1$	-817.433210	0.207308	0.057924	-817.283826	32.3	-7.3	5.6	-12.9	1.5	-28.8
I	-817.468564	0.214955	0.060816	-817.314425	13.1	-10.3	6.0	-16.3	2.0	-36.6
TS$_2$	-817.433043	0.207311	0.058627	-817.284359	32.0	-8.1	5.9	-14.0	1.7	-31.4
P$(H_2O)_2$	-817.496582	0.215015	0.064487	-817.346054	-6.7	-2.6	7.0	-9.6	0.9	-21.0

Table 3S. B3LYP/6-31G(d) calculations of species involved in neutral ester hydrolysis mechanisms. Energetics using the implicit solvent model for ε = 10, representing the effective dielectric constant in the β-CD environment. Notation and units, see Table 2S.

Species	E_{sol}	H_{gas}	TS_{gas}	G	ΔG	ΔG_{solv}	$\Delta G^{non\text{-}elec}{}_{solv}$	$\Delta G^{elec}{}_{solv}$	E_s^{pol}	E_s^{el}
R$(H_2O)_2$	-817.480365	0.214443	0.066620	-817.332542	0	-3.2	7.8	-10.9	0.9	-23.6
TS_c	-817.416082	0.206991	0.059807	-817.268898	39.9	-8.6	6.1	-14.7	1.6	-32.6
TS_1	-817.430216	0.207308	0.057924	-817.280832	32.4	-5.4	5.6	-11.0	1.1	-24.2
I	-817.464647	0.214955	0.060816	-817.310508	13.8	-7.8	6.1	-13.9	1.4	-30.6
TS_2	-817.429730	0.207311	0.058627	-817.281046	32.3	-6.0	5.9	-11.9	1.2	-26.2
P$(H_2O)_2$	-817.494449	0.215015	0.064487	-817.343921	-7.1	-1.2	7.0	-8.2	0.7	-17.8

Table 4S. Binding energy analysis (kcal mol^{-1}) for *head-first* (**H-F**) and *tail-first* (**T-F**) modes of complexation of the ester reactant with the β-CD. Energies are calculated from the expression $\langle E_{CD\text{-}ester} \rangle - \langle E_{CD} \rangle - E_{ester}$, where E_S refers to the MM energy of system S in water solution (a continuum model is employed to account for solvation energy. Averages are computed over 250 structures that have been optimized starting from snapshots of the MD simulations in water solution.

	H-F	**T-F**
ΔE_{vdw}	-23.0	-22.1
ΔE_{elec}	-1.2	-1.3
ΔE_{solv}	5.8	5.5
$\Delta E_{stretch}$	-0.9	-0.8
ΔE_{bend}	-0.9	-1.0
$\Delta E_{torsion}$	-4.4	-3.7
ΔE_{bind}	**-24.6**	**-23.4**