Shape Theory and DFT Methods in Complete Route and Dissociation Mode of the O-H Bond in betanidin and molecular interactions

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Supporting information

Tables

Table S1. Clusterization by grouping the extremal Riemannian distance (first deprotonation).

Quadrilateral				Riemannian Distance	Cluster
2	15	17	5	0.1739982	Low
2	17	16	5	0.1750406	Low
2	15	17	16	0.1750411	Low
2	17	16	6	0.2063031	Low
2	15	17	6	0.2085463	Low
2	17	6	5	0.2085471	Low
15	17	16	5	0.9597192	High
2	15	16	5	0.9609802	High
15	16	6	5	0.996004	High
15	17	6	5	1.0143631	High
17	16	6	5	1.018622	High
15	17	16	6	1.0186227	High
2	15	6	5	1.032853	High
2	16	6	5	1.0382936	High
2	15	16	6	1.0382954	High

Table S2. Clusterization by grouping the extremal Riemannian distance (second deprotonation).

Low cluster:		
Route	**pK_a**	**RD**
C2C17-COOH	1.17	0.03057668
C6C17-COOH	1.18	0.02404829
C15C17-COOH	1.30	0.02775259
C2C15-COOH	2.57	0.02108612
C5C17-COOH	2.70	0.01989275
C15C2-COOH	2.81	0.02768809
C17C2-COOH	2.87	0.03778869
C17C15-COOH	3.04	0.01271396
C6C2-COOH	3.13	0.01987726
C6C15-COOH	3.30	0.01226299
C5C15-COOH	3.66	0.03369306
C5C2-COOH	3.86	0.02312037
C16C2-COOH	4.50	0.01783635
C16C17-COOH	5.04	0.04225589
C16C15-COOH	5.69	0.01783658
High Cluster:		
Route	**pK_a**	**RD**
C2C5-COOH	11.68	0.03432945
C2C6-COOH	9.789	0.02407259
C2C16-COOH	12.12	0.00964120
C5C6-COOH	13.77	0.03445150
C5C16-COOH	14.65	0.02936308
C6C16-COOH	12.90	0.03369117
C15C16-COOH	13.89	0.02267662
C17C16-COOH	15.34	0.01890652
C6C5-COOH	14.92	0.03057986
C15C5-COOH	11.99	0.02933161
C16C5-COOH	14.74	0.03777423
C15C6-COOH	10.44	0.05840921
C17C6-COOH	10.27	0.01113999
C16C6-COOH	11.94	0.01756996

Table S3. Clusterization by grouping the extremal Riemannian distance (third deprotonation).

Low cluster:		
Route	**pK_a**	**RD**
C2C5C15-COOH	4.040641	0.03184669
C2C5C17-COOH	2.559508	0.03567296
C2C6C15-COOH	4.11196	0.02868663
C2C15C17-COOH	1.895092	0.02412021

C2C16C15-COOH	6.087724	0.04892679
C2C16C17-COOH	5.190026	0.03223093
C2C17C15-COOH	3.560734	0.02182678
C5C2C15-COOH	4.088042	0.0318347
C5C2C17-COOH	2.612431	0.03567449
C5C6C2-COOH	3.981745	0.03464038
C5C6C15-COOH	4.832051	0.03075638
C5C6C17-COOH	4.810425	0.04158344
C5C15C2-COOH	4.240334	0.03185571
C5C15C17-COOH	2.884354	0.01854838
C5C16C2-COOH	4.994014	0.03256714
C5C16C17-COOH	5.792785	0.04748235
C5C17C2-COOH	3.500458	0.01608804
C5C17C15-COOH	3.834966	0.01854182
C6C2C15-COOH	4.15568	0.02868962
C6C2C17-COOH	2.394333	0.02211777
C6C5C2-COOH	4.023624	0.03462641
C6C5C15-COOH	4.873929	0.03075456
C6C15C2-COOH	3.932512	0.0415645
C6C15C17-COOH	1.828835	0.07688511
C6C16C2-COOH	4.418861	0.02735647
C6C16C15-COOH	6.843244	0.03528778
C6C16C17-COOH	7.699991	0.05170627
C6C17C2-COOH	4.286806	0.0647466
C6C17C5-COOH	4.849543	0.0248142
C6C17C15-COOH	6.815636	0.06196777
C15C2C17-COOH	2.429303	0.0217884
C15C5C2-COOH	4.257827	0.03181731
C15C5C17-COOH	2.900467	0.01854813
C15C6C2-COOH	3.990496	0.02872013
C15C6C17-COOH	1.881757	0.02736015
C15C6C2-COOH	4.807204	0.04894383
C15C16C17-COOH	6.066098	0.05082758
C15C16C17-COOH	3.877758	0.02174538
C16C2C15-COOH	6.172854	0.04895076
C16C2C17-COOH	5.304604	0.03217205
C16C5C2-COOH	5.046015	0.03256322
C16C5C15-COOH	6.486656	0.04886661
C16C5C17-COOH	5.844326	0.04748235
C16C6C2-COOH	4.723469	0.04246386
C16C6C15-COOH	9.44156	0.07688696

C16C6C17-COOH	4.936966	0.06124167
C16C15C2-COOH	4.855065	0.04903403
C16C15C17-COOH	6.1204	0.05080701
C16C17C2-COOH	5.211659	0.05951797
C16C17C15-COOH	6.748006	0.05083987
C17C2C15-COOH	4.119331	0.0217638
C17C6C2-COOH	4.131754	0.02211784
C17C6C15-COOH	3.519791	0.01999184
C17C15C2-COOH	3.934362	0.0217446
C17C6C2-COOH	5.119167	0.04144685
C17C16C15-COOH	6.331128	0.05086966
High Cluster:		
Route	**pk_a**	**RD**
C2C5C6-COOH	13.88265	0.03460986
C2C5C16-COOH	15.56946	0.03662038
C2C6C5-COOH	15.77191	0.03463583
C2C6C16-COOH	14.53832	0.03420869
C2C15C5-COOH	13.13955	0.0318373
C2C15C6-COOH	11.32069	0.02866096
C2C15C16-COOH	15.66378	0.04895076
C2C16C5-COOH	15.32697	0.03250511
C2C16C6-COOH	11.84891	0.03145929
C2C17C5-COOH	12.83173	0.01609826
C2C17C6-COOH	10.96548	0.02210366
C2C17C16-COOH	17.07866	0.04151977
C5C2C6-COOH	13.93143	0.03460457
C5C2C16-COOH	15.61824	0.03661774
C5C6C16-COOH	17.33126	0.03841974
C5C15C6-COOH	14.88204	0.03395749
C5C15C16-COOH	17.39844	0.04886264
C5C16C6-COOH	17.42605	0.03081434
C5C17C6-COOH	14.96164	0.02468243
C5C17C16-COOH	17.36669	0.03154302
C6C2C5-COOH	15.81655	0.03463981
C6C2C16-COOH	14.58296	0.03420586
C6C5C16-COOH	17.37544	0.03841084
C6C15C5-COOH	16.38755	0.02868429
C6C15C16-COOH	19.08985	0.03387069
C6C16C5-COOH	20.37773	0.03565426
C6C17C5-COOH	17.5581	0.02210511

C6C17C16-COOH	16.70596	0.06124167
C15C2C5-COOH	13.43082	0.03183298
C15C2C6-COOH	11.61564	0.02869935
C15C2C16-COOH	15.92146	0.04902514
C15C5C6-COOH	14.90735	0.03395642
C15C5C16-COOH	17.40903	0.04886935
C15C6C5-COOH	16.44554	0.0338829
C15C6C16-COOH	16.4569	0.05168047
C15C16C5-COOH	15.47375	0.04886597
C15C16C6-COOH	12.99369	0.05167268
C15C17C5-COOH	13.53526	0.0185696
C15C17C6-COOH	10.72989	0.01992568
C15C17C16-COOH	18.63663	0.05083987
C16C2C5-COOH	15.37713	0.03250546
C16C2C6-COOH	11.89769	0.0314596
C16C5C6-COOH	17.47805	0.03081554
C16C6C5-COOH	20.36669	0.04244721
C16C15C5-COOH	15.51793	0.04886555
C16C15C6-COOH	15.69462	0.07688696
C16C17C5-COOH	15.54922	0.04749038
C16C17C6-COOH	11.45137	0.05610294
C17C2C5-COOH	13.40827	0.0160782
C17C2C6-COOH	11.53788	0.02212678
C17C2C16-COOH	16.78281	0.03217784
C17C6C5-COOH	17.5986	0.02446831
C17C6C16-COOH	16.54216	0.06124167
C17C15C5-COOH	13.59232	0.01856994
C17C15C6-COOH	10.74969	0.02001957
C17C15C16-COOH	18.67759	0.05085876
C17C16C5-COOH	15.08863	0.04712702
C17C16C6-COOH	11.73572	0.04110981

Molecular Dynamics for systems from conventional software

The molecular dynamics study's objective is to simulate the local conformational changes in the complex that result from the binding between the protein pocket and the ligand. The procedure gives flexibility to the ligand and the protein residues to arrive at a conformation in a steady state. We chose for molecular dynamics the best conformation obtained from the molecular Docking stage via via conventional software. We used the NAMD program, and the force field used is CHARMM36m which can calculate parameters of bound or unbound molecules. Then we create an environment to put the molecule to interact with the water. In this case, the protein is in a rectangular system with the correct amount of water molecules needed to solvate the box

dimensiones. We add KCl 0.15 M necessary in the solution, which is necessary in solution to eliminate electrostatic interactions between dissolved molecules.

At the end of the simulation, a file with the extensión *.dcd was obtained, containing the residues' trajectories during molecular dynamics. These trajectories are crucial to calculating the protein's RMSD during the simulation, which is a widely used measure to quantify the structural deformation of the protein compared to the initial reference point. Figure S1 y Figure S2 show that the complexes formed with Ligand 1 (C17C15C2-COO-) and Ligand 2 (C6C15C17-COO-) during the molecular dynamics (DM) simulations have high stability during the simulation time. We can see that the structure does not vary significantly; in this case, there is an increase in the RMSD until reaching a point where the values fluctuate around 0.47 and 1.24 Å of RMSD (Root-mean-square deviation), case Ligand 1. For Ligand 2, the RMSD value is between 0.41 and 1.54 Å. The structures remain within the parameter that considers the system equilibrium. Therefore, neither of the two complexes suffered a loss of its structure during the simulation. We can observe from Figure S1 and Figure S2 that the deviations fall within normality. The average of this measure is similar for the two systems, 1.002 and 1.105, respectively.

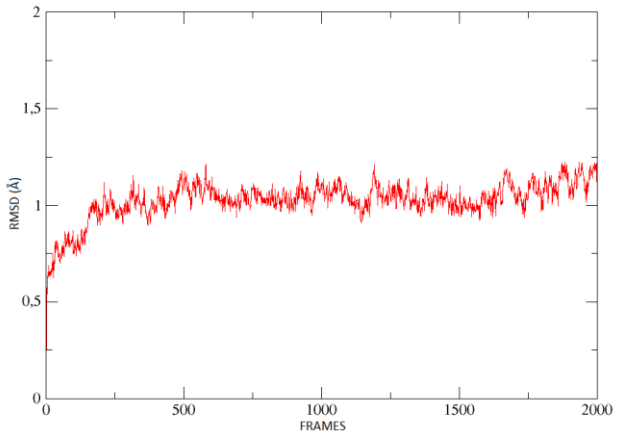

Figure S1. RMSD of the protein backbone in complex with Ligand 1 during the simulation of DM trajectories

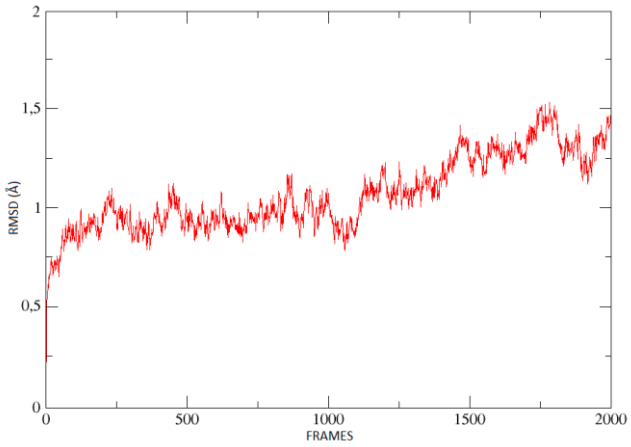

Figure S2. RMSD of the protein backbone in complex with Ligand 2 during the simulation of DM trajectories

To analyze the complexes formed in the computational study, we obtained the last trajectory (frame) and the most energetically stable of each molecular dynamics performed. We observed the interactions of each of the compounds with the enzyme aldose reductase (AR). Figures S3 and S3 represent the potential interactions of the Ligand 1-AR and Ligand 2-AR complexes.

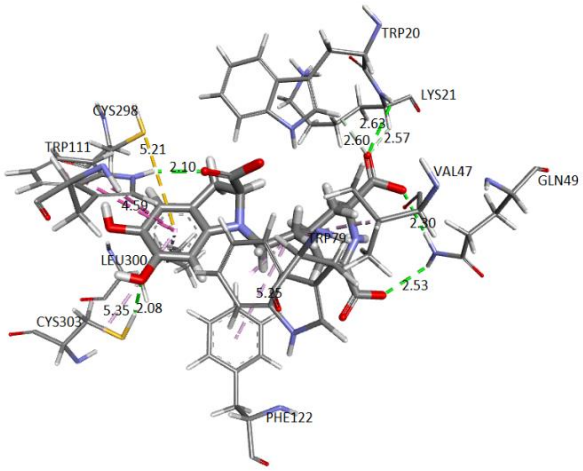

Figure S3. Molecular basis of potential active site interactions with deprotonated Bd (C17C15C2-COOH).

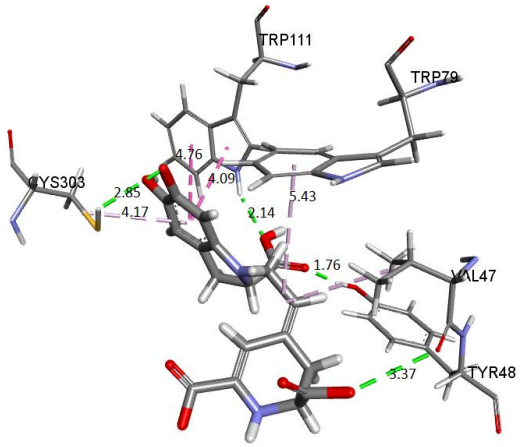

Figure S4. Molecular basis of potential active site interactions with deprotonated Bd (C6C15C17-COOH)

Similarly, we tabulate the interactions between the amino acids of the protein pocket and the ligands considered here (see Table S4 and Table S5).

Table S4 Interactions between the deprotonated Bd (C17C15C2-COOH) and the receptor pocket.

Name	**Distance (Å)**	**Category/Type**
LYS21:H- Bd:O	2.63	Hydrogen Bond
GLN49:H - H:Bd:O	2.53	Hydrogen Bond
GLN49:H - H:Bd:O	2.30	Hydrogen Bond
TRP111:H - H:Bd:O	2.12	Hydrogen Bond
CYS303:H - H:Bd:O	2.08	Hydrogen Bond
TRP20:H - H:Bd:O	2.60	Hydrogen Bond
LYS21:H - H:Bd:O	2.57	Hydrogen Bond
TRP111 - H:Bd	4.60	Hydrophobic/Pi-Pi Stacked
VAL47 - H:Bd	4.66	Hydrophobic/Alkyl
TRP79 - H:Bd	4.86	Hydrophobic/Pi-Alkyl
PHE122 - H:Bd	5.24	Hydrophobic/Pi-Alkyl
H:Bd - LEU300	4.65	Hydrophobic/Pi-Alkyl
H:Bd - CYS303	5.35	Hydrophobic/Pi-Alkyl
LYS21:H - Bd:O	2.63	Hydrogen Bond
GLN49:H - Bd:O	2.53	Hydrogen Bond
GLN49:H - Bd:O	2.30	Hydrogen Bond
TRP111:H - Bd:O	2.11	Hydrogen Bond
CYS303:H - Bd:O	2.08	Hydrogen Bond
TRP20:H - Bd:O	2.60	Hydrogen Bond
LYS21:H - H:Bd:O	2.57	Hydrogen Bond

Table S5 Interactions between the deprotonated Bd (C6C15C17-COOH) and the receptor pocket

Name	**Distance (Å)**	**Category/Type**
TYR48:H - Bd:O	1.76	Hydrogen Bond
TRP111:H - Bd:O	2.14	Hydrogen Bond
CYS303:H - Bd:O	2.85	Hydrogen Bond
Bd:O - VAL47:O	3.37	Hydrogen Bond
TRP111 - Bd	4.09	Hydrophobic/Pi-Pi Stacked
TRP111 - Bd	4.76	Hydrophobic/Pi-Pi Stacked
VAL47 - Bd	4.43	Hydrophobic/Alkyl
TRP79 - Bd	5.43	Hydrophobic/Pi-Alkyl
Bd - CYS303	4.11	Hydrophobic/Pi-Alkyl