Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supporting information for: Bexarotene cannot reduce amyloid beta plaques through inhibition of production of amyloid beta peptides: *In silico* and *in vitro* study

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Table S1: Atom name, atom type, and charge of bexarotene.

Num.	Atom name	Atom Type	Charge
1	C1	CT	-0.077810
2	C2	CT	0.537189
3	C3	CT	-0.110215
4	C4	CA	-0.071271
5	C5	CA	-0.140981
6	C6	CA	-0.384321
7	C7	CT	0.561644
8	C8	CA	-0.246028
9	C9	CA	0.215507
10	C10	CA	0.072981
11	H1	HC	0.005864
12	H2	HC	0.005864
13	H3	HC	0.014390
14	H4	HC	0.014390
15	H5	HA	0.193910
16	H6	HA	0.149062
17	C11	CD	-0.053301
18	C12	CM	-0.390605
19	H7	HA	0.165233
20	H8	HA	0.165233
21	C13	CA	0.204433
22	C14	CA	-0.189451
23	C15	CA	-0.130122
24	H9	HA	0.144582
25	C16	CA	-0.165782
26	H10	HA	0.149271
27	C17	CA	-0.130122
28	C18	CA	-0.189451
29	H11	HA	0.149271
30	H12	HA	0.144582
31	C19	C	0.820182
32	O1	O	-0.541187
33	O2	OH	-0.635151
34	H13	HO	0.407750
35	C20	CT	-0.322763
36	H14	HC	0.092808
37	H15	HC	0.092808
38	H16	HC	0.092808
39	C21	CT	-0.423075
40	H17	HC	0.089443
41	H18	HC	0.089443
42	H19	HC	0.089443
43	C22	CT	-0.423075
44	H20	HC	0.089443
45	H21	HC	0.089443
46	H22	HC	0.089443
47	C23	CT	-0.430289
48	H23	HC	0.091479
49	H24	HC	0.091479
50	H25	HC	0.091479
51	C24	CT	-0.430289
52	H26	HC	0.091479
53	H27	HC	0.091479
54	H28	HC	0.091479

Table S2: Results for docking of bexarotene to equilibrium structures of receptor PPAR-γ. In each MD trajectory, a set of 100 structures of PPAR-γ, collected regularly at equilibration, were used to dock with bexarotene. Totally 400 docking attempts were made.

PPAR-γ	
Trajectory	Average of binding affinity over snapshots in each trajectory (kcal/mol)
Traj 1	-9.09 +/- 0.81
Traj 2	-8.71 +/- 0.80
Traj 3	-9.17 +/- 0.79
Traj 4	-8.75 +/- 1.02
Average over all trajectories	**-8.93 +/- 0.23**

Table S3: The same as table S2 but for receptor RXR-α. Totally 400 docking attempts were made.

RXR-alpha	
Trajectory	Average of binding affinity over snapshots in each trajectory (kcal/mol)
Traj 1	-9.07 +/- 1.60
Traj 2	-8.29 +/- 1.54
Traj 3	-8.99 +/- 1.70
Traj 4	-9.39 +/- 1.64
Average over all trajectories	**-8.94 +/- 0.46**

Table S4 : Docking energy of bexarotene to β-secreatse. Results were obtained from 1500 docking attempts using snapshots collected at equibrium in 30 MD runs as targets (see the main text for more details).

Beta-secretase docking		
Mode	Trajectory	Average binding affinity (kcal/mol)
Mode 1	Traj 1	-7.72 +/- 0.45
	Traj 2	-8.11 +/- 0.63
	Traj 3	-9.00 +/- 0.81
	Traj 4	-8.82 +/- 0.45
	Traj 5	-8.78 +/- 0.95
	Traj 6	-8.80 +/- 0.75
	Traj 7	-8.38 +/- 0.65
	Traj 8	-9.12 +/- 0.81
	Traj 9	-7.78 +/- 0.48
	Traj 10	-7.94 +/- 0.46
	Average over mode 1	**-8.45 +/- 0.53**
Mode 2	Traj 1	-7.86+/- 0.56
	Traj 2	-7.70 +/- 0.41
	Traj 3	-7.48 +/- 0.38
	Traj 4	-7.89 +/- 0.58
	Traj 5	-7.63 +/- 0.39
	Traj 6	-8.72 +/- 0.78
	Traj 7	-7.71 +/- 0.58
	Traj 8	-8.10 +/- 0.64
	Traj 9	-7.77 +/- 0.49
	Traj 10	-7.77 +/- 0.59
	Average over mode 1	**-7.86 +/- 0.34**
Mode 3	Traj 1	-7.87 +/- 0.50
	Traj 2	-7.72 +/- 0.40
	Traj 3	-7.85 +/- 0.56
	Traj 4	-7.75 +/- 0.40
	Traj 5	-7.76 +/- 0.49
	Traj 6	-7.73 +/- 0.50
	Traj 7	-8.00 +/- 0.51
	Traj 8	-7.89 +/- 0.44
	Traj 9	-7.54 +/- 0.43
	Traj 10	-7.77 +/- 0.40
	Average over mode 3	**-7.79 +/- 0.12**
Average over all modes		**-8.03 +/- 0.46**

Table S5: Binding free energy of bexarotene to PPAR-γ. See Fig. 3 in the main text for evolution of RMSD and interaction energy.

Traj	ΔE_{vdW}	ΔE_{ele}	ΔG_{PB}	ΔG_{SUR}	$-T\Delta S$	ΔG_{bind}
1	-50.0	-19.3	35.5	-4.5	19.6	-18.7
2	-48.6	-14.9	30.3	-4.5	22.4	-15.3
3	-50.7	-17.6	36.0	-4.5	20.9	-15.9
4	-49.8	-14.4	36.5	-4.7	17.6	-14.8
Average	-49.8±0.9	-16.5±2.3	34.6±2.9	-4.6±0.1	20.1±1.4	-16.2±1.8

Table S6: Binding free energy of bexarotene to RXR-α. See Fig. S1 in SI for the evolution of RMSD and interaction energy.

Traj	ΔE_{vdW}	ΔE_{ele}	ΔG_{PB}	ΔG_{SUR}	$-T\Delta S$	ΔG_{bind}
1	-52.6	-17.5	38.9	-4.5	20.9	-14.9
2	-55.8	-14.9	34.0	-4.4	20.4	-20.6
3	-53.0	-17.8	39.2	-4.5	17.9	-18.1
4	-52.9	-20.4	42.7	-4.5	21.0	-14.1
Average	-53.6±1.5	-17.6±2.3	38.7±3.6	-4.5±0.1	20.1±1.4	-16.9±3.0

Table S7. Decomposition of the interaction energy into 4 groups of bexarotene (Figure S4). For PPAR-γ (4EMA) and RXR-α (4K6I) the results were averaged over four MD trajectories, while for β-secreatase (1M4H) the average over 30 trajectories of 3 modes was made.

		E_{elec}	E_{vdW}	$E_{elec} + E_{vdW}$
4EMA	Group 1	-10.49	-6.22	-16.70
	Group 2	0.77	-10.79	-10.02
	Group 3	-1.86	-29.50	-31.36
	Group 4	-4.95	-3.28	-8.24
4K6I	Group 1	-10.01	-6.24	-16.25
	Group 2	-2.87	-12.54	-15.41
	Group 3	0.17	-30.94	-30.77
	Group 4	-4.94	-3.84	-8.78
1M4H	Group 1	-3.26	-2.46	-5.72
	Group 2	-2.03	-6.34	-8.38
	Group 3	0.21	-15.29	-15.08
	Group 4	-5.07	-2.39	-7.45

Table S8: Binding free energy ,by MMPBSA method, between beta-secretase and bexarotene. Snapshots from the last 100ns were used to estimate the binding free energy (kcal/mol).

		ΔE_{vdW}	ΔE_{ele}	ΔG_{SUR}	ΔG_{PB}	$-T\Delta S$	ΔG_{bind}	Average
Mode 1	Traj 1	-31.40	-13.05	-3.89	33.08	12.57	-2.70	**-3.57 ± 6.88**
	Traj 2	-36.69	-12.14	-4.17	39.38	13.89	0.28	
	Traj 3	-39.79	-21.65	-4.50	45.40	16.56	-3.98	
	Traj 4	-31.44	-26.58	-4.01	42.17	16.43	-3.43	
	Traj 5	-40.51	-20.88	-4.53	45.06	7.37	-13.50	
	Traj 6	-39.38	-19.69	-4.31	40.32	22.14	-0.92	
	Traj 7	-37.05	-5.60	-4.00	27.76	9.11	-9.78	
	Traj 8	-37.73	-27.11	-4.32	46.07	10.09	-13.00	
	Traj 9	-28.99	-12.38	-3.69	30.70	18.06	3.70	
	Traj 10	-27.86	-1.57	-3.59	23.36	17.24	7.59	
Mode 2	Traj 1	-20.43	-6.09	-2.31	18.11	16.48	5.77	**-0.46 ± 7.24**
	Traj 2	-21.63	-9.65	-2.44	19.95	21.74	7.97	
	Traj 3	-25.35	-7.95	-2.90	18.98	18.35	1.13	
	Traj 4	-29.00	-2.48	-3.10	17.00	19.36	1.78	
	Traj 5	-16.13	-3.07	-1.92	10.54	16.03	5.45	
	Traj 6	-44.93	-6.50	-4.47	22.89	15.75	-17.26	
	Traj 7	-25.58	-10.17	-2.98	21.54	12.75	-4.44	
	Traj 8	-25.59	-12.92	-2.88	22.72	17.98	-0.69	
	Traj 9	-18.81	-5.25	-2.26	15.66	11.33	0.66	
	Traj 10	-22.93	-16.37	-2.81	25.34	11.84	-4.93	
Mode 3	Traj 1	-19.83	-6.73	-2.30	17.62	15.79	4.54	**2.34 ± 2.12**
	Traj 2	-19.32	-9.06	-2.38	19.26	12.89	1.39	
	Traj 3	-19.93	-1.03	-2.53	9.63	16.62	2.76	
	Traj 4	-12.31	-3.84	-1.60	9.57	10.19	2.00	
	Traj 5	-14.78	-5.82	-1.88	12.87	7.98	-1.63	
	Traj 6	-21.79	-9.38	-2.62	20.23	17.59	4.02	
	Traj 7	-25.33	-5.89	-2.88	20.84	17.39	4.14	
	Traj 8	-20.88	-9.70	-2.48	19.45	14.03	0.41	
	Traj 9	-13.30	-7.34	-1.49	14.76	12.30	4.93	
	Traj 10	-25.84	-9.63	-2.94	20.89	18.35	0.84	
Average		-26.48 ± 8.78	-10.32 ± 6.95	-3.07 ± 0.92	24.37 ± 10.97	14.94 ± 3.82	**-0.56 ± 6.20**	

Table S9: Binding free energy ,by MMPBSA method, between beta-secretase and ionized bexarotene. Snapshots from the last 100ns were used to estimate the binding free energy (kcal/mol). Results were obtained for mode 1.

Traj.	ΔE_{vdw}	ΔE_{ele}	ΔG_{PB}	ΔG_{SUR}	$-T\Delta S$	ΔG_{bind}
1	-33.76	105.44	-83.97	-3.93	12.18	-4.04
2	-34.69	98.87	-76.67	-3.90	9.50	-6.88
3	-33.99	37.73	-18.46	-4.42	15.10	-4.05
4	-34.94	119.94	-96.93	-3.93	11.77	-4.10
5	-36.20	132.87	-110.10	-3.95	13.56	-3.82
6	-35.57	118.60	-95.81	-3.96	21.65	+4.91
7	-31.39	90.19	-72.29	-3.78	21.15	+3.87
8	-35.33	103.51	-75.52	-4.10	6.93	-4.50
9	-31.79	82.45	-65.77	-3.89	10.77	-8.23
10	-38.18	98.21	-71.05	-4.05	9.41	-5.66
average	-34.58±2.01	98.78±26.11	-76.66±24.74	-3.99±0.18	13.20±4.88	**-3.25±4.28**

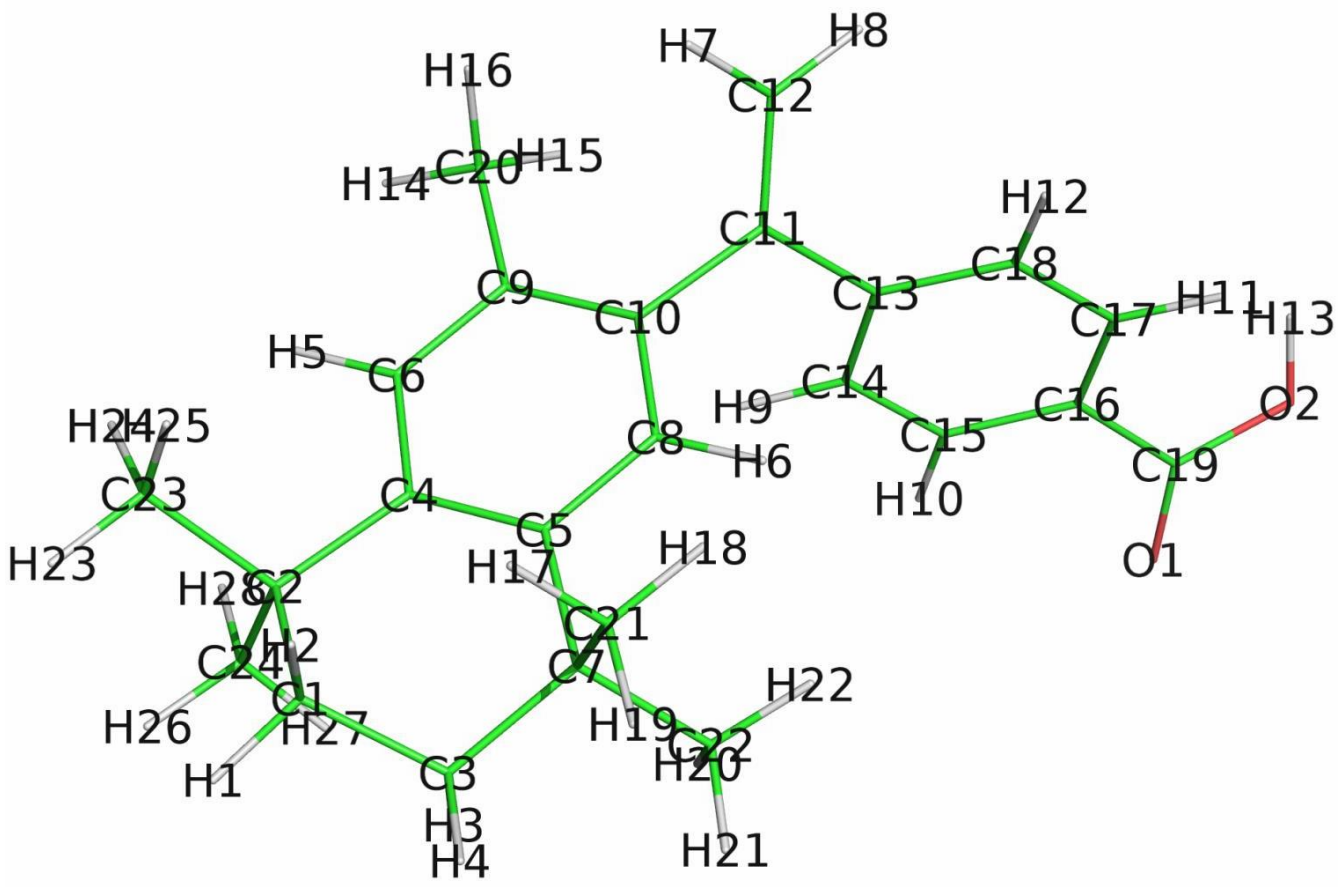

Figure S1: Structure of bexarotene which was optimized by Gaussian version 09 with the use of Hatree-Fock method and basis set 6-31G*.

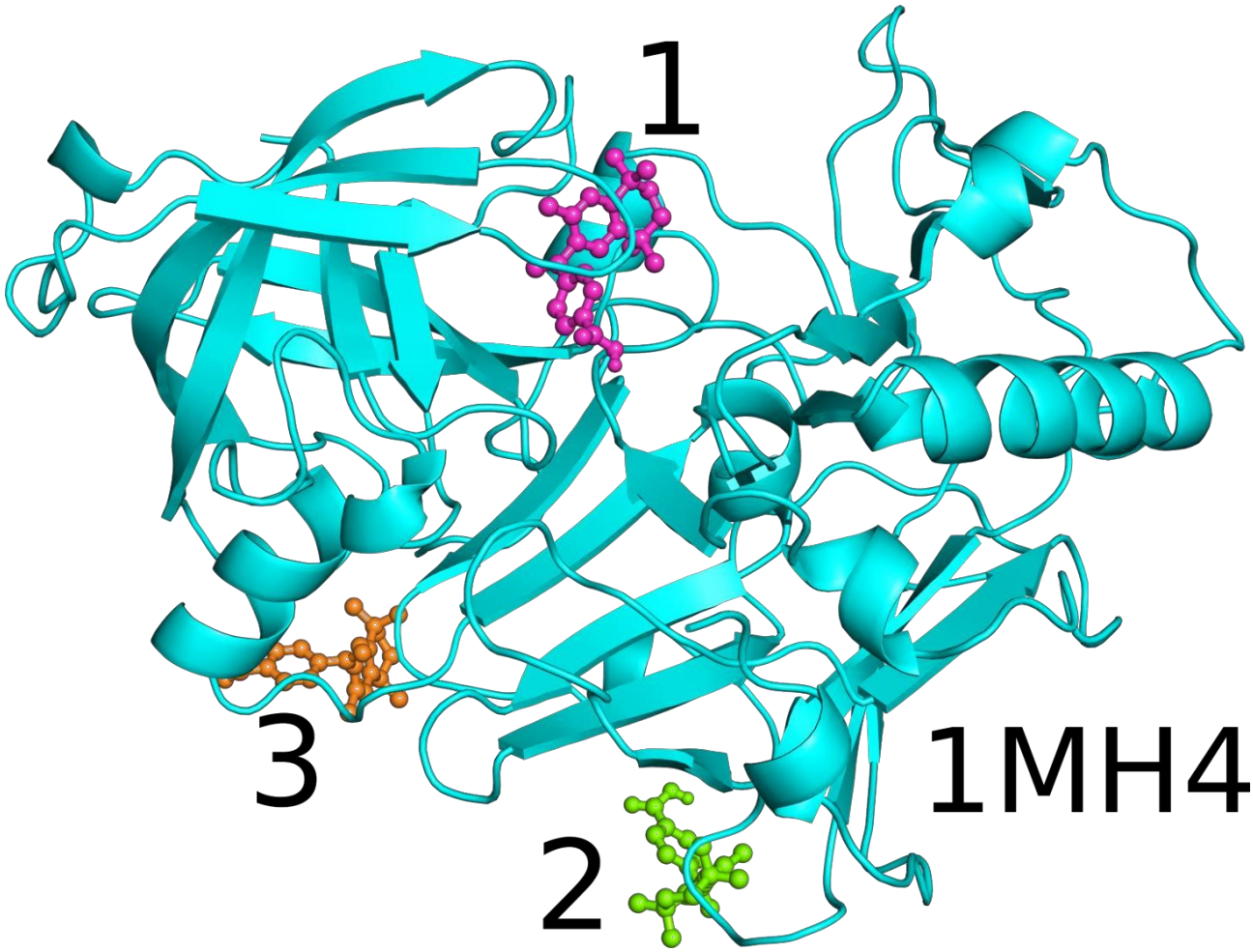

Figure S2. Three best docking modes (1, 2 and 3) of bexarotene to β-secretase. These binding positions have been used as starting configurations for three independent sets of MD simulation.

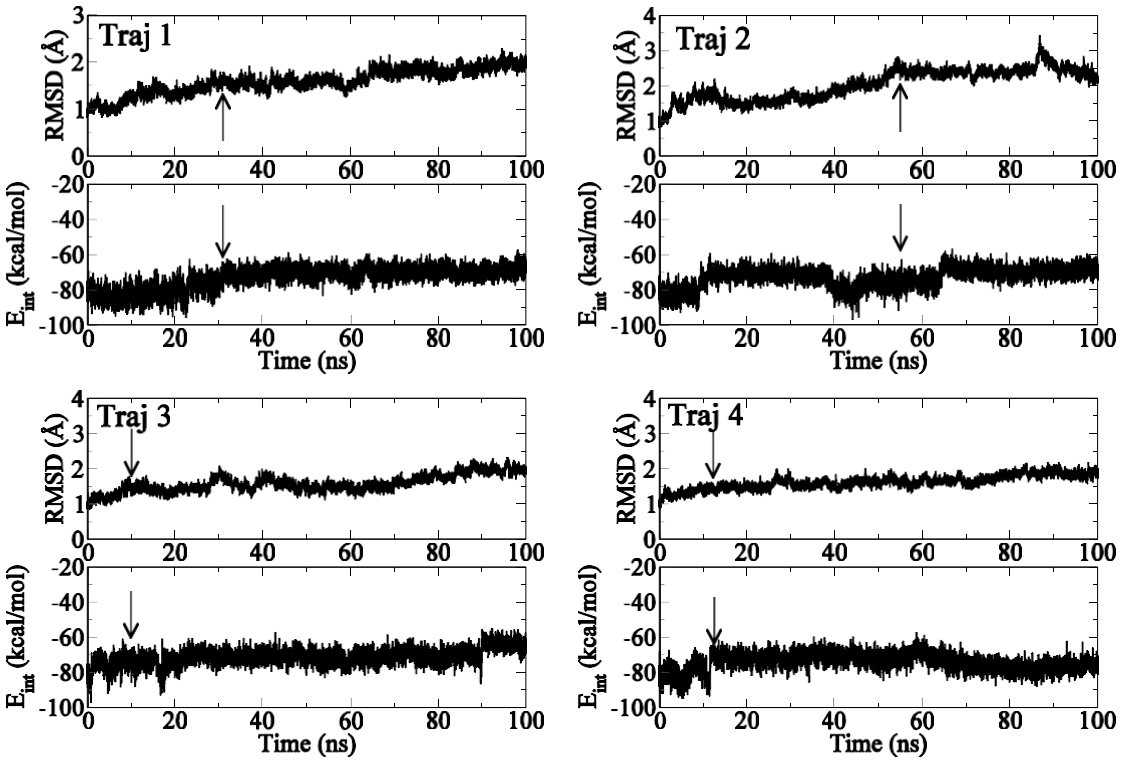

Figure S3: Time dependence of RMSD and the interaction energy of RXR-α+bexarotene complex. The arrow indicates time when the complex reaches equilibrium

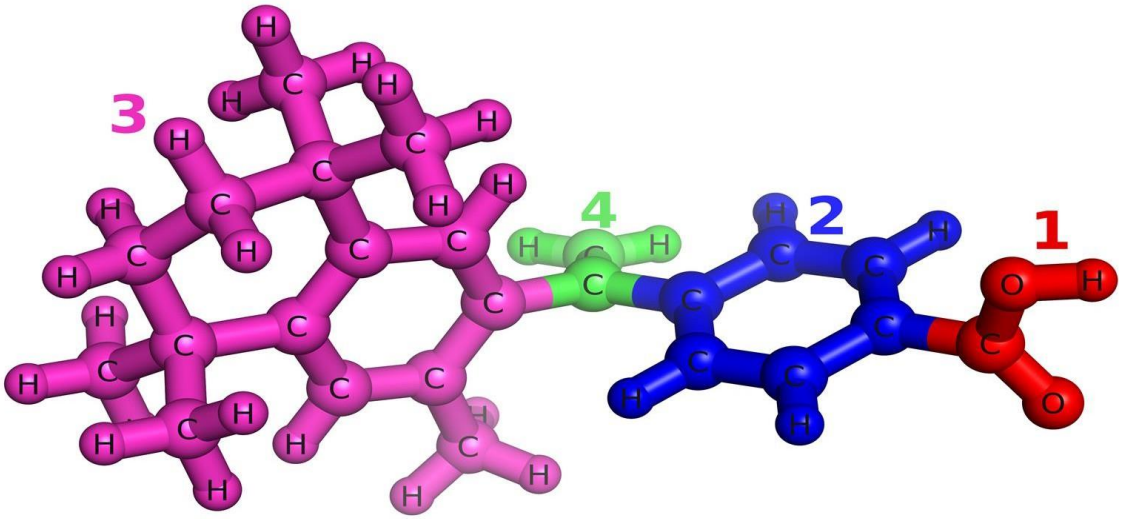

Figure S4. Bexarotene is divided into four groups denoted by different colors.

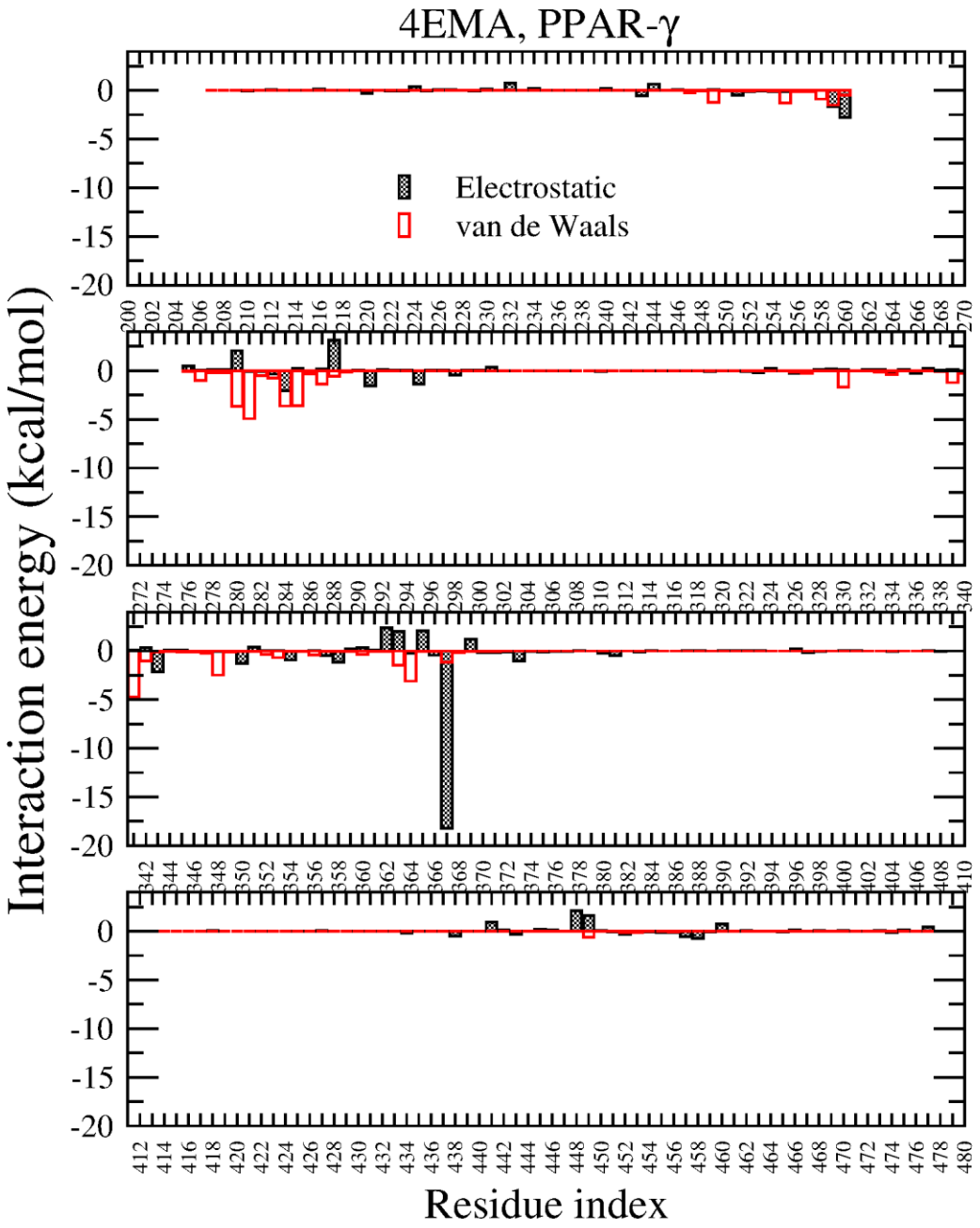

Figure S5. Per-residue interaction energies for PPAR-γ. Results were averaged over 4 MD runs.

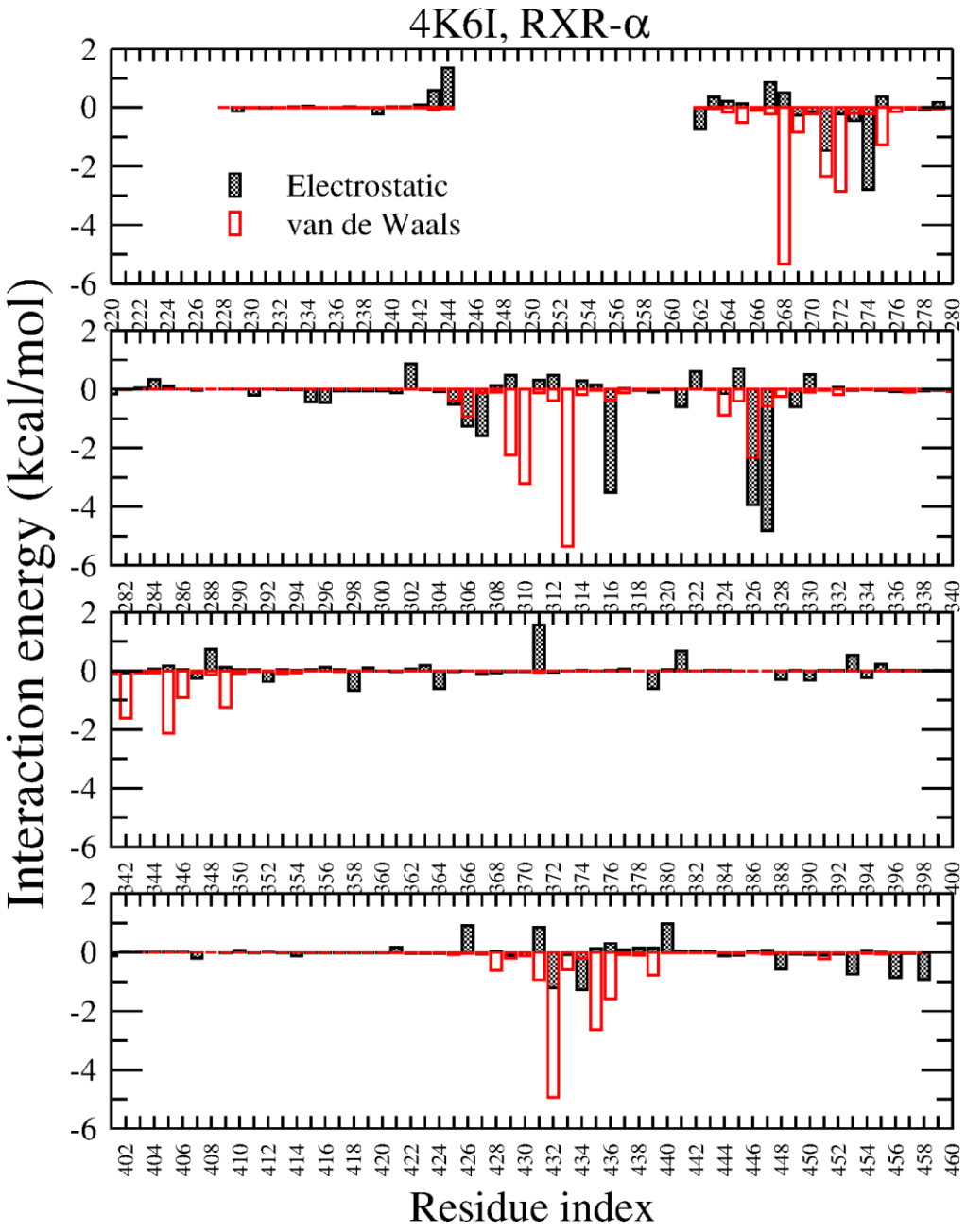

Figure S6. Per-residue interaction energies for RXR-α. Results were averaged over 4 MD runs.

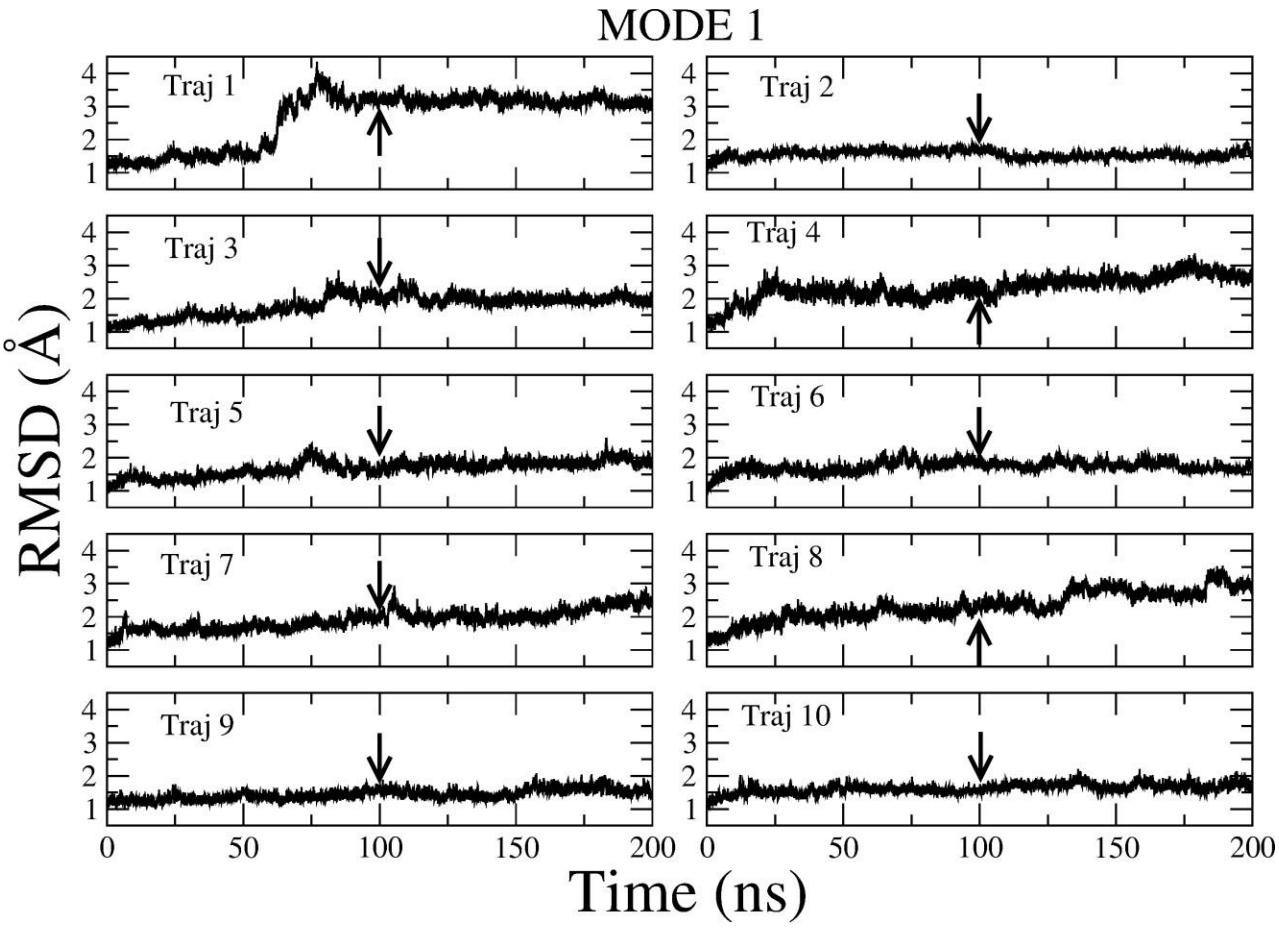

Figure S7: Time dependence of RMSD of β-secretase+bexarotene in the case where the MD simulation was performed using the configuration, obtained in Mode 1 (Fig. S2), as an initial configuration . The arrow indicates 100ns after which we have collected snapshots for estimating the binding free energy by the MM-PBSA method.

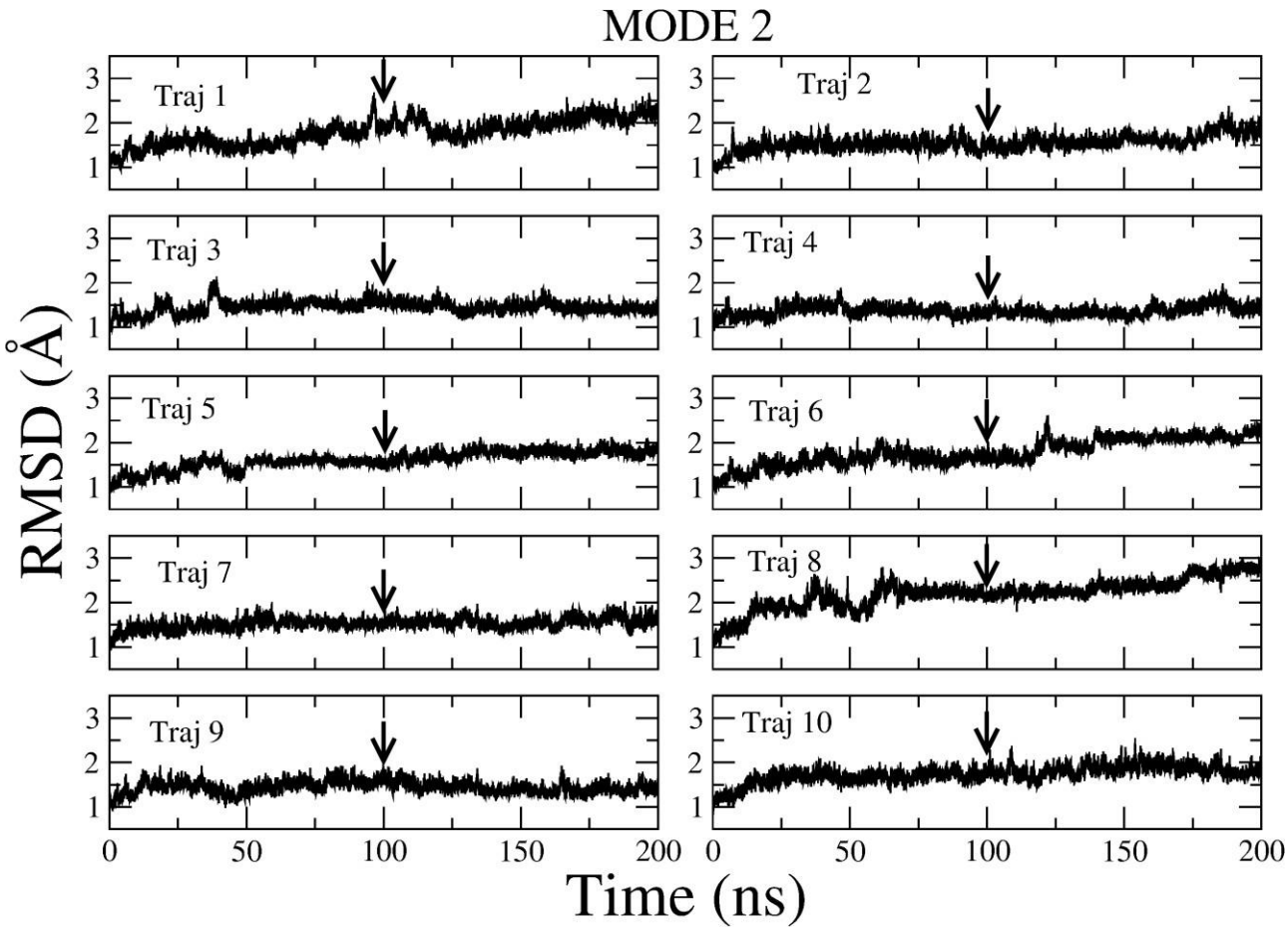

Figure S8: The same as in Figure S4 but for the case where the MD simulation was performed using the configuration, obtained in Mode 2 (Fig. S2), as an initial configuration.

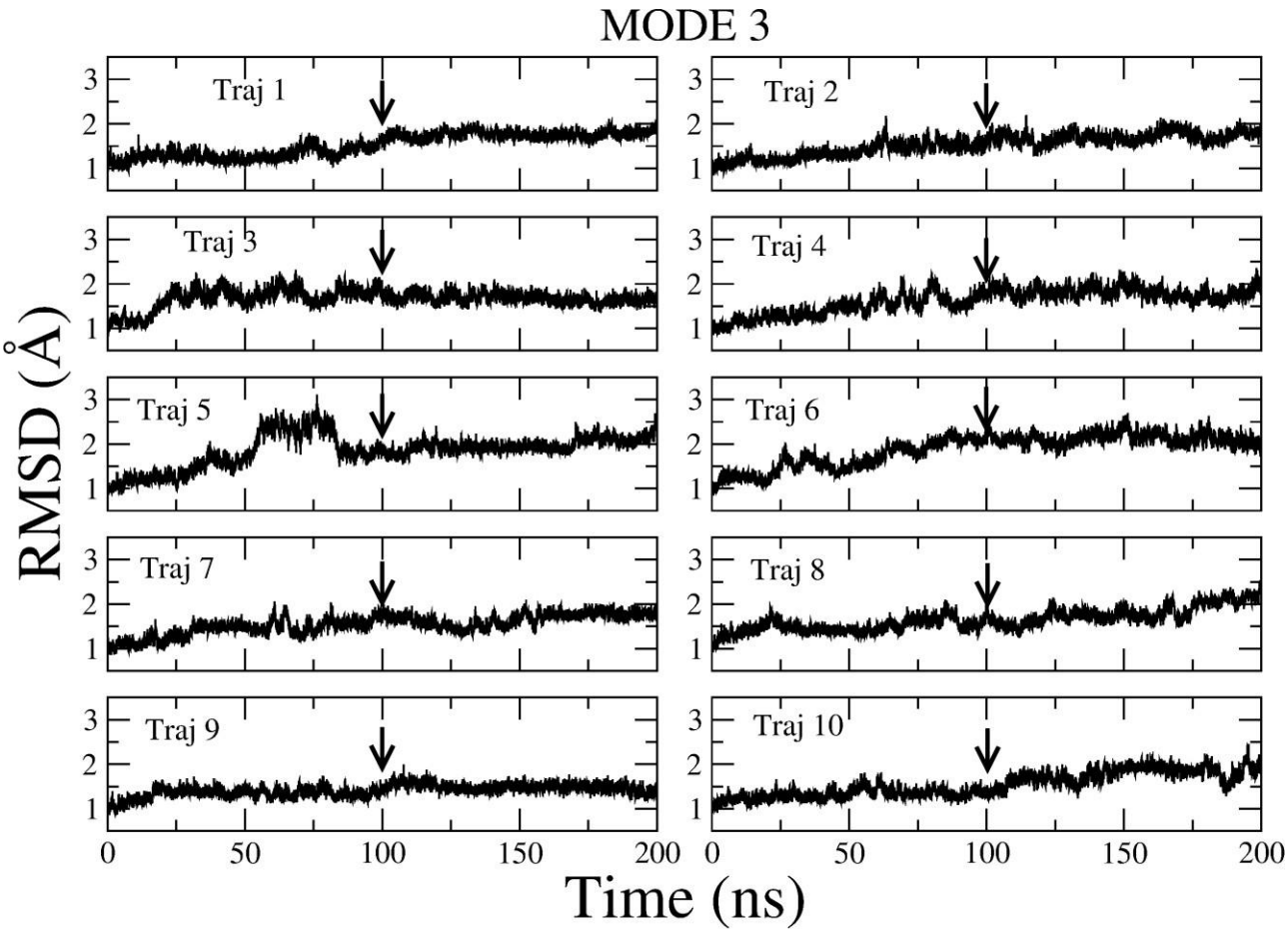

Figure S9: The same as in Figure S4 but for the case where the MD simulation was performed using the configuration, obtained in Mode 3 (Fig. S2), as an initial configuration.

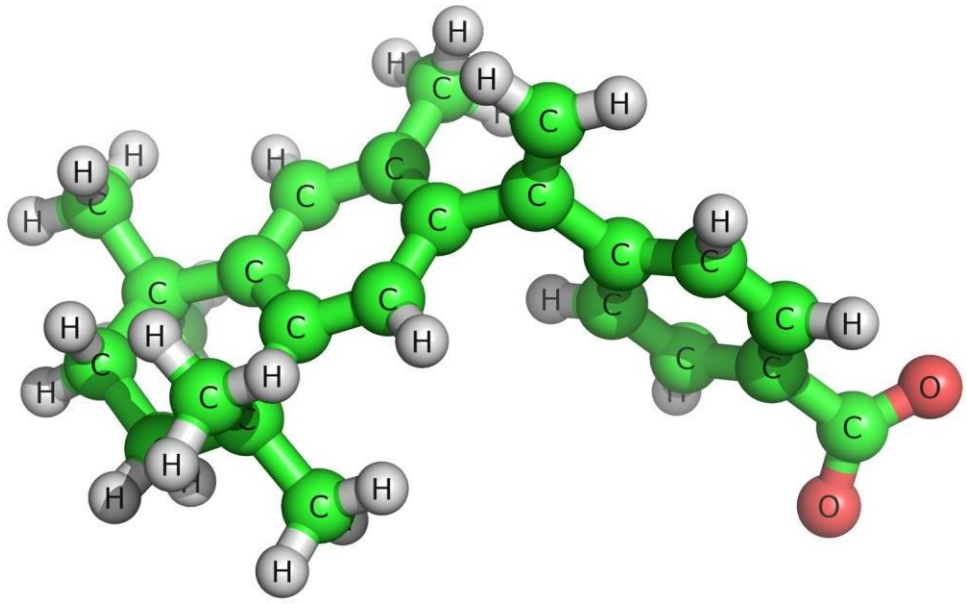

Figure S10: Three-dimensional structure of ionized bexarotene. The hydrogen atom from the carboxyl group is dissociated and bexarotene becomes negatively charged (-1).