On the choice of optimal conformation in linear free-energy relationships. Reactivity of 2-[(carboxymethyl)sulfanyl]-4-oxo-4-arylbutanoic acids with diphenyldiazomethane

Branko J. Drakulić,[*] *Aleksandar D. Marinković*, *Ivan O. Juranić*

Table S1. The second-order rate constants for esterification of **1-11** by DDM (k_2), their logarithmic values, the Swain-Lupton F and R constants, the backbone RMSD (MD minimums *vs*. same conformations optimized at the semiempirical level), the range of solvent accessible surface area from MD trajectory (Range SA), the same value divided by the molecular weight of compounds (Range SA/M_w).

Compound	**R-**	**k_2 (dm^3 mol^{-1} s^{-1})**	**logk_2**	**log(k/k_0)**	**F**	**R***	**Backbone RMSD**	**Range SA**	**Range SA/M_w**
1	H-	0.282	–0.5498	/	0	0	0.640	89.09	0.332
2	4-Me-	0.315	–0.5017	0.9125	0.01	–0.18	0.922	88.80	0.315
3	4-Et-	0.339	–0.4698	0.8545	0	–0.30	0.781	104.50	0.353
4	4-*i*-Pr-	0.346	–0.4609	0.8383	0.04	–0.32	0.279	109.11	0.352
5	4-*n*-Bu-	0.323	–0.4908	0.8927	–0.01	–0.28	0.460	135.92	0.419
6	4-*t*-Bu-	0.278	–0.5560	1.0112	–0.02	–0.04	0.599	108.93	0.336
7	4-F-	0.378	–0.4225	0.7685	0.45	–0.39	0.708	89.16	0.311
8	4-Cl-	0.329	–0.4828	0.8781	0.42	–0.19	0.526	91.86	0.303
9	4-Br-	0.351	–0.4547	0.8270	0.45	–0.30	0.362	93.76	0.270
10	3,4-di-Me-	0.368	–0.4342	0.7897	0.02	–0.36	0.540	98.29	0.332
11	2,5-di-Me-	0.385	–0.4145	0.7540	/	/	0.313	102.03	0.344

* R^+ given in red; R^- given in blue.

Table S2. Values of highest occupied molecular orbitals (HOMO), lowest occupied molecular orbitals (LUMO), and their differences (diff), for compounds **1-11**; as obtained by the semiempirical PM6 method, and by single point calculations using the DFT and MP2 methods.

Compound	**R-**	PM6			DFT			MP2		
		HOMO	**LUMO**	**diff**	**HOMO**	**LUMO**	**diff**	**HOMO**	**LUMO**	**diff**
1	H-	–9.660	–0.813	–8.847	–6.5413	–1.8955	–4.6458	–9.4195	2.0343	–11.4538
2	4-Me-	–9.662	–0.807	–8.855	–6.4592	–1.9154	–4.5438	–9.1789	1.9464	–11.1254
3	4-Et-	–9.694	–0.784	–8.910	–6.5506	–1.8931	–4.6575	–9.1716	2.0147	–11.1863
4	4-*i*-Pr-	–9.731	–0.836	–8.895	–6.7321	–1.7453	–4.9868	–9.1452	2.1598	–11.3050
5	4-*n*-Bu-	–9.692	–0.787	–8.905	–6.6102	–1.7565	–4.8537	–9.0932	2.1304	–11.2236
6	4-*t*-Bu-	–9.445	–1.031	–8.414	–6.2385	–2.1195	–4.1190	–9.1147	1.7783	–10.8930
7	4-F-	–9.898	–0.939	–8.959	–6.7985	–1.7374	–5.0610	–9.5066	2.2036	–11.7102
8	4-Cl-	–9.605	–1.004	–8.601	–6.3647	–1.8406	–4.5242	–9.3809	2.0332	–11.4141
9	4-Br-	–9.776	–1.038	–8.738	–6.6404	–1.8904	–4.7500	–9.3966	1.9649	–11.3616
10	3,4-di-Me-	–9.583	–0.872	–8.711	–6.5473	–1.6351	–4.9122	–8.9721	2.2833	–11.2554
11	2,5-di-Me-	–9.428	–0.654	–8.774	–6.3084	–1.1902	–5.1182	–8.7974	3.0801	–11.8775

---

[*] B.J.D. Department of Chemistry, Institute of Chemistry, Technology and Metallurgy; University of Belgrade, Njegoševa 12, Belgrade, Serbia. E-mail: bdrakuli@chem.bg.ac.rs ; Phone: +381 11 3336738; Fax: +381 11 2636061.

Table S3. The experimental and predicted rate constants, as obtained by the Swain-Lupton approach; and by the semiempirical (PM6), DFT, and MP2 calculations. The average polar surface area (PSA) derived from MD trajectories.

Compound		Experimental		Calculated				
				Swain-Lupton	PM6	DFT	MP2	
	R-	**log k_2**	**log(k/k_0)***	**log k_2**	**log(k/k_0)**	**log(k/k_0)**	**log(k/k_0)**	**Average PSA** (Å^2)
1	H-	–0.5498	/	–0.5592	/	/	/	223.525
2	4-Me-	–0.5017	0.9125	–0.5043	0.8863	0.9008	0.9007	224.776
3	4-Et-	–0.4698	0.8545	–0.4683	0.8697	0.8746	0.8868	223.043
4	4-*i*-Pr-	–0.4609	0.8383	–0.4606	0.8504	0.7987	0.8596	223.108
5	4-*n*-Bu-	–0.4908	0.8927	–0.4747	0.8707	0.8294	0.8782	220.633
6	4-*t*-Bu-	–0.5560	1.0112	–0.5479	0.9991	0.9987	0.9540	223.395
7	4-F-	–0.4225	0.7685	–0.4232	0.7636	0.7816	0.7667	221.638
8	4-Cl-	–0.4828	0.8781	–0.4850	0.9159	0.9053	0.8346	223.084
9	4-Br-	–0.4547	0.8270	–0.4505	0.8271	0.8533	0.8466	220.873
10	3,4-di-Me-	–0.4342	0.7897	–0.4493	/	0.8159	0.8709	223.695
11	2,5-di-Me-	–0.4145	0.7540	/	/	0.7684	0.7284	218.968

* k_0 – refer to the second order rate constant for unsubstituted derivative (**1**)

Table S4. Estimated pK_a values for compounds **1-11**, see Figure S9.

Compound	**R-**	**pK_{a1}**	**pK_{a2}**
1	H-	3.27	4.62
2	4-Me-	3.28	4.63
3	4-Et-	3.31	4.67
4	4-*i*-Pr-	3.33	4.69
5	4-*n*-Bu-	3.35	4.73
6	4-*t*-Bu-	3.34	4.72
7	4-F-	3.24	4.57
8	4-Cl-	3.17	4.44
9	4-Br-	3.25	4.54
10	3,4-di-Me-	3.28	4.63
11	2,5-di-Me-	3.27	4.62

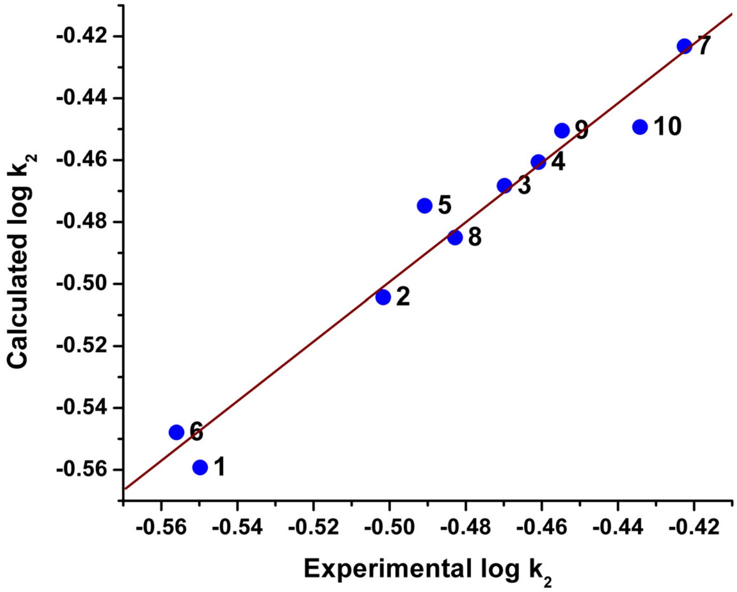


Figure S1. Experimental *vs*. calculated log k_2 for compounds **1-10**.

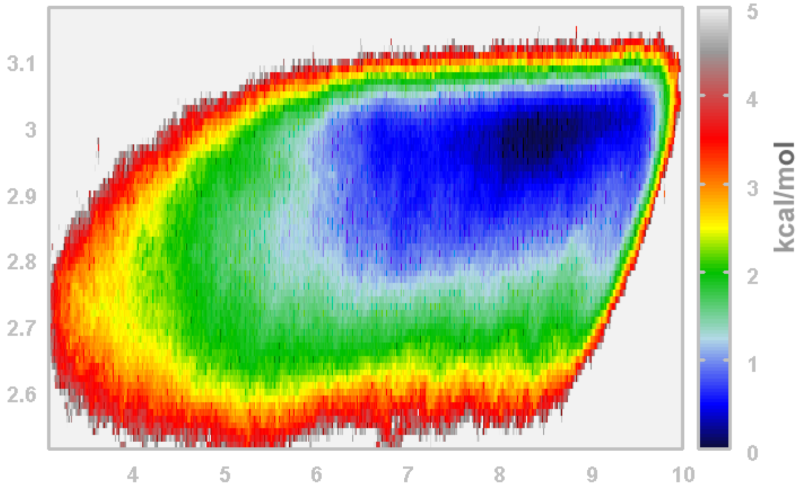
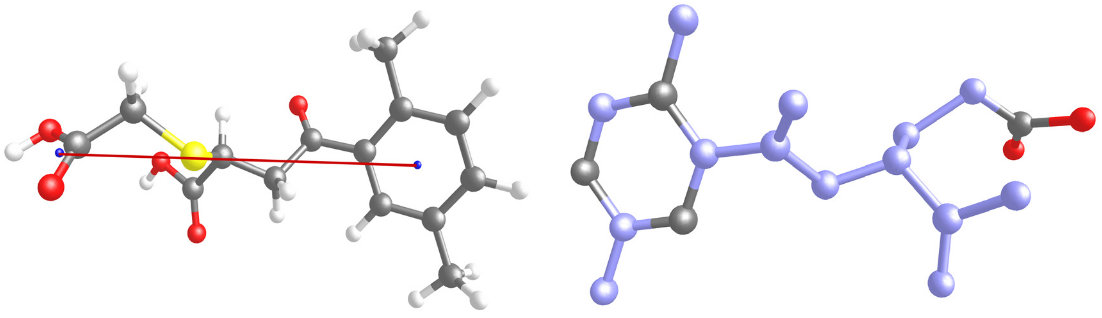


Figure S2. The two-dimensional free energy landscape of compound **11,** obtained by the ABF calculation. X-axis shows distance between centroids defined on the phenyl, and on the distal carboxyl (collective variable 1). Y-axis show radius of gyration of heavy atoms (collective variable 2). See Figure S3.



a) **b)**

Figure S3. a) Collective variable 1; distance is given as a red line. c) Collective variable 2; radius of gyration is measured for all heavy atoms, except for those included in the first collective variable. Exemplified for compound **11**.

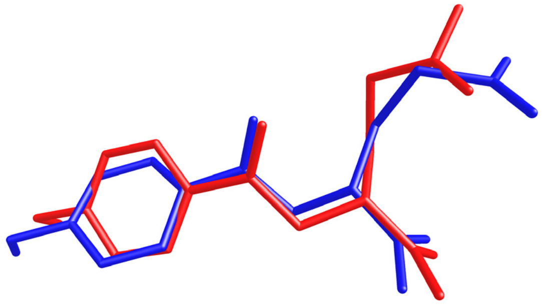


Figure S4. Root-mean-square deviation (rmsd) of MD minimum *vs*. the same conformation optimized on semiempirical level, for heavy atoms of backbone (excluding substituents), ending on carboxyl carbons (**<u>Ph</u>**-<u>**C**(O)</u>-**<u>C</u>**H_2-**<u>C</u>**H(**<u>S</u>**-**<u>C</u>**H_2-**<u>C</u>**OOH)-**<u>C</u>**OOH). The main contribution to the rmsd were Ph-C(O) torsion. The initial MD minimum is given in blue, the same conformation optimized on the semiempirical level is given in red. Exemplified for compound **3**.

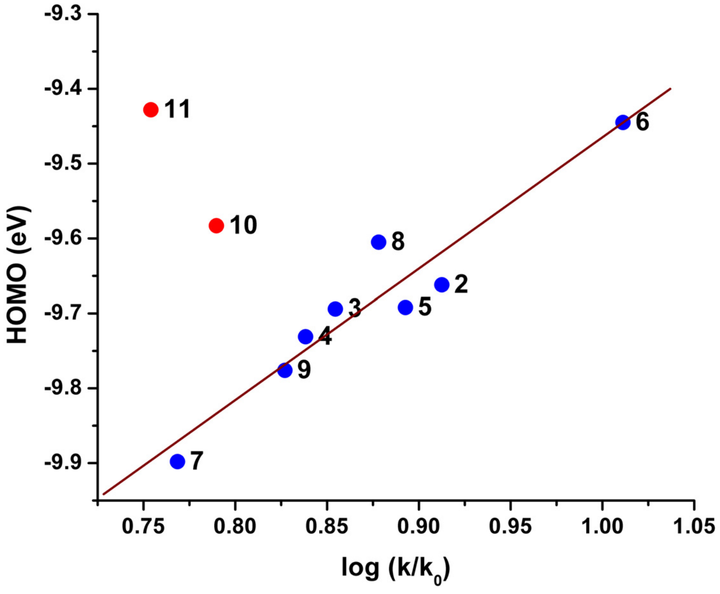


Figure S5. Experimental log(k/k_0) *vs*. highest occupied molecular orbital (HOMO) energy, obtained by the semiempirical calculations, for compounds **1-11**.

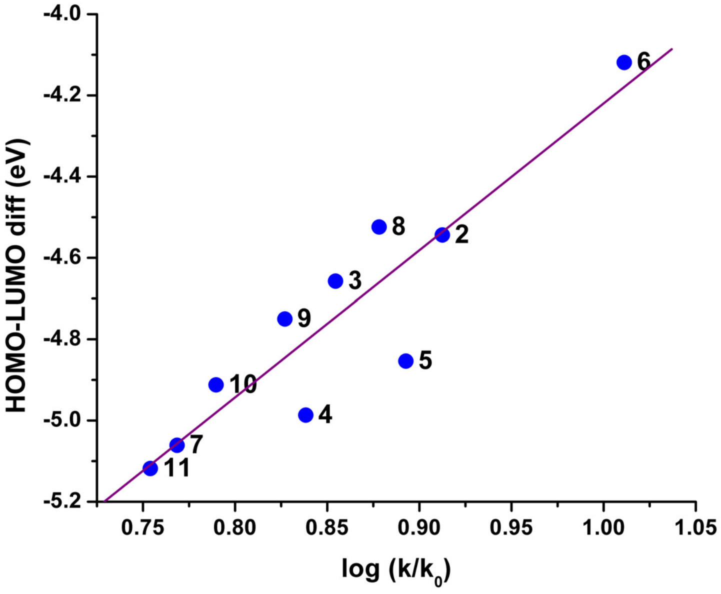


Figure S6. Experimental log(k/k$_0$) *vs*. energy difference between highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals, obtained by the DFT calculations, for compounds **2-11**.

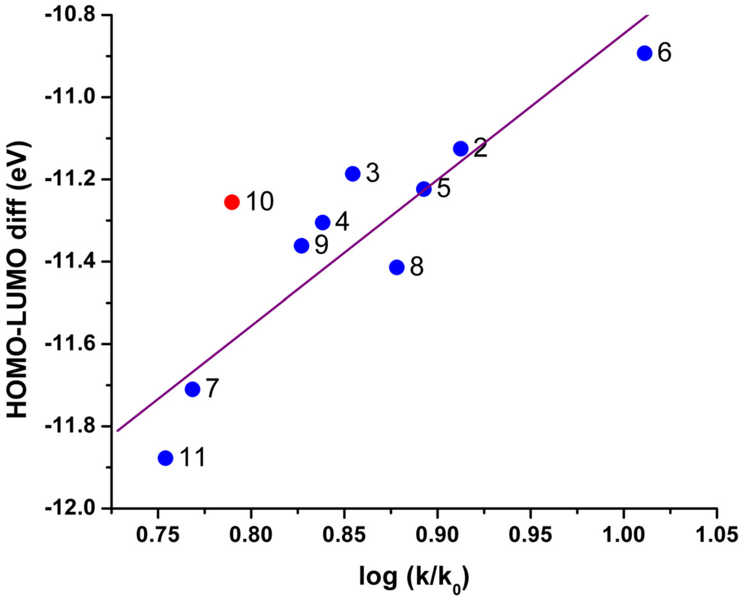


Figure S7. Experimental log(k/k$_0$) *vs*. energy difference between highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals, obtained by the MP2 calculations, for compounds **2-11**.

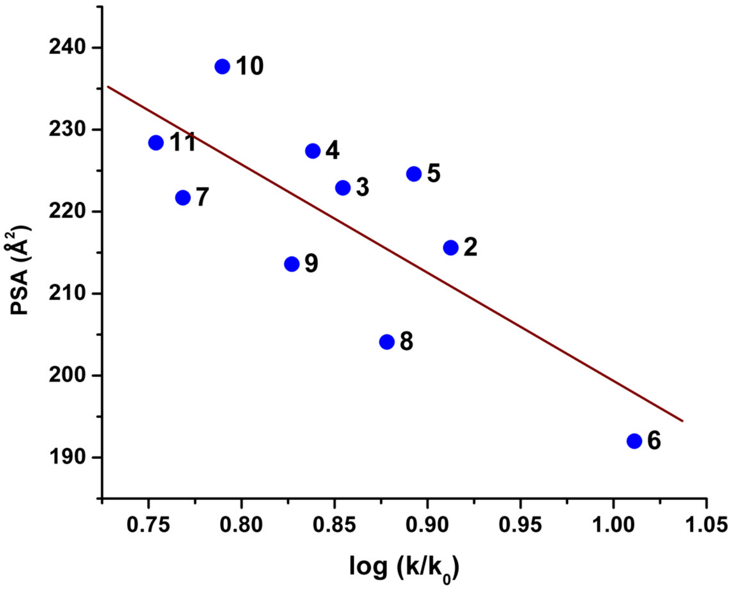
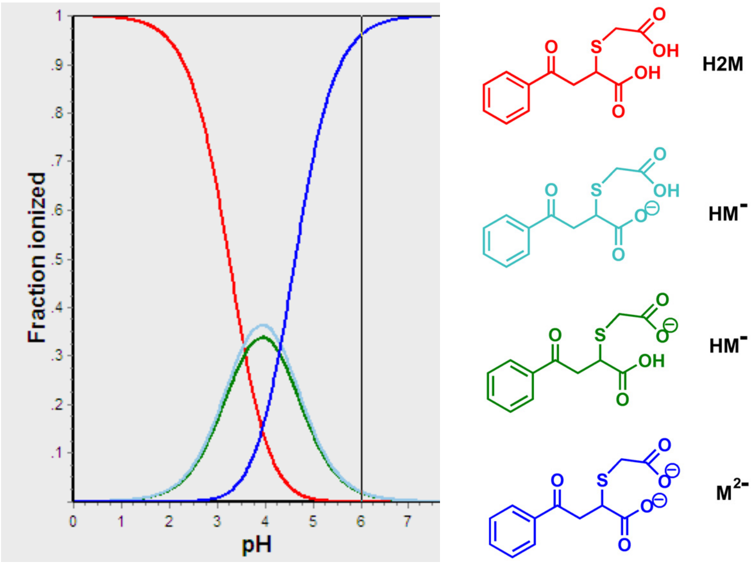
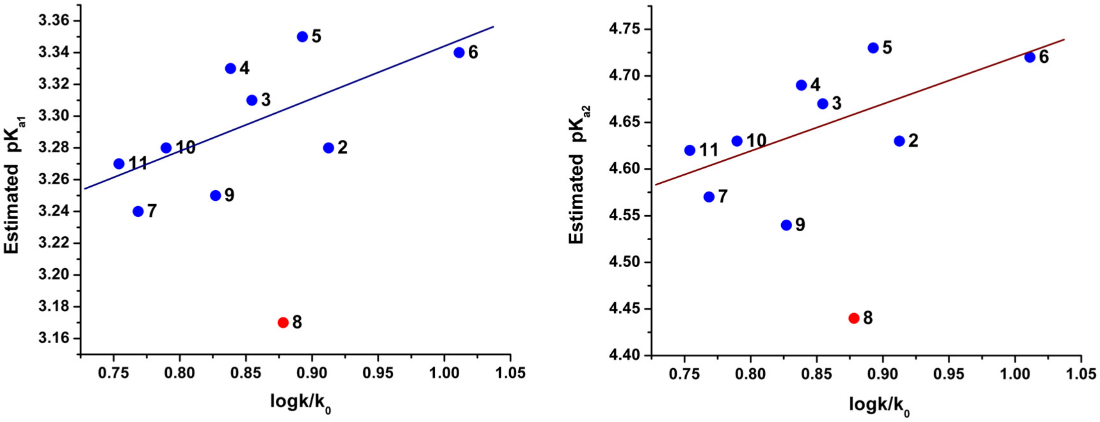


Figure S8. Experimental log(k/k$_0$) *vs*. conformation (3D) dependent polar surface area (PSA) of compounds **2-11**. Trend is assigned by colored line.



a) b)

Figure S9. Estimated pH profile for compound **1**.



a) **b)**

Figure S10. Experimentally obtained log(k/k$_0$) *vs*. estimated pK_{a1} (a) and pK_{a2} (b) for compounds **2-11**. Compound **8** is outlier. Trend is assigned by colored line.