Pharmacophoric Features of Biguanide Derivatives: An Electronic Structure Analysis

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SUPPORTING INFORMATION

Tables S1-S6 with absolute energies, NPA charges, second order delocalisations, HOMA delocalisation parameters are given below.

Table S1: Absolute Energies (a.u, ZPE corrected values, which have been scaled by a factor of 0.9153, 0.9806, and 0.9661 for HF, B3LYP, and MP2(full) levels respectively) of various conformers of Biguanides.

Conformer	HF/6-31+G*	B3LYP/6-31+G*	MP2(full)/6-31+G*	G2MP2
BG1	-351.966057	-354.101841	-353.069721	-353.660672
BG2-1	-351.956429	-354.092037	-353.063523	-353.652452
BG2-2	-351.956470	-354.091757	-353.063302	-353.652428
BG4	-351.954024	-354.089705	-353.057948	-353.651657
BG5	-351.949810	-354.086062	-353.055043	-353.648267
BG6	-351.948118	-354.083094	-353.054314	-353.645781
BG7	-351.947342	-354.083537	-353.053839	-353.645481
BG8	-351.945896	-354.081999	-353.051938	-353.644632
BG9	-351.945890	-354.082400	-353.051900	-353.644408
BG10	-351.945260	-354.080441	-353.051634	-353.643197
BG11	-351.936310	-354.071540	-353.042861	-353.643099
BG1-TS1	-351.948771	-354.095671	-353.061375	-353.654003
BG1-TS2	-351.882466	-354.037502	-353.004165	-353.598697
BG1-TS3	-351.948244	-354.083656	-353.052738	-353.643991
BG1-TS4	-351.943863	-354.082080	-353.049837	-353.643005
BG1-TS5	-351.943839	-354.080984	-353.048873	-353.640922

Table S2: Absolute Energies (a.u, ZPE corrected values, which have been scaled by a factor of 0.9153, 0.9806, and 0.9661 for HF, B3LYP, and MP2(full) levels respectively) of various conformers of protonated BG1

Conformer	HF/6-31+G*	B3LYP/6-31+G*	MP2(full)/6-31+G*	G2MP2
BGP1	-352.360812	-354.486909	-353.447856	-354.045230
BGP2	-352.340107	-354.469117	-353.432112	-354.030716
BGP3	-352.548607	-354.670666	-353.629139	-354.231483

Table S3: Absolute Energies (a.u, ZPE corrected values, which have been scaled by a factor of 0.9153, 0.9806, and 0.9661 for HF, B3LYP, and MP2(full) levels respectively) of various conformers of deprotonated BG1

Conformer	HF/6-31+G*	B3LYP/6-31+G*	MP2(full)/6-31+G*	G2MP2
BGA1	-351.390243	-353.536569	-352.511960	-353.094789
BGA2	-351.392250	-353.539773	-352.513748	-353.097013
BGA3	-351.381409	-353.530577	-352.503790	-353.088979

Table S4: NPA charge analysis for **BG1, BG3** and **BG5**

Atom	BG1	BG3	BG5
N1	-0.94	-0.89	-0.82
C2	0.81	0.75	0.70
N3	-0.92	-0.95	-0.95
N4	-0.79	-0.76	-0.79
C5	0.75	0.76	0.74
N6	-0.95	-0.90	-0.85
N7	-0.93	-0.94	-0.94
H8(N1)	0.49	0.37	0.42
H9(N1)	0.42	0.45(N4)	0.44(N4)
H10(N3)	0.43	0.47	0.40
H11(N3)	0.41	0.42	0.43
H12(N6)	0.37	0.38	0.38
H13(N7)	0.43	0.42	0.42
H14(N7)	0.41	0.42	0.42

Table S5: Important second order delocalisation noticed in **BG1**, its protonated, diprotonated and deprotonated forms using NBO analysis at the MP2(full)/6-31+G* Level.

Structure	interaction	second-order interaction			Occupancy of lone pairs on nitrogens	
		$E^{(2)}$ [a]	$E_i - E_j$ [b]	F_{ij} [b]	$\rho n_{(N)}$	ρ_{π^*}
BG1	$n_{N1} \rightarrow \pi^*_{C2-N4}$	83.38	0.58	0.203	$1.80_{(N1)}$	0.317 (N1)
	$n_{N3} \rightarrow \pi^*_{C2-N4}$	51.28	0.63	0.169	$1.87_{(N3)}$	
	$n_{N4} \rightarrow \sigma^*_{N1-C2}$	21.72	1.24	0.149	$1.91_{(N4)}$	
	$n_{N6} \rightarrow \sigma^*_{C5-N7}$	19.35	1.25	0.140	$1.92_{(N6)}$	
	$n_{N6} \rightarrow \sigma^*_{N1-H8}$	20.81	1.28	0.140		
	$n_{N7} \rightarrow \pi^*_{C5-N6}$	50.36	0.65	0.167	$1.87_{(N7)}$	0.248 (N3)
BGP1	$n_{N1} \rightarrow \pi^*_{C2-N3}$	92.12	0.54	0.210	1.80	0.423
	$n^1_{N4} \rightarrow \sigma^*_{C2-N1}$	16.98	1.23	0.132	1.87	
	$n^1_{N4} \rightarrow \sigma^*_{C5-N6}$					
	$n^1_{N4} \rightarrow \pi^*_{C2-N3}$	12.13	0.60	0.083	1.87	0.423
	$n^1_{N4} \rightarrow \pi^*_{C5-N7}$					
	$n^2_{N4} \rightarrow \pi^*_{C2-N3}$	139.62	0.38	0.207	1.55	0.423
	$n^2_{N4} \rightarrow \pi^*_{C5-N7}$					
	$n_{N6} \rightarrow \pi^*_{C5-N7}$	92.12	0.54	0.210	1.80	0.423
BGP2	$n_{N3} \rightarrow \pi^*_{N1-C2}$	105.85	0.51	0.217	$1.78_{(N3)}$	0.378
	$n_{N4} \rightarrow \pi^*_{N1-C2}$	86.23	0.52	0.195	$1.76_{(N4)}$	
	$n_{N4} \rightarrow \pi^*_{C5-N6}$	41.84	0.62	0.145		0.206
	$n_{N7} \rightarrow \pi^*_{C5-N6}$	53.65	0.63	0.167	$1.85_{(N7)}$	
	$n_{N6} \rightarrow \sigma^*_{C5-N7}$	22.11	1.27	0.151	$1.91_{(N6)}$	
	$n_{N6} \rightarrow \sigma^*_{N1-H8}$	22.94	1.25	0.153		
BGP3	$n_{N1} \rightarrow \sigma^*_{C2-N3}$	102.49	0.60	0.224	1.70	
	$n_{N4} \rightarrow \pi^*_{C2-N3}$	22.99	0.65	0.112	1.77	0.331
	$n_{N4} \rightarrow \pi^*_{C5-N7}$					
	$n_{N4} \rightarrow \sigma^*_{C2-N3}$	15.02	1.08	0.118	1.77	
	$n_{N4} \rightarrow \sigma^*_{C5-N7}$					
	$n_{N6} \rightarrow \pi^*_{C5-N7}$	102.49	0.60	0.224	1.70	0.331
BGA2	$n_{N1} \rightarrow \pi^*_{C2-N3}$	40.42	0.68	0.153	1.93	0.250
	$n_{N3} \rightarrow \sigma^*_{C2-N4}$	17.71	1.32	0.137	1.95	
	$^1n_{N4} \rightarrow \sigma^*_{C5-N6}$	15.61	1.25	0.125	1.91	
	$^1n_{N4} \rightarrow \sigma^*_{C2-N1}$	14.87	1.19	0.120		
	$^1n_{N4} \rightarrow \pi^*_{C5-N6}$	10.34	0.71	0.081		0.323
	$^2n_{N4} \rightarrow \pi^*_{C5-N6}$	105.97	0.47	0.203	1.58	
	$n_{N7} \rightarrow \pi^*_{C5-N6}$	24.70	0.73	0.128	1.92	
	$^2n_{N4} \rightarrow \pi^*_{C2-N3}$	67.2	0.48	0.167	1.58	0.250
	$n_{N6} \rightarrow \sigma^*_{C5-N7}$	17.80	1.19	0.130	1.93	
	$n_{N6} \rightarrow \sigma^*_{N1-H8}$	13.52	1.31	0.120		

Table S6: The HOMA delocalization parameters in **BG1** and related structures.

Molecules	HOMA
BG1	0.819
BG3	0.741
BG5	0.615
BG1-TS1	0.911
BGP2	0.794
BGP1	0.985
BGP3	0.892
BGA2	0.806