Indian Journal of Chemistry
Vol. 56A, November 2017, pp. 1143-1153

A computational study on relationship between quantum chemical parameters and reactivity of the zwitterionic GABA and its agonists: Solvent effect

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Received 10 November 2016; revised and accepted 24 October 2017

The agonist activity of the title compounds on $GABA_C$ receptor as well as GABA uptake inhibition activity is reported. B3LYP/6-311++G(d,p) calculations have been performed to obtain the quantum chemical descriptors such as global hardness, electrophilicity, the electronic chemical potential of the title compounds. Polarized continuum model has been used to explore the solvent effect on activity of the title compounds in four solvent media, viz., chloroform, ethanol, DMSO, and water. The results obtained from the quantum chemical calculations show that the calculated energy gap and the global hardness, as well as molecular electrostatic potential values, are in good agreement with the experimental data.

Keywords: Theoretical chemistry, Density functional calculations, Quantum chemical parameters, Global hardness, Electrophilicity, Chemical reactivity, Molecular electrostatic potential, Energy gap, Solvent effects, GABA, Chloroform, Ethanol

Neurotransmitters are small chemicals in the mammalian central nervous system (CNS) responsible for the synaptic transmission which is excitatory or inhibitory depending on the type of neurotransmitter[1]. Any functional loss or deficit of the transmission process can strongly cause neurodegenerative disorders such as epilepsy[2], depression[3], anxiety[4], schizophrenia[5], Alzheimer's disease[6], Parkinson's disease[7], Huntington's chorea[8]. GABA (γ-amino-*n*-butyric acid) as the principle inhibitory transmitter in CNS acts on three classes' receptors as $GABA_A$, $GABA_B$, and $GABA_C$[9, 10] and it is estimated that at least 20% of brain neurons are GABAergic[11]. Just like the other biomolecules with both an amino group and a carboxylic acid group in solution and in the solute phase, GABA exists in zwitterionic form. There are plenty of experimental research on GABA, on its analogs and on its receptor[11-15], but computational/ theoretical searches are limited.[16-32] In theoretical/ computational chemistry, the first step is to determine the global minimum structure to evaluate the biochemical, pharmaceutical, neurophysiological, physicochemical properties, etc. One of the preliminary works on conformational research was performed for GABA and muscimol molecules using molecular orbital study with extended Hückel theory[17]. Subsequently, Lorenzini *et al.*[19] have also studied conformational structures of $GABA_A$ derivatives by using PM3 calculations. Ramek and Nagy[32] have investigated tautomeric equilibrium of GABA conformers in the aqueous phase by HF method. Since the beginning of the twenty-first century, the physicochemical parameters such as atomic charges and electrochemical potentials have also been investigated. One of these studies was conducted by Odai *et al.*[20] on the electrostatic and structural investigation of GABA and glutamat molecules. As is well-known, there is very strong evidence about relationship between chemical reactivity and the electrostatic properties, and Shikata and co-worker[22] have searched dielectric features of GABA and Glutamate molecules with HF theory. Crittenden *et al.*[25] have performed QSAR to determine the key interaction at the $GABA_C$ receptor binding site for GABA and its analogs which act on $GABA_C$ receptors. Srivastava *et al.*[28] have calculated the inhibitory properties related to the conformational structure for both GABA and bicuculline molecules to get the best quantum chemical descriptors to explain the chemical reactivity using DFT calculations. Still, many scientists have continued to study the conformational analysis. Song and co-worker[29] have researched the conformational structure GABA and its zwitterionic form by using M06-2X/cc-pVTZ level of theory in the gas phase and in water. The solvation effects on physicochemical properties of GABA have

been investigated by Jalili *et al.*[30] and they concluded that the solvent kind has strong effect on association of GABA.

The present work deals with the GABA (γ-amino-*n*-butyric acid)[20,23] as well as its analogs, i.e., TACA (*trans*-4-aminobut-2-enoic acid),[24,25] CACA (*cis*-4-aminobut-2-enoic acid),[24,25] muscimol (5-(aminomethyl)-3-isoxazolol)[25], and DABA (L-2,4-diamino-*n*-butyric acid).[18] Among the studied analogs, TACA and CACA are known well as conformational restricted GABA analogs and DABA is the structural GABA analog. On the other hand, muscimol, as well as the other studied analogs, act on GABA receptors and GABA-transporters. The DFT calculations have been conducted to determine the quantum chemical descriptors such as the electronic chemical potential (μ), the global hardness (η), the electrophilicity (ω) and maximum charge transfer index (Δ*N*) to explain the agonist activity of the agonists. First, the ground state geometries of each molecule have been optimized and then the optimized geometries have been used to get the energetic and structural parameters, both in the gas phase and each of four dielectric media studied herein. Finally, the calculated results have been compared with the observed activity on $GABA_C$ receptor and on GABA uptake inhibition.

Computational Details

All DFT calculations for GABA and its agonists were computed without any symmetry restriction at the B3LYP/6-311++G** level of theory with the Gaussian 03W package program.[33] B3LYP functional is a combination of Becke's three-parameter hybrid exchange functional[34] and the Lee-Yang-Parr correlation functional[35]. The potential energy surface (PES) scan were conducted at B3LYP/631G(d,p) level of the theory in the gas phase. The stable conformers of each molecule were verified by the absence of any imaginary frequency with frequency calculations at the same theory level. The isodensity version of PCM (polarized continuum model)[36] was used to estimate the solvent effect of four solvent media, viz., chloroform, ethanol, DMSO, and water, on the structure, charges, and quantum chemical descriptors of the studied molecules. The geometry optimizations in the solvent with ε = 4.9 to simulate $CHCl_3$ (chloroform), ε = 24.55 to simulate C_2H_5OH (ethanol), ε = 46.7 to simulate DMSO (dimethyl sulfoxide) and ε = 78.39 to simulate H_2O (water) were carried out at the 6-311++G** level using IPCM model. The atomic charges were calculated using Mulliken population analysis[37], natural population analysis (NPA)[38-39], electrostatic potential fitted charges, CHELPG and ESPDip[40-43] methods.

Theoretical background

The quantum chemical descriptors such as global hardness, electronic chemical potential, electrophilicity and maximum charge transfer index are very useful tools to explain chemical reactivity on any chemical process. According to Koopmans Theorem[44] the ionization energy (*I*) and electron affinity (*E*)[45] can be expressed through HOMO and LUMO orbital energies as following:

$$I = -E_{HOMO} \quad \ldots (1)$$

$$A = -E_{LUMO} \quad \ldots (2)$$

Parr and co-workers[45] have represented electronic chemical potential (μ), global hardness (η), electrophilicity (ω) and the maximum charge transfer index (ΔN_{max}) as follows:

$$\mu = -\frac{I+A}{2} \quad \ldots(3)$$

$$\eta = \frac{I-A}{2} \quad \ldots(4)$$

$$\omega = \frac{\mu^2}{2\eta} \quad \ldots(5)$$

$$\Delta N = \frac{I+A}{(I-A)} \quad \ldots(6)$$

These quantum chemical parameters have been determined for GABA and its agonist and compared with experimental data to explain their chemical reactivity. It is hoped that these descriptors can help to understand and to predict the activity of the new pharmaceutical agents in the future.

Results and Discussion

In theoretical and computational investigations, it is very important to determine a basic structural requirement of any molecular system. Figures 1–5 show the optimized structures of each studied compound having minimum in potential energy minima at B3LYP/6-311++G(d,p) level of the theory in aqueous phase obtained by PCM (polarized continuum model). Also, Fig. 6 presents some critical

structural and electrostatic parameters such as non-bonding distances, bond angles, atomic charges of nitrogen and oxygen atoms as the charged ends of each investigated structures, as well as the distance between negative and positive ends play an important role in determining or in predicting the relationship

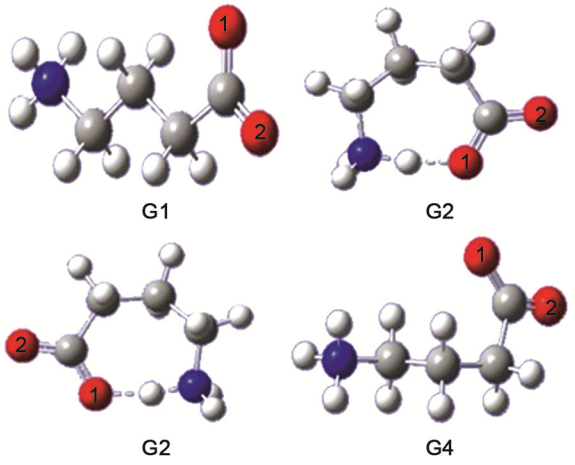

Fig. 1 — GABA conformers having minimum energy obtained from B3LYP/6-311++G(d,p) in the water phase. [The dotted lines show the intramolecular hydrogen bonds].

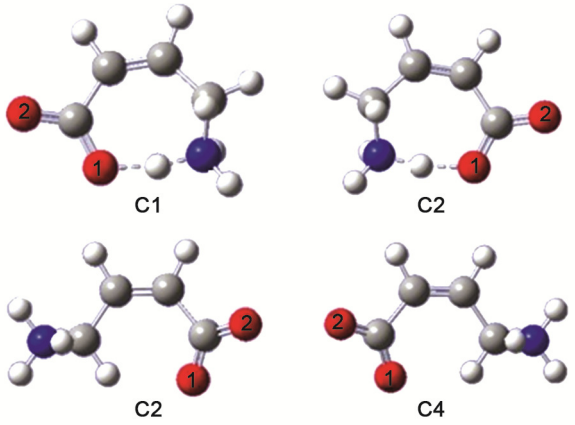

Fig. 2 — CACA conformers having minimum energy obtained from B3LYP/6-311++G(d,p) in the water phase. [The dotted lines show the intramolecular hydrogen bonds].

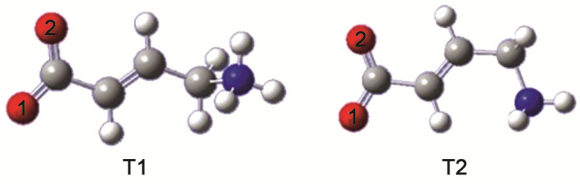

Fig. 3 — TACA conformers having minimum energy obtained from B3LYP/6-311++G(d,p) in the water phase.

structure and chemical activity. The present study reveals that there are very small differences in prediction of the bond and dihedral angles with change in solvent dielectric constant. Table 1 shows some important dihedral angles for each studied conformer of GABA and its agonist, in the aqueous phase. Complete data, including the original atom labeling for each compound, are given in Table S1 and Figs S1-S5 (Supplementary Data).

Here, the non-bonding length should be discussed because all the molecules are in zwitterionic form and have two opposite charged regions. Lorenzini *et al.*[31] have suggested that $GABA_A$ agonist activity strongly depends on the distance between negative and positive charge ends as COO^- and $^+NH_3$, and have determined this distance to be larger than 5.3 Å. Also, Kier and Truit[17] have clarified that the $O^-....N^+$

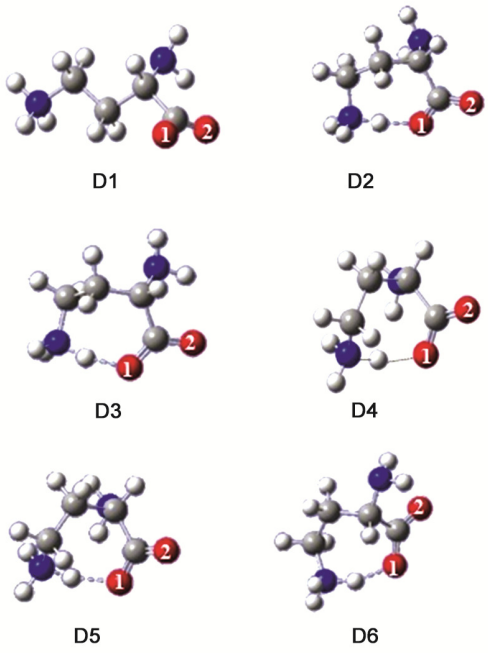

Fig. 4 — DABA conformers having minimum energy obtained from B3LYP/6-311++G(d,p) in the water phase. [The dotted lines show the intramolecular hydrogen bonds].

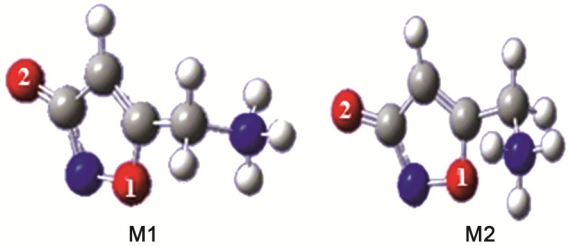

Fig. 5 — Muscimol conformers having minimum energy obtained from B3LYP/6-311++G(d,p) in the water phase.

Table 1 — The characteristic dihedral angles and energetic parameters for the stable aqueous phase conformers of the investigated molecules at the B3LYP/6-311++G(d,p) level of the theory

Conformers	N-C-C-C (°)	O1-C-C-C (°)	O2-C-C-C (°)	C-C-C-C (°)	ΔG (kcal mol^{-1})
G1	179.696 (179.19)[a]	175.747 (178.71)[a]	-4.706	177.669	10.174
G2	-73.312	148.924	-33.064	73.617	0
G3	73.251	-148.808	33.172	-73.730	0.014
G4	-179.204	-169.555	11.440	67.096	10.427
D1	175.815 (179.95)[b]	-74.330	104.272	171.189	1.772
D2	70.451	56.228	-125.573	-75.450	2.794
D3	83.557	-5.623	176.090	-59.514	6.141
D4	-47.012	76.917	-102.531	-34.430	0
D5	-73.850	-43.403	139.825	77.100	3.033
D6	42.277	-75.174	104.922	41.881	1.772
C1	43.411	-17.583	161.851	2.543	0.005
C2	-43.403	17.540	-161.896	-2.530 (-2.5)[c]	9.741
C3	118.458	27.933	-151.714	-3.643	0
C4	-118.490	-28.004	151.642	3.660	9.749
T1	-114.856	2.701	-177.005 (175.2)[c]	-179.240 (-179.5)[c]	0
T2	0.154 (0.4)[c]	-179.854	0.143	179.980	2.474
M1	-113.864	0.169	179.764	179.977 (-176.8)[d]	0.008
M2	113.938	-0.177	-179.752	179.994	0

Data in paranthesis are taken from literature: [a]Ref. 23: [b]Ref. 18: [c]Ref. 24: [d]Ref. 46.

distance for muscimol is 5.8 Å while it is in the range of 5.0 Å - 6.1 Å for GABA. As seen clearly from Fig. 6, in the present study the same distance is found to be 5.19 Å for GABA, 5.08 Å for TACA, 2.54 Å for DABA, 5.72 Å for muscimol and 4.42 Å for CACA. The non-bonding distance of the GABA and its agonists are in good agreement with the structural requirements for the agonist activity on GABA receptors. Another important point is the atomic charge distribution of the two oxygen atoms in the carboxylate region, that is, the calculated net charges of the two oxygen atoms, are almost similar to each other, for all charge values obtained from the four different population methods, because the π electrons on negative C-terminal are delocalized on both the oxygen atoms equally. Here, only the results obtained from the aqueous phase calculations are given in Fig. 6, but the same is also valid for the other solvent media. The numerical data about atomic charge are given in Table S2 (Supplementary Data).

The solvation electronic energy and solvation free energy for the most stable conformers of each compound are given in Figs 7 and 8, respectively. It is very clear that all structures are stabilized by solvent dielectric media. The change in solvation free energy between gas phase and water phase increases in the following order: GABA (11.31 kcal/mol) < CACA (11.39 kcal/mol) < DABA (11.87 kcal/mol) < muscimol (47.84 kcal/mol) <TACA (54.11 kcal/mol). Here, it is clear that the smallest change in free energy is for GABA, CACA and DABA, having the intramolecular hydrogen bonding between the positive nitrogen atom and the negative oxygen atom. Of course, the only factor affecting the stabilization energy is not the delocalization or resonance; the inductive effect is also one of the important parameters for determining the stabilization. However, here all the structures are similar to each other and with a positively charged N-terminal and a negatively charged C-terminal, and no other heteroatom on carbon backbone to affect the stabilization.

As it well-known, lower potential energy indicates a more stable structure thermodynamically, and the stability of the structure is usually determined by free energy. Hence, it is important to evaluate the free

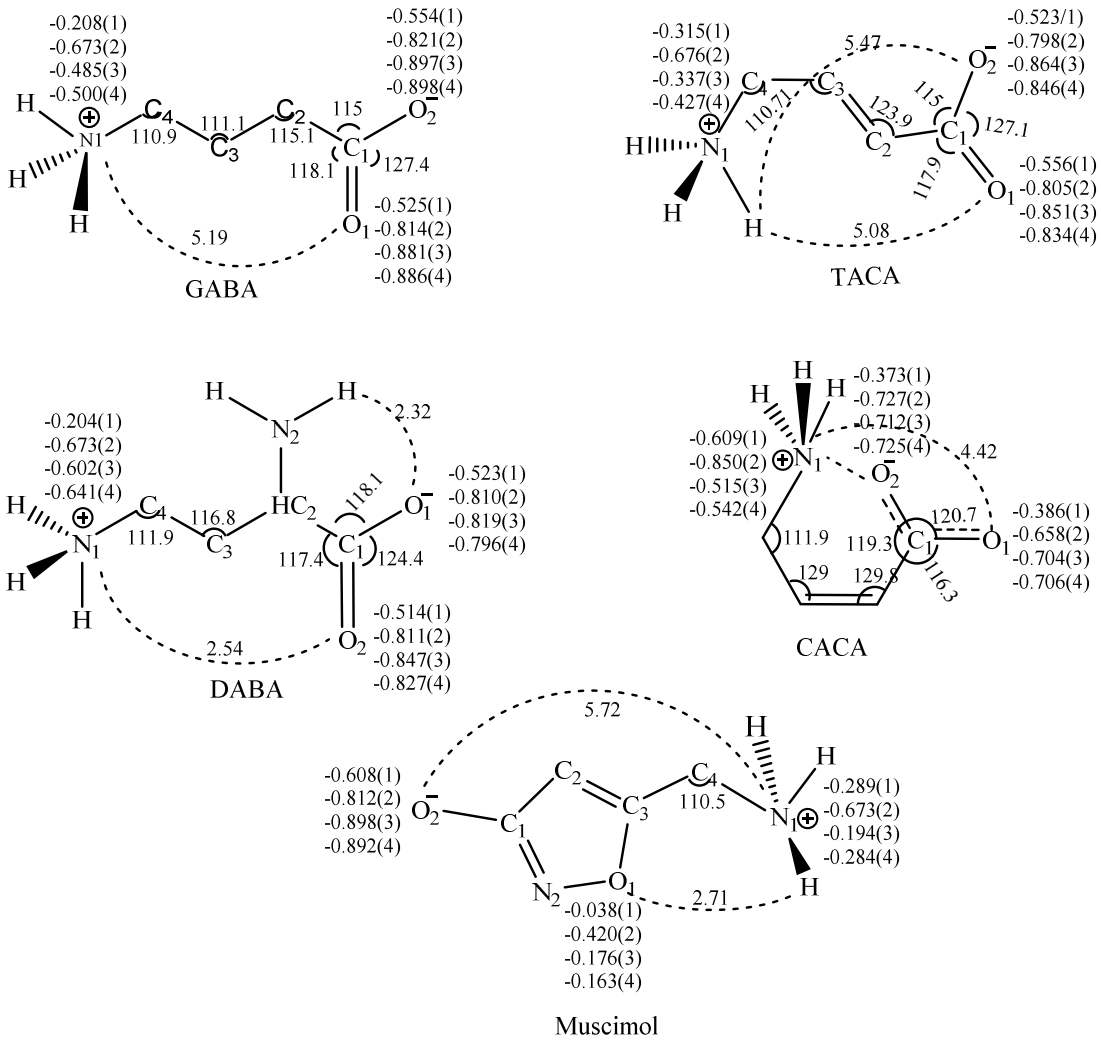

Fig. 6 — Selected atomic charges, bond angles and the non-bonding distances for the stable GABA and its agonists. [Herein, net atomic charges for nitrogen atom on N-terminal and two oxygen atoms on C-terminal, in-aqueous phase are given. Net charges on each atom from top to down are depicted as (1) Mülliken population analysis, (2) NPA (Natural population analysis), (3) CHELPG, and, (4) ESPDip].

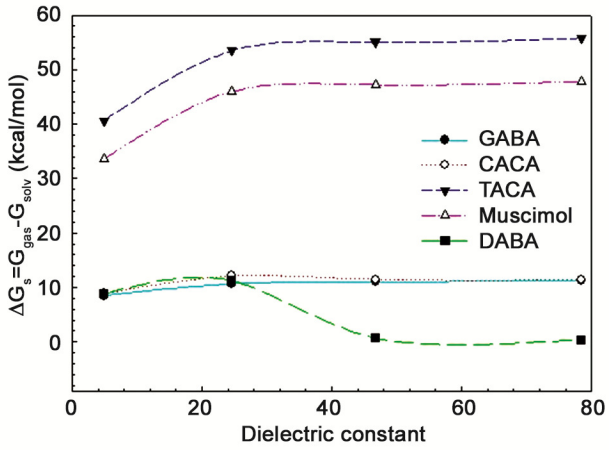

Fig. 7 — Solvation free energies (ΔG_S) (kcal/mol) of the most stable GABA, DABA, TACA, CACA and muscimol molecules.

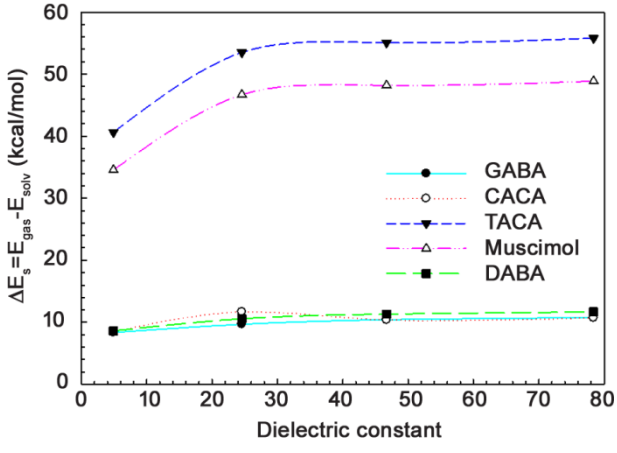

Fig. 8 — Solvation energies (ΔE_S) (kcal/mol) of the most stable GABA, DABA, TACA, CACA and muscimol molecules.

energy change to get a good prediction of the chemical reactivity of the studied structures. TACA is most affected by solvent dielectric media because there is no intramolecular hydrogen bonding possibility just as in CACA.

This study aims to predict the best descriptor for the chemical reactivity on GABA receptors. For this reason, the other quantum chemical parameters, i.e., global hardness, electronic chemical potential, maximum charge transfer index, and electrophilicity have been calculated. Tables 2–6 give the DFT-quantum chemical parameters of all stable conformers including the GABA and its agonists at the B3LYP/ 6-311++G** level of theory.

All quantum chemical and the energetic parameters strongly depend on the solvent media. From Tables 2–6, it is observed that all gauche conformers of studied molecules have higher energy gap (ΔE) value than those of the extended conformers because of the intramolecular hydrogen bonding that provides higher stability. Also, the gauche conformers have less electronic chemical potential values than those of the extended conformers. Also, these conformers have higher hardness values than those the extended conformers. It is well-known that the highest energy gap, the lowest electronic chemical potential (μ), and the highest global hardness (η) value mean less chemical reactivity. From Table 2, it can be easily seen that the conformers **G2** and **G3** are less reactive structures than the conformers **G1** and **G4** because they have lowest energy gap, lowest electronic chemical potential, and highest global hardness values than the other conformers. For example, the six stable zwDABA conformers (**D1**-**D6**) were determined, and the ΔE (eV) values of these conformers vary as follows: **D1** (5.450) < **D6** (6.136) < **D2** (6.188) < **D4** (6.241) < **D5** (6.259) < **D3** (6.265) in the water phase. Furthermore, the electronic chemical potential of these conformers are: **D1** (-3.325) > **D6** (-3.462) > **D5** (-3.469) > **D3** (-3.528) > **D2** (-3.532) > **D4** (-3.561) in the water phase. The global hardness values of DABA conformers have been calculated and are in the following order: **D5** (1.922) < **D6** (1.954) < **D3** (1.987) < **D2** (2.016) < **D1** (2.028) < **D4** (2.032) in the water phase. For CACA conformers, the ΔE order is as follows: **C3** (5.264) < **C4** (5.265) < **C1** (5.667) < **C2** (5.666); μ order is as: **C1** (-4.229) < **C2** (-4.229) < **C3** (-3.825) < **C4** (-3.824) while the order of η is: **C3** (2.632) = **C4** (2.632) < **C1** (2.833) = **C2** (2.833), in the water phase.

Table 2 — The calculated quantum chemical parameters of zw-GABA at B3LYP/6-311++G(d,p)

Solvent	Conformer	HOMO (-*I*) (au)	LUMO (-*A*) (au)	ΔE (eV)	μ (eV)	*H* (eV)	Ω (eV)	ΔN (eV)	Dipole moment (D)
Gas	G1	-0.258	-0.031	6.157	-3.933	3.078	2.512	1.278	7.320
	G2	-0.258	-0.031	6.159	-3.933	3.079	2.512	1.277	7.316
	G3	-0.258	-0.031	6.158	-3.933	3.079	2.512	1.277	7.320
	G4	-0.258	-0.031	6.159	-3.933	3.079	2.512	1.277	7.316
Chloroform	G1	-0.211	-0.044	4.558	-3.465	2.279	2.634	1.520	25.471
	G2	-0.266	-0.016	6.817	-3.842	3.409	2.166	1.127	9.033
	G3	-0.266	-0.016	6.818	-3.842	3.409	2.165	1.127	9.034
	G4	-0.215	-0.040	4.767	-3.462	2.384	2.513	1.452	21.183
Ethanol	G1	-0.227	-0.025	5.493	-3.438	2.746	2.152	1.252	26.726
	G2	-0.249	-0.014	6.398	-3.571	3.199	1.993	1.116	13.881
	G3	-0.249	-0.014	6.398	-3.571	3.199	1.993	1.116	13.880
	G4	-0.229	-0.024	5.563	-3.437	2.782	2.123	1.236	22.916
DMSO	G1	-0.229	-0.023	5.603	-3.437	2.801	2.108	1.227	26.865
	G2	-0.249	-0.013	6.407	-3.559	3.203	1.977	1.111	14.306
	G3	-0.249	-0.013	6.408	-3.560	3.204	1.978	1.111	14.296
	G4	-0.230	-0.022	5.661	-3.435	2.831	2.084	1.214	23.111
Water	G1	-0.230	-0.022	5.654	-3.436	2.827	2.088	1.216	26.928
	G2	-0.249	-0.013	6.419	-3.557	3.210	1.971	1.108	14.445
	G3	-0.249	-0.013	6.419	-3.557	3.209	1.971	1.108	14.448
	G4	-0.231	-0.021	5.706	-3.434	2.853	2.067	1.204	23.200

Table 3 — The calculated quantum chemical parameters of zw-CACA at B3LYP/6-311++G(d,p)

Solvent	Conformer	HOMO (-*I*) (au)	LUMO (-*A*) (au)	ΔE (eV)	μ (eV)	H (eV)	Ω (eV)	ΔN (eV)	Dipole moment (D)
Gas	C1	-0.268	-0.063	5.575	-4.515	2.788	3.657	1.620	7.411
	C2	-0.268	-0.064	5.575	-4.515	2.788	3.657	1.620	7.410
	C3	-0.268	-0.063	5.575	-4.515	2.788	3.656	1.620	7.412
	C4	-0.268	-0.063	5.575	-4.515	2.788	3.656	1.620	7.412
Chloroform	C1	-0.276	-0.061	5.852	-4.576	2.926	3.578	1.564	9.623
	C2	-0.276	-0.061	5.852	-4.576	2.926	3.578	1.564	9.622
	C3	-0.276	-0.061	5.852	-4.576	2.926	3.578	1.564	9.622
	C4	-0.276	-0.061	5.853	-4.576	2.927	3.577	1.563	9.625
Ethanol	C1	-0.277	-0.060	5.909	-4.586	2.955	3.559	1.552	10.525
	C2	-0.277	-0.060	5.909	-4.586	2.954	3.559	1.552	10.526
	C3	-0.236	-0.045	5.203	-3.816	2.601	2.799	1.467	20.344
	C4	-0.236	-0.045	5.202	-3.816	2.601	2.800	1.467	20.347
DMSO	C1	-0.260	-0.052	5.674	-4.239	2.837	3.167	1.494	13.932
	C2	-0.260	-0.052	5.674	-4.239	2.837	3.167	1.494	13.931
	C3	-0.237	-0.044	5.243	-3.820	2.622	2.784	1.457	20.949
	C4	-0.237	-0.044	5.243	-3.821	2.621	2.785	1.458	20.950
Water	C1	-0.260	-0.051	5.667	-4.229	2.833	3.155	1.492	14.181
	C2	-0.260	-0.051	5.666	-4.228	2.833	3.155	1.492	14.184
	C3	-0.237	-0.044	5.264	-3.825	2.632	2.779	1.453	21.094
	C4	-0.237	-0.044	5.265	-3.824	2.632	2.778	1.453	21.094

Table 4 — The calculated quantum chemical parameters of zw-TACA at B3LYP/6-311++G(d,p)

Solvent	Conformer	HOMO (-*I*) (au)	LUMO (-*A*) (au)	ΔE (eV)	μ (eV)	H (eV)	Ω (eV)	ΔN (eV)	Dipole moment (D)
Gas	T2	-0.185	-0.100	2.315	-3.869	1.158	6.467	3.343	18.838
Chloroform	T1	-0.220	-0.054	4.538	-3.728	2.269	3.062	1.643	24.028
	T2	-0.220	-0.044	4.789	-3.599	2.395	2.705	1.503	23.273
Ethanol	T1	-0.235	-0.048	5.075	-3.844	2.537	2.912	1.515	25.400
	T2	-0.234	-0.033	5.479	-3.629	2.740	2.403	1.325	24.569
DMSO	T1	-0.236	-0.048	5.127	-3.865	2.563	2.914	1.508	25.554
	T2	-0.236	-0.033	5.512	-3.658	2.756	2.427	1.327	24.726
Water	T1	-0.237	-0.048	5.150	-3.876	2.575	2.916	1.505	25.627
	T2	-0.237	-0.033	5.528	-3.672	2.764	2.439	1.328	24.799

The order of energy gap for the most stable conformers of studied compounds are: **M1** (4.79) < **T1** (5.15) < **C1** (5.67) < **D5** (6.26) < **G2** (6.42) in the water phase. Also, this order for each of the solvent is similar to the order in the water phase. The electronic chemical potential for the most stable conformers changes as: **C1** (-4.23) < **T1** (-3.88) < **G2** (-3.56) < **D5** (-3.47) < **M1** (-3.32) for the water phase, whereas this order is **C1** (-4.52) < **G2** (-3.93) < **T1** (-3.87) < **D5** (-3.85) < **M1** (-3.53) in the gas phase. The order of the global hardness for the most stable conformers is as follows: **M1** (2.40) < **T1** (2.58) < **C1** (2.83) < **D5** (3.13) < **G2** (3.21) for water phase, while it is **M1** (1.072) < **T1** (1.16) < **C1** (2.79) < **D5** (3.03) < **G2** (3.08) for the gas phase. According to these results, it can be suggested that **M1** is the most reactive molecule because it has the lowest energy gap value, and the highest electronic chemical potential and the smallest hardness value. Also, **G2** has the less chemical reactivity than the other stable conformers because it has the highest hardness value, indicating resistance to change in the electron distribution for any molecular system. The electrophilicity increases in the following order: **D5** (2.45) < **G2** (2.52) < **C1** (3.66) < **M1** (5.80) < **T1** (6.47) for gas phase; **D5** (1.92) < **G2** (1.97) < **M1** (2.30) < **T1** (2.92) < **C1** (3.16) for water phase (also for the ethanol and chloroform phases). Although depending on the solvent media there are some differences in the order of the electrophilicity index of

Table 5 — The calculated quantum chemical parameters of zw-DABA at B3LYP/6-311++G(d,p)

Solvent	Conformer	HOMO (-*I*) (au)	LUMO (-*A*) (au)	ΔE (eV)	μ (eV)	H (eV)	Ω (eV)	ΔN (eV)	Dipole moment (D)
Gas	D1	-0.173	-0.100	1.983	-3.703	0.991	6.917	3.735	18.909
	D2	-0.245	-0.032	5.780	-3.766	2.890	2.454	1.303	6.182
	D3	-0.245	-0.032	5.780	-3.766	2.890	2.454	1.303	6.496
	D4	-0.248	-0.034	5.821	-3.831	2.911	2.521	1.316	7.404
	D5	-0.253	-0.030	6.055	-3.852	3.027	2.450	1.272	6.077
	D6	-0.255	-0.030	6.123	-3.867	3.061	2.442	1.263	5.443
Chloroform	D1	-0.209	-0.042	4.540	-3.412	2.270	2.564	1.503	22.802
	D2	-0.253	-0.020	6.340	-3.721	3.170	2.184	1.174	10.154
	D3	-0.259	-0.017	6.568	-3.759	3.284	2.151	1.145	8.467
	D4	-0.253	-0.018	6.381	-3.688	3.190	2.132	1.156	9.411
	D5	-0.258	-0.015	6.596	-3.713	3.298	2.091	1.126	7.768
	D6	-0.259	-0.017	6.596	-3.754	3.298	2.137	1.138	6.853
Ethanol	D1	-0.220	-0.025	5.321	-3.337	2.660	2.093	1.254	23.899
	D2	-0.243	-0.017	6.133	-3.536	3.067	2.038	1.153	15.653
	D3	-0.244	-0.015	6.228	-3.532	3.114	2.003	1.134	13.163
	D4	-0.245	-0.018	6.184	-3.569	3.092	2.060	1.154	15.435
	D5	-0.243	-0.014	6.234	-3.485	3.117	1.948	1.118	13.171
	D6	-0.240	-0.016	6.099	-3.475	3.049	1.981	1.140	12.769
DMSO	D1	-0.222	-0.023	5.410	-3.329	2.705	2.048	1.230	24.029
	D2	-0.243	-0.016	6.170	-3.533	3.085	2.023	1.145	15.919
	D3	-0.245	-0.015	6.253	-3.529	3.127	1.992	1.129	13.368
	D4	-0.245	-0.017	6.223	-3.563	3.111	2.041	1.145	15.674
	D5	-0.242	-0.013	6.249	-3.473	3.124	1.930	1.112	13.458
	D6	-0.240	-0.015	6.124	-3.466	3.062	1.962	1.132	12.994
Water	D1	-0.222	-0.022	5.450	-3.325	2.725	2.028	1.220	24.089
	D2	-0.244	-0.016	6.188	-3.532	3.094	2.016	1.142	16.059
	D3	-0.245	-0.015	6.265	-3.528	3.133	1.987	1.126	13.462
	D4	-0.246	-0.016	6.241	-3.561	3.120	2.032	1.141	15.784
	D5	-0.242	-0.012	6.259	-3.469	3.129	1.922	1.108	13.568
	D6	-0.240	-0.014	6.136	-3.462	3.068	1.954	1.129	13.095

Table 6 — The calculated quantum chemical parameters of zw-Muscimol at B3LYP/6-311++G(d,p)

Solvent	Conformer	HOMO (-*I*) (au)	LUMO (-*A*) (au)	ΔE (eV)	μ (eV)	H (eV)	Ω (eV)	ΔN (eV)	Dipole moment (D)
Gas	M1	-0.169	-0.090	2.145	-3.528	1.072	5.804	3.290	17.143
	M2	-0.169	-0.090	2.145	-3.528	1.073	5.803	3.289	17.143
Chloroform	M1	-0.196	-0.047	4.076	-3.307	2.038	2.684	1.623	22.395
	M2	-0.196	-0.047	4.076	-3.308	2.038	2.684	1.623	22.395
Ethanol	M1	-0.208	-0.035	4.698	-3.313	2.349	2.336	1.410	23.986
	M2	-0.208	-0.035	4.698	-3.312	2.349	2.335	1.410	23.989
DMSO	M1	-0.210	-0.034	4.766	-3.318	2.383	2.310	1.393	24.177
	M2	-0.210	-0.034	4.766	-3.318	2.383	2.310	1.393	24.177
Water	M1	-0.210	-0.034	4.796	-3.321	2.398	2.300	1.385	24.268
	M2	-0.210	-0.034	4.795	-3.321	2.398	2.300	1.385	24.266

the most stable conformers, it can be suggested that **D5** is the best electrophile in according with these results. Finally, the maximum charge transfer index (ΔN) increases as follows: **D5** (1.27) < **G2** (1.28) < **T1** (1.34) < **C1** (1.62) < **M1** (3.29) for gas phase; **D5** (1.11) = **G2** (1.11) < **M1** (1.39) < **C1** (1.45) < **T1** (1.51) for water phase. For the other solvents, ΔN ordering are calculated as follows: **D5** (1.13) = **G2** (1.13) < **C1** (1.56) < **M1** (1.62) < **T1** (1.64) for chloroform; **D5** (1.12) < **G2** (1.16) < **M1** (1.41) < **T1** (1.52) < **C1** (1.55) for ethanol, and **D5** (1.11) < **G2** (1.11) < **M1** (1.39) < **C1** (1.49) < **T1** (1.51) for DMSO phase.

Conformational analysis is very important in understanding which conformational structure will be

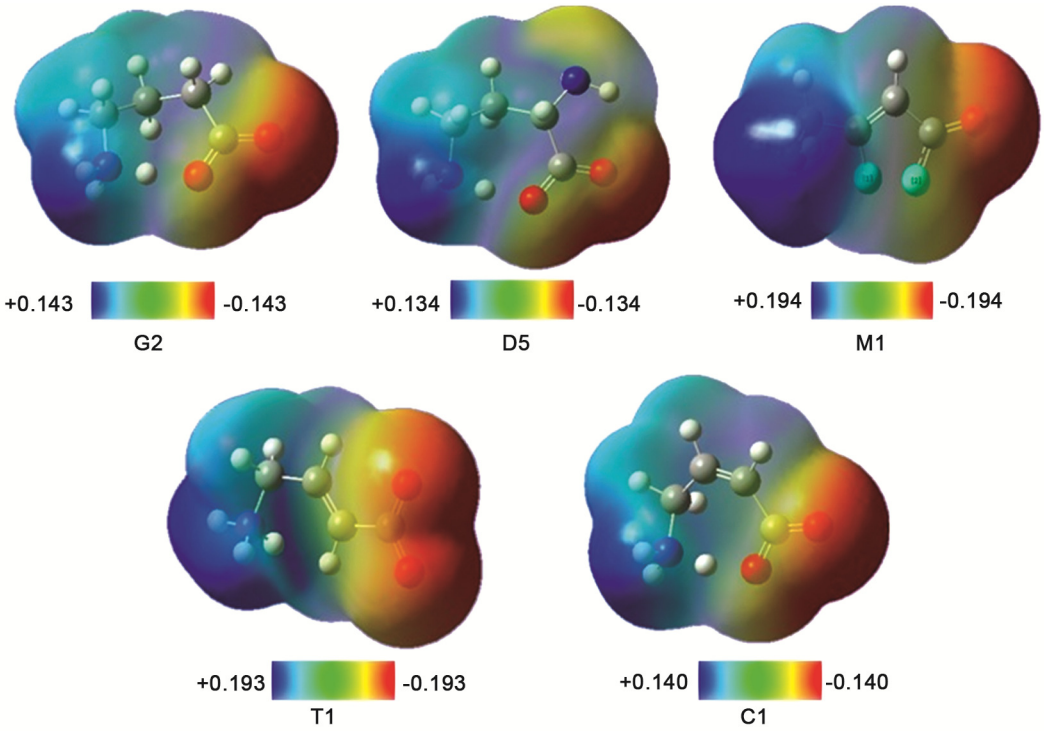

Fig. 9 — ESP (electrostatic potential) mapped on the electron density surface calculated by B3LYP/6-311++G** level of theory for GABA, DABA, TACA, CACA and muscimol molecules in the aqueous phase.

effective on the receptor of interest because the activity of interested molecule on any receptor site depends on the conformation of the molecule. Gao *et al.*[11] have tested twenty compounds related to the GABA transport in mammalian cells for their ability to block [^{3}H] GABA transport by TrnGAT-baculovirus-infected cells and have determined the six most active inhibitors for [^{3}H] GABA uptake. They have determined the inhibition of TrnGAT uptake activity in the following order: TACA (1.72 %) > DABA (26.1 %) ≥ CACA (27.6 %) > Muscimol (31.6 %). In this work, the energy gap and global hardness are predicted as follows: **G1** (5.65) > **T1** (5.52) > **D1** (5.45) > **C3**(5.26) > **M1** (4.79) and **G1** (2.83) > **T2** (2.76) > **D1** (2.73) > **C3** (2.63) > **M1** (2.39), in the water phase. Also, the electronic chemical potential (μ) and maximum charge transfer capability (ΔN_{max}) indexes of these conformers have been calculated as follows: **T1** (-3.88) > **C3** (-3.83) > **D1** (-3.33) > **M1** (-3.32) and **T1** (1.51) > **C3** (1.45) > **M1** (1.38) > **D1** (1.22). According to the energy gap and global hardness values, the orders of these parameters are compatible with the activities of GABA uptake inhibitor in the experiment. It also should be noted that the electronic chemical potential (μ) order is also in agreement with the calculated values, though the **C3** and **D1** conformers are interchanged with each other in the ordering of this parameter.

Figure 9 shows the electrostatic potential mapped on the electron density surface calculated by B3LYP/6-311++G** level of theory for the most stable GABA, DABA, TACA, CACA and muscimol conformers in the aqueous phase. For each stable conformers, the red color on the C-terminal (nucleophilic) site shows the electron-rich region where the electrophilic attack and blue color on the N-terminal (electrophilic) site indicates the electron-poor region where the nucleophilic attack. Figure 9 shows that the electrostatic potential value on the total density surface for each stable conformers has increased in the following order: **D5** (+0.134) > **C1** (+0.140) > **G2** (+0.143) > **T1** (+0.193) > **M1** (+0.194). The agonist potency of GABA and its analogs on $GABA_C$ receptors have been determined by Crittenden *et al.*[25] in the following order: CACA (37.4) > muscimol (1.48) > GABA (1.01) > TACA (0.53). According to the order of EP value, the C1 molecule has the least EP value on itself which explains why the **C1** has the least activity on $GABA_C$ receptor as compared to the other molecules.

Conclusions

In this work, the quantum chemical descriptors including global hardness, electrophilicity, maximum charge transfer index, electronic chemical potential have been calculated to explain the agonist activity of GABA and its agonists in zwitterion with four different solvent media, viz., chloroform, ethanol, DMSO, and water. The electronic charge distribution of the investigated molecules shows that CACA (**C1**) with the least positive charge on the N-terminal region is the least active molecule on $GABA_C$ receptors. The energy gap and global hardness values of the GABA agonists are in good agreement with the GABA uptake inhibitor values reported in literature. Moreover, the electronic chemical potential (μ) order is also in agreement with the experimental GABA uptake inhibitor values reported in literature, although the **C3** and **D1** conformers are interchanged with each other in the order of this parameter. This study shows that the quantum chemical parameters may be used to estimate the molecular reactivity, but it is important to keep in mind that there can be many other parameters contribute to chemical interactions and reactivity for any biochemical process.

Supplementary Data

Supplementary data associated with this article are available in the electronic form at http://www.niscair.res.in/jinfo/ijca/IJCA_56A(11)1143-1153_SupplData.pdf.

Acknowledgment

The financial support of the scientific research projects of Cumhuriyet University (F-222), Sivas, Turkey is acknowledged. All calculations have been conducted at TUBITAK (the scientific and technological Research Council), ULAKBIM (Turkish academic Network and information center), High Performance and Grid Computing Center (TR-Grid e-Infrastructure), Turkey.

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