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A Computational Study on the Nucleophilic Substitution Reaction between 2-Bromoacetophenone and Azole Derivatives

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Abstract

In this study, it was aimed to investigate the reaction of 2-bromoacetophenone with various azole derivatives, such as imidazole, benzimidazole, 1,2,4-triazole and benzotriazole computationally. For this purpose, some Density Functional Theory (DFT) calculations have been carried out on the reactants and products at B3LYP (Becke, three-parameter, Lee-Yang-Parr) level of theory using various basis sets, including 6-31G(d), 6-31G(d,p), 6-311G(d,p) and 6-311+G(2d,p). Geometry optimizations, Single Point Energy (SPE) calculations, frequency analysis, frontier molecular orbital calculations, molecular electrostatic potential (MEP) map calculations, and determination of global reactivity descriptors have been carried out at the same levels of theory. In NMR calculations, both Continuous Set of Gauge Transformations (CSGT) and Gauge-Independent Atomic Orbital (GIAO) methods have been used and computationally obtained data have been compared with the experimental data.
Keywords: Computational chemistry, DFT, 2-bromoacetophenone, azole.

1. Introduction

Azole derivatives are important compounds in organic and pharmaceutical chemistry. They can act as antifungal, antibacterial, anticonvulsant agents etc. [1] In most commercially available azoles such as, clotrimazole, miconazole, econazole, oxiconazole etc, *gem*-phenyl-(1*H*-imidazol-1-ylmethyl) group is thought to be responsible for the biological activity (Figure 1). [2]

In literature, the synthesis of substituted 1-phenylethanone derivatives via the reaction of 2-bromoacetophenone with various azole derivatives such as imidazole, [1, 3, 4] benzimidazole, [2, 3, 5] 1,2,4-triazole [1, 6-8] and benzotriazole [3, 9, 10] have been reported.

In this study, the nucleophilic substitution reaction of 2-bromoacetophenone with imidazole, benzimidazole, 1,2,4-triazole and benzotriazole have been investigated computationally. For this purpose, some DFT calculations have been performed on the reactants and products which take place in the investigated reactions (Figure 2).

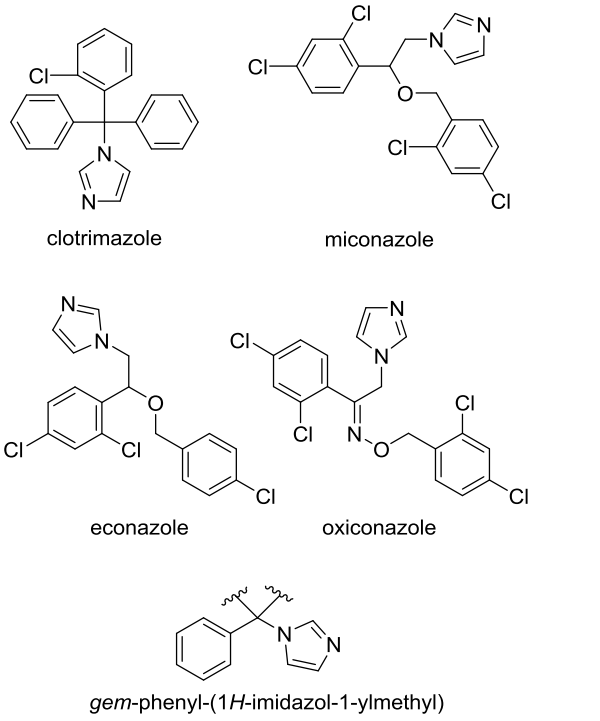

Figure 1. Some commercially available azole derivatives and *gem*-phenyl-(1*H*-imidazol-1-ylmethyl) group.

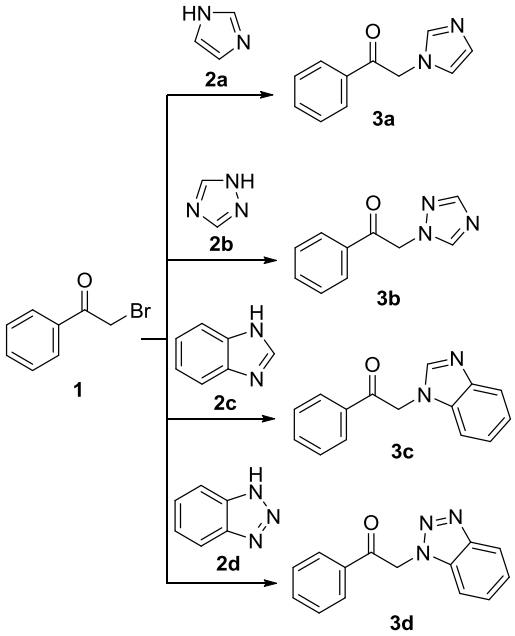

Figure 2. Investigated reactions.

2. Materials and Methods

All calculations have been carried out using Gaussian 09. Revision D.01 Program Package [11], Avogadro 1.1.1. [12] and GaussView5 [13].

2.1 Geometry Optimizations

Geometry optimizations have been performed at DFT B3LYP level of theory using various basis sets including 6-31G(d), 6-31G(d,p), 6-311G(d,p) and 6-311+G(2d,p). For initial geometries, conformer search calculations have been performed to obtain the global minimum for each molecule. A frequency analysis has also been performed to confirm that there is no imaginary frequency for each molecule. No imaginary frequency was found and it was confirmed that all the optimized structures are true minima. Optimized structures of the compounds at B3LYP 6-311+G(2d,p) level of theory are given in Figures 3 and 4. For instance, some selected geometric parameters for compound 3c are given in Table 1.

2.2 Single Point Energies

SPE calculations have been performed at DFT B3LYP level of theory using various basis sets including 6-31G(d), 6-31G(d,p), 6-311G(d,p) and 6-311+G(2d,p). Computational results are given in Table 2. As can be seen from Table 2, the larger basis sets estimate the higher single point energy for all compounds.

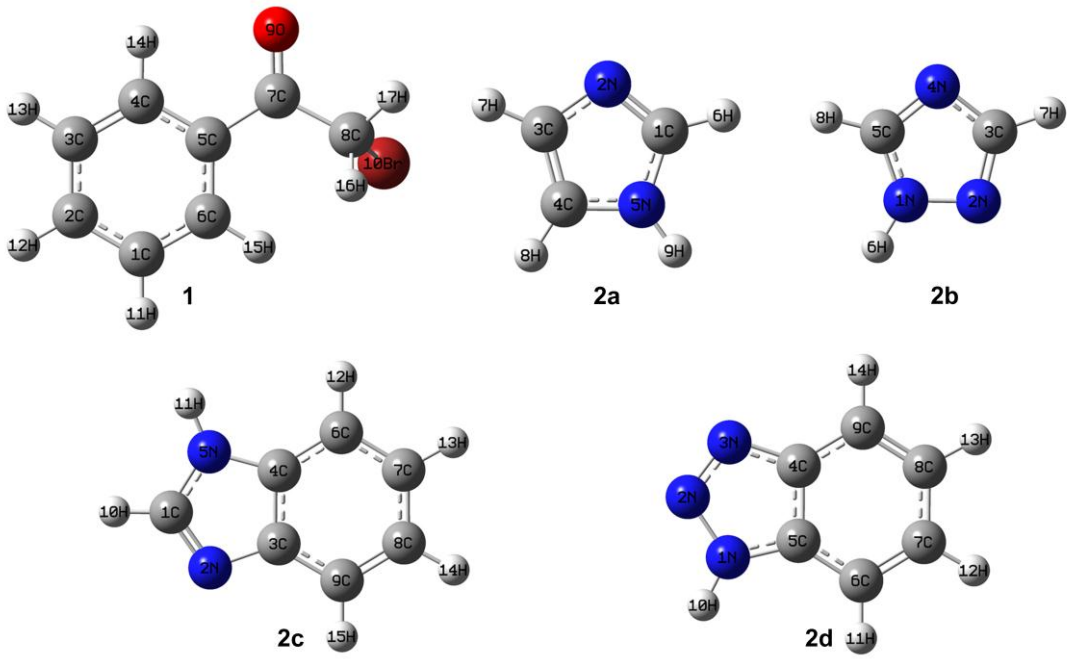

Figure 3. Optimized structures of compounds 1 and 2a-d.

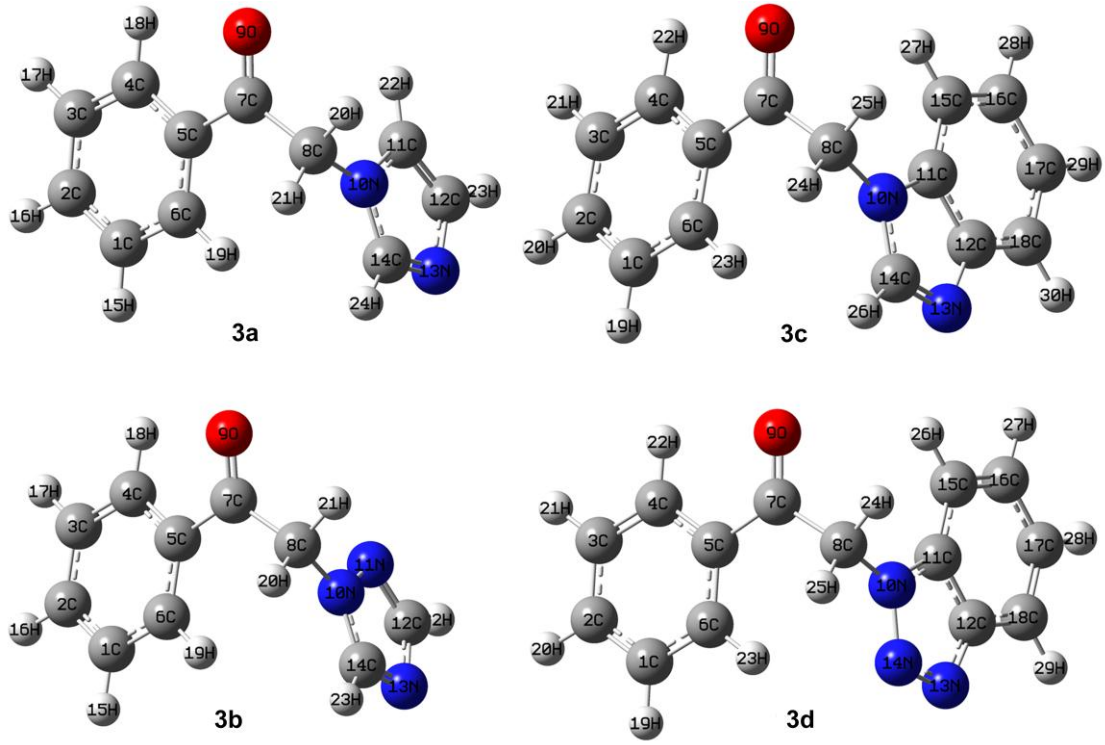

Figure 4. Optimized structures of compounds 3a-d.

Table 1. Selected Geometric Parameters for Compound 3c.

Atoms	Bond Lengths (Å)	Atoms	Bond Angles (°)	Atoms	Dihedral Angles (°)
5C-7C	1.490	4C-5C-7C	118.0	3C-4C-5C-7C	-178.9
7C-8C	1.543	6C-5C-7C	122.9	7C-5C-6C-1C	178.3
7C-9O	1.214	5C-7C-8C	120.6	4C-5C-7C-8C	-168.8
8C-10N	1.449	5C-7C-9O	121.5	4C-5C-7C-9O	11.9
		8C-7C-9O	118.0	6C-5C-7C-8C	12.6
		7C-8C-10N	114.5	6C-5C-7C-9O	-166.6
		8C-10N-11C	127.0	5C-7C-8C-10N	60.2
		8C-10N-14C	127.0	9O-7C-8C-10N	-120.5
				7C-8C-10N-11C	60.5
				7C-8C-10N-14C	-124.2

Table 2. Calculated SPEs of the investigated molecules.

	opt1[a] (eV)	opt2[b] (eV)	opt3[c] (eV)	opt4[d] (eV)
1	-80436.76	-80437.06	-80505.83	-80506.15
2a	-6155.61	-6155.85	-6157.31	-6157.60
2b	-6591.94	-6592.12	-6593.69	-6594.03
2c	-10336.69	-10337.00	-10339.26	-10339.70
2d	-10772.10	-10772.37	-10774.72	-10775.22
3a	-16596.30	-16596.72	-16600.47	-16601.16
3b	-17032.66	-17033.03	-17036.89	-17037.63
3c	-20777.38	-20777.88	-20782.42	-20783.25
3d	-21212.95	-21213.41	-21218.06	-21218.93

[a] B3LYP/6-31G(d)
[b] B3LYP/6-31G(d,p)
[c] B3LYP/6-311G(d,p)
[d] B3LYP/6-311+G(2d,p)

2.3 NMR Spectral Analysis

^{1}H NMR chemical shifts have been computationally determined at the same level of theory using the same basis sets with GIAO and CSGT methods. A comparison has been made between experimental and computationally obtained data. Experimental data have been obtained from the literature. [2, 7, 14] Computationally obtained data for compounds 3a-d are given in Tables 3, 4, 5 and 6. In order to express the agreement between experimental and computationally obtained data, a color scale from red to green has been applied to Tables 3, 4, 5 and 6. Green color represents the best agreement between experimental and computational data while red color represents the worst. It can be seen from Tables 3, 4, 5 and 6 that, GIAO methods are more successful than CSGT methods in all cases.

Table 3. Experimental and computationally obtained ^{1}H NMR chemical shifts for compound 3a.

	EXP.[14]	CSGT1[a]	CSGT2[b]	CSGT3[c]	CSGT4[d]	GIAO1[a]	GIAO2[b]	GIAO3[c]	GIAO4[d]
20-H	5.41	2.47	2.93	3.64	4.78	4.66	4.76	4.87	5.06
21-H	5.41	2.47	2.93	3.64	4.78	4.66	4.76	4.87	5.06
22-H	6.88-6.99	3.74	4.52	5.87	6.65	6.57	6.88	6.85	6.87
23-H	7.09-7.15	3.84	4.57	5.89	6.88	6.79	7.07	7.12	7.20
15-H	7.45-7.59	4.75	5.30	6.44	7.31	7.26	7.45	7.54	7.61
17-H	7.45-7.59	4.75	5.30	6.44	7.31	7.26	7.45	7.54	7.61
24-H	7.45-7.59	3.70	4.62	6.26	7.30	7.04	7.35	7.44	7.62
16-H	7.60-7.75	4.83	5.37	6.49	7.45	7.35	7.53	7.63	7.74
18-H	7.90-8.02	5.13	5.69	6.87	7.97	7.95	8.20	8.25	8.37
19-H	7.90-8.02	5.13	5.69	6.87	7.97	7.95	8.20	8.25	8.37
[a] B3LYP/6-31G(d) ; [b] B3LYP/6-31G(d,p) ; [c] B3LYP/6-311G(d,p) ; [d] B3LYP/6-311+G(2d,p)									

Table 4. Experimental and computationally obtained ^{1}H NMR chemical shifts for compound 3b.

	EXP.[7]	CSGT1[a]	CSGT2[b]	CSGT3[c]	CSGT4[d]	GIAO1[a]	GIAO2[b]	GIAO3[c]	GIAO4[d]
20-H	5.78	2.59	3.09	3.80	4.89	4.81	4.92	5.06	5.18
21-H	5.78	2.59	3.09	3.80	4.89	4.81	4.92	5.06	5.18
15-H	7.55	4.69	5.23	6.37	7.24	7.18	7.37	7.46	7.55
17-H	7.55	4.69	5.23	6.37	7.24	7.18	7.37	7.46	7.55
16-H	7.68	4.78	5.32	6.44	7.39	7.28	7.47	7.58	7.68
22-H	7.98-8.00	4.25	5.13	6.62	7.52	7.49	7.78	7.79	7.85
18-H	7.98-8.00	4.92	5.47	6.64	7.70	7.68	7.92	7.96	8.10
19-H	8.11	4.92	5.47	6.64	7.70	7.68	7.92	7.96	8.10
23-H	8.74	4.23	5.20	6.80	7.86	7.61	7.96	8.01	8.17
[a] B3LYP/6-31G(d) ; [b] B3LYP/6-31G(d,p) ; [c] B3LYP/6-311G(d,p) ; [d] B3LYP/6-311+G(2d,p)									

Table 5. Experimental and computationally obtained ^{1}H NMR chemical shifts for compound 3c.

	EXP. [2]	CSGT1[a]	CSGT2[b]	CSGT3[c]	CSGT4[d]	GIAO1[a]	GIAO2[b]	GIAO3[c]	GIAO4[d]
24-H	5.54	2.70	3.17	3.87	5.00	4.88	4.98	5.07	5.28
25-H	5.54	2.70	3.17	3.87	5.00	4.88	4.98	5.07	5.28
28-H	7.18-7.32	4.54	5.07	6.19	7.10	7.07	7.25	7.39	7.39
29-H	7.18-7.32	4.52	5.06	6.18	7.09	7.10	7.27	7.39	7.43
27-H	7.18-7.32	4.69	5.29	6.53	7.32	7.31	7.54	7.63	7.57
19-H	7.50-7.58	4.75	5.30	6.45	7.27	7.25	7.44	7.54	7.58
21-H	7.50-7.58	4.75	5.30	6.45	7.27	7.25	7.44	7.54	7.58
20-H	7.64	4.82	5.36	6.48	7.39	7.32	7.50	7.61	7.69
30-H	7.84	4.83	5.46	6.74	7.68	7.47	7.71	7.91	7.96
26-H	7.91	4.15	5.04	6.56	7.68	7.42	7.70	7.79	8.02
22-H	8.05	5.20	5.76	6.93	8.02	8.03	8.28	8.32	8.37
23-H	8.05	5.20	5.76	6.93	8.02	8.03	8.28	8.32	8.37
[a] B3LYP/6-31G(d) ; [b] B3LYP/6-31G(d,p) ; [c] B3LYP/6-311G(d,p) ; [d] B3LYP/6-311+G(2d,p)									

Table 6. Experimental and computationally obtained ^{1}H NMR chemical shifts for compound 3d.

	EXP.[14]	CSGT1[a]	CSGT2[b]	CSGT3[c]	CSGT4[d]	GIAO1[a]	GIAO2[b]	GIAO3[c]	GIAO4[d]
24-H	6.21	3.18	3.68	4.40	5.57	5.45	5.57	5.66	5.88
25-H	6.21	3.18	3.68	4.40	5.57	5.45	5.57	5.66	5.88
28-H	7.36-7.47	4.57	5.13	6.23	7.17	7.19	7.36	7.47	7.49
19-H	7.36-7.47	4.76	5.30	6.44	7.30	7.26	7.44	7.53	7.61
21-H	7.48-7.59	4.76	5.30	6.44	7.30	7.26	7.44	7.53	7.61
27-H	7.48-7.59	4.71	5.26	6.37	7.31	7.31	7.47	7.60	7.64
20-H	7.61-7.73	4.81	5.34	6.46	7.41	7.31	7.49	7.59	7.70
26-H	7.84-7.96	4.86	5.49	6.74	7.51	7.54	7.77	7.82	7.77
29-H	7.84-7.96	5.08	5.73	7.02	7.96	7.81	8.05	8.21	8.29
22-H	7.98-8.08	5.43	6.03	7.19	8.36	8.32	8.59	8.65	8.74
23-H	7.98-8.08	5.43	6.03	7.19	8.36	8.32	8.59	8.65	8.74
[a] B3LYP/6-31G(d) ; [b] B3LYP/6-31G(d,p) ; [c] B3LYP/6-311G(d,p) ; [d] B3LYP/6-311+G(2d,p)									

CSGT method is becoming more successful as the basis set is getting bigger. Acceptable results for CSGT method can be obtained only at the B3LYP 6-311+G(2d,p) level of theory. For GIAO method, except some certain types of hydrogen, the best results generally obtained with 6-311G(d,p) basis set. For compound 3b (Table 4), 6-311+G(2d,p) basis set is more successful than 6-311G(d,p) basis set.

2.4 Molecular Electrostatic Potential Maps

MEP maps are important for the representation of the electron deficient and electron rich parts of the investigated molecule. MEP calculations have been performed at DFT B3LYP level of theory using the same basis sets. The results obtained from DFT B3LYP/6-311+G(2d,p) level of theory are given in Figures 5 and 6.

2.5 Frontier Molecular Orbitals

Frontier Molecular Orbital (FMO) calculations have also been performed at DFT B3LYP level of theory using various basis sets including 6-31G(d), 6-31G(d,p), 6-311G(d,p) and 6-311+G(2d,p) basis sets. Global reactivity descriptors of the investigated molecules have been determined at B3LYP/6-311+G(2d,p) level of theory and are given in Tables 7 and 8. In determination of electron affinity (A), ionization potential (I), electronegativity (χ), chemical softness (S), chemical hardness (η), electronic chemical potential (μ) and electrophilicity index (ω), Equations 1-7 were used. [15-20].

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

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

$$\chi = (I + A)/2 \quad (3)$$

$$\eta = (I - A)/2 \quad (4)$$

$$S = 1/2\eta \quad (5)$$

$$\mu = -(I + A)/2 \quad (6)$$

$$\omega = \mu^2/2\eta \quad (7)$$

Table 7. HOMO-LUMO energies and the global reactivity descriptors of compounds 1 and 2a-d.

	1	2a	2b	2c	2d
LUMO	-2.4542	-0.2324	-0.3932	-0.8558	-1.6028
HOMO	-7.3855	-6.5414	-7.7634	-6.4336	-6.9327
Gap	4.9313	6.3090	7.3702	5.5778	5.3299
I	7.3854	6.5413	7.7634	6.4336	6.9326
A	2.4542	0.2324	0.3932	0.8558	1.6028
χ	4.9198	3.3869	4.0783	3.6447	4.2677
η	2.4656	3.1545	3.6851	2.7889	2.6650
S	0.2028	0.1585	0.1357	0.1793	0.1876
μ	-4.9198	-3.3868	-4.0783	-3.6447	-4.2677
ω	4.9084	1.8182	2.2567	2.3816	3.4172

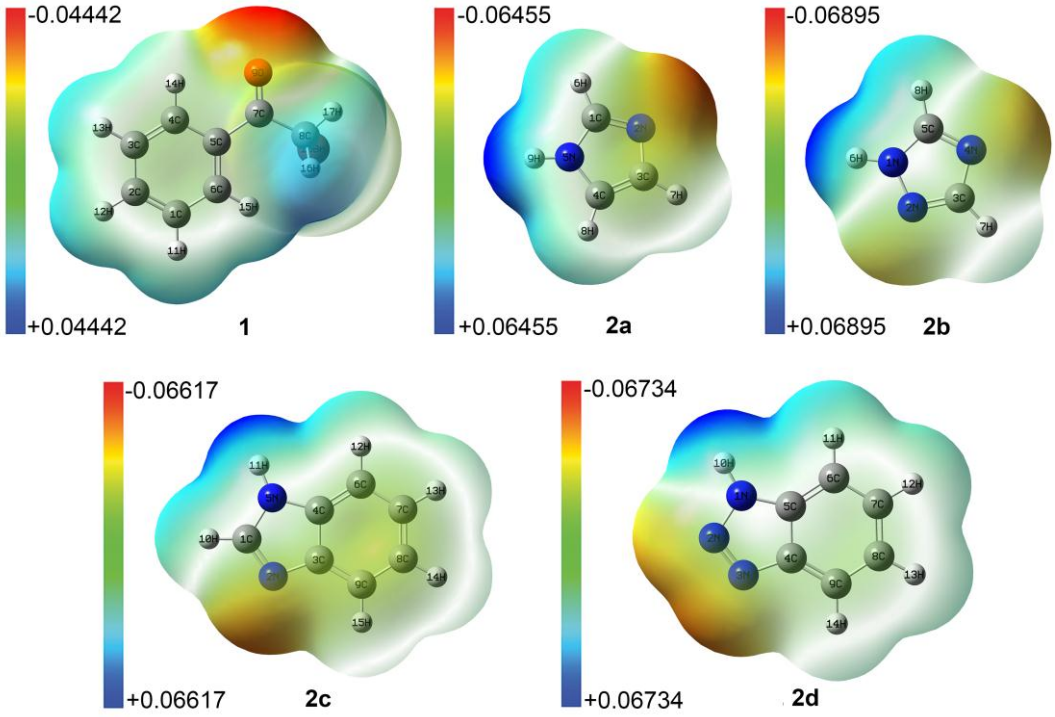

Figure 5. MEP maps of compounds 1 and 2a-d.

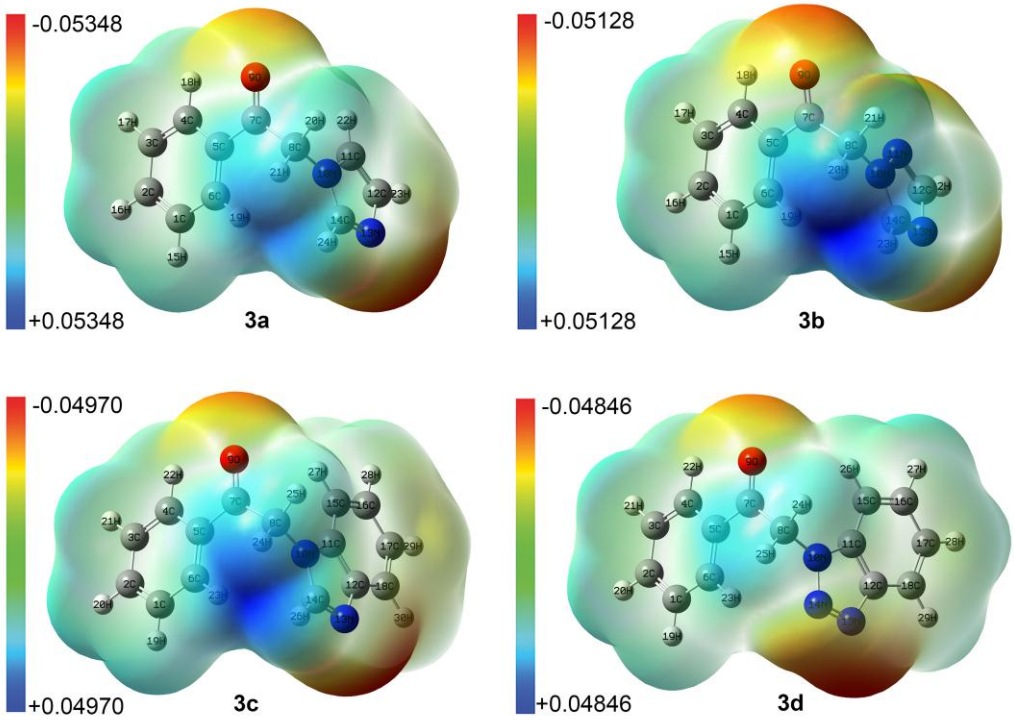

Figure 6. MEP maps of compounds 3a-d.

Table 8. HOMO-LUMO energies and the global reactivity descriptors of compounds 3a-d.

	3a	3b	3c	3d
LUMO	-2.3696	-2.2321	-2.3625	-2.3690
HOMO	-6.5802	-7.3865	-6.3868	-6.7588
Gap	4.2107	5.1544	4.0243	4.3897
I	6.5803	7.3865	6.3868	6.7588
A	2.3696	2.2322	2.3625	2.3692
χ	4.4749	4.8093	4.3746	4.5639
η	2.1053	2.5772	2.0121	2.1949
S	0.2375	0.1940	0.2485	0.2278
μ	-4.4749	-4.8093	-4.3746	-4.5639
ω	4.7557	4.4874	4.7555	4.7450

Highest occupied molecular orbitals (HOMO) and lowest unoccupied molecular orbitals (LUMO) of the investigated molecules are given in Figure 7. Interactions between the LUMO of 2-bromoacetophenone and the HOMO of the azole derivatives are represented in Figure 8. It was found that the interaction between the HOMO of the azole derivative and the LUMO of the 2-bromoacetophenone is important, as expected, since the azole derivative is the nucleophile and 2-bromoacetophenone is the substrate. It can be seen from Figure 8, the order of the HOMO-LUMO gap is as follows: $HOMO_{2c}$-$LUMO_1$ < $HOMO_{2a}$-$LUMO_1$ < $HOMO_{2d}$-$LUMO_1$ < $HOMO_{2b}$-$LUMO_1$.

3. Results and Discussion

In this study, the nucleophilic substitution reaction between 2-bromoacetophenone (1) and various azole rings (2a-d) have been investigated computationally. Geometry optimizations, SPE calculations, NMR spectral analysis, vibrational analysis, NMR spectral analysis, MEP calculations, frontier molecular orbital calculations and global reactivity descriptor determinations have been performed at DFT B3LYP level of theory using 6-31G(d), 6-31G(d,p), 6-311G(d,p) and 6-311+G(2d,p) basis sets.

In ^{1}H NMR calculations, both GIAO and CSGT methods have been used for the estimation of chemical shifts. As can be seen from Tables 3, 4, 5 and 6, generally, GIAO method is more successful than CSGT method. For CSGT method, it is necessary to use larger basis sets, acceptable results can only be obtained with the 6-311+G(2d,p) basis set. On the other hand, for GIAO method it has been observed that relatively small basis sets are more successful. Relatively larger basis sets with GIAO method generally overestimate the ^{1}H NMR chemicals shifts. For compound 3a (Table 3) the best results have been obtained with the 6-311G(d,p) basis set and GIAO method. For compound 3b (Table 4), the best basis set is 6-311+G(2d,p). For compound 3c (Table 5), 6-311G(d,p) is the most successful basis set and for compound 3d (Table 6), 6-31G(d,p) basis set is the best.

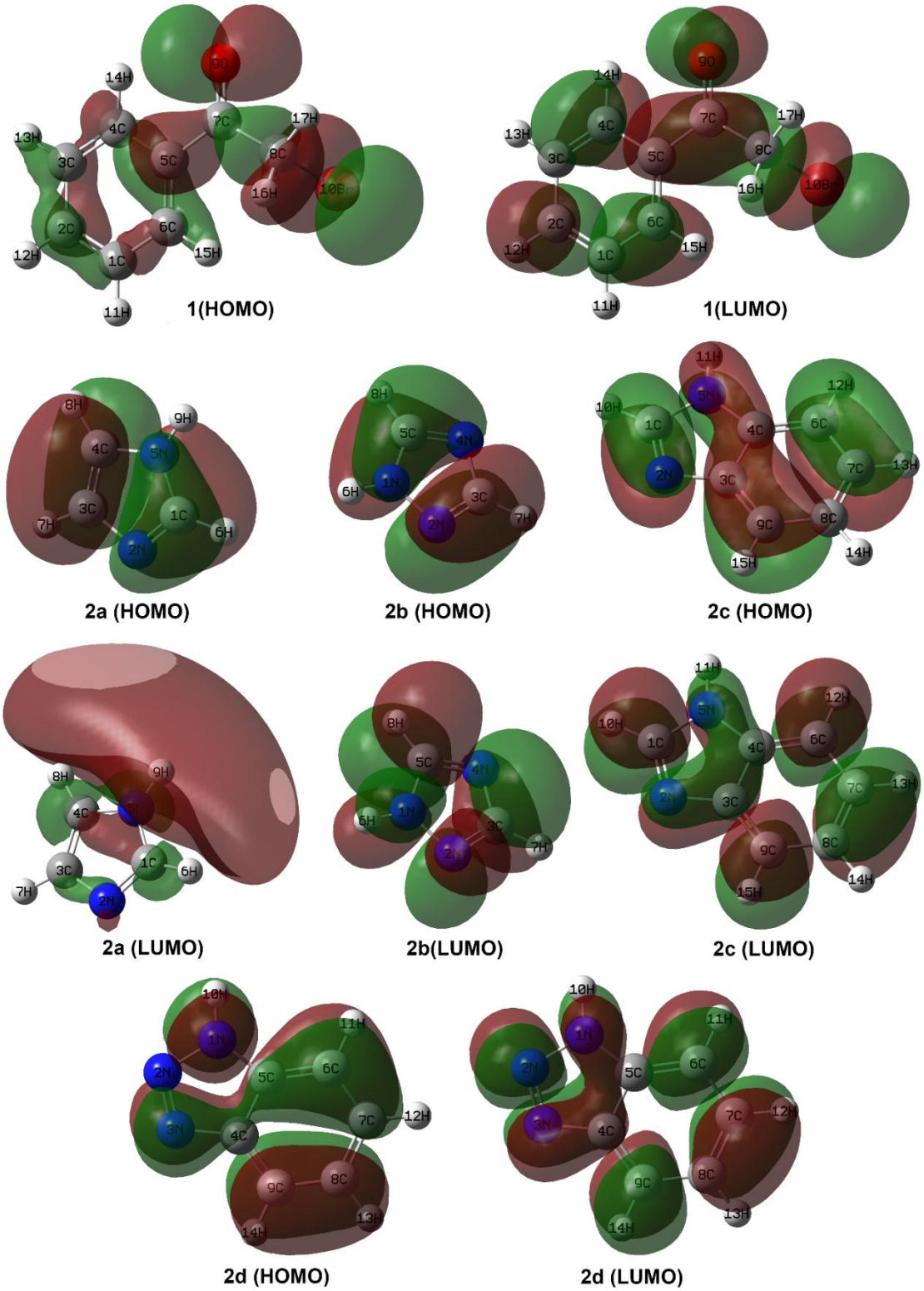

Figure 7. HOMO and LUMOs of the compounds (1 and 2a-d).

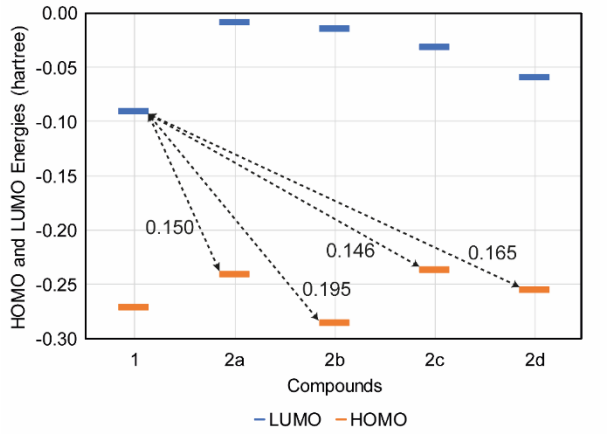

Figure 8. HOMO-LUMO interactions between the FMOs of the reactants.

HOMO-LUMO interactions between the reactants have also been investigated and represented in Figure 8. Because the azole derivatives are the electron donor reactants, the reaction take place via the interaction between HOMO of the azole derivative and the LUMO of the 2-bromoacetophenone. As we know that, the reaction can be readily take place if the energy gap between HOMO and LUMO is small. As shown in Figure 8, the smallest energy gap is for the $HOMO_{2c}$-$LUMO_1$ interaction, while the largest one is for the $HOMO_{2b}$-$LUMO_1$ interaction.

Since the energy gap between HOMO and LUMO is a useful quantity for examining the kinetic stability, it can be said that the stability order of the products is as follows: 3b > 3d > 3a > 3c.

4. Conclusion

In conclusion, in this study we have investigated the reaction between 2-bromoacetophenone (1) with various azole derivatives (2a-d). We have performed some DFT calculations at the B3LYP level of theory using various basis sets including 6-31G(d), 6-31G(d,p), 6-311G(d,p) and 6-311+G(2d,p). We have made comparisons between experimental and computationally obtained data. On the other hand, the results obtained from the calculations at different levels of theory has also been compared with each other.

Acknowledgements

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