JOURNAL OF SCIENCE
SAKARYA UNIVERSITY

Sakarya University Journal of Science

ISSN 1301-4048 | e-ISSN 2147-835X | Period Bimonthly | Founded: 1997 | Publisher Sakarya University | http://www.saujs.sakarya.edu.tr/

Title: Nucleophilic Substitution Reaction of Imidazole with Various 2-Bromo-1-arylethanone Derivatives: A Computational Study

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Recieved: 2018-04-25 00:00:00

Accepted: 2018-11-27 00:00:00

Article Type: Research Article
Volume: 23
Issue: 3
Month: June
Year: 2019
Pages: 322-332

How to cite
Taner Erdoğan, Fatma Oğuz Erdoğan; (2019), Nucleophilic Substitution Reaction of Imidazole with Various 2-Bromo-1-arylethanone Derivatives: A Computational Study. Sakarya University Journal of Science, 23(3), 322-332, DOI: 10.16984/saufenbilder.418343
Access link
http://www.saujs.sakarya.edu.tr/issue/41686/418343

Sakarya University Journal of Science 23(3), 322-332, 2019

Nucleophilic Substitution Reaction of Imidazole with Various 2-Bromo-1-arylethanone Derivatives: A Computational Study

Taner Erdogan*[1], Fatma Oguz Erdogan[1]

Abstract

In this study, it was intended to investigate the reactions between imidazole and 2-bromo-1-arylethanones such as 2-bromoacetophenone, 2-bromo-1-(4-chlorophenyl)ethan-1-one, 2-bromo-1-(2,4-dichlorophenyl)ethan-1-one and 2-bromo-1-(furan-2-yl)ethan-1-one, computationally. In the study, some Density Functional Theory (DFT) calculations have been performed on the chemical species involved in the investigated chemical reactions. DFT calculations have been performed at DFT B3LYP (Becke, three-parameter, Lee-Yang-Parr) level of theory using 6-31G(d), 6-31G(d,p), 6-311G(d,p) and 6-311+G(2d,p) basis sets. Single Point Energy (SPE) calculations, geometry optimizations, vibrational analysis, Frontier Molecular Orbital (FMO) calculations, global reactivity descriptor determinations, Molecular Electrostatic Potential (MEP) map calculations and estimation of the nuclear magnetic shielding tensors have been carried out at the same levels of theory. In ^{1}H-NMR calculations, CSGT (Continuous Set of Gauge Transformations) and GIAO (Gauge-Independent Atomic Orbital) models were used and experimental data have been compared with the computationally obtained data.

Keywords: imidazole, phenacyl bromide, computational chemistry, azoles, DFT

1. INTRODUCTION

Imidazole substituted structures are important compounds in organic and pharmaceutical chemistry. They can act as antibacterial, anticonvulsant, antifungal agents etc. and have been used commercially for many years. Econazole, miconazole, clotrimazole and oxiconazole are the important examples of commercially available pharmaceuticals bearing imidazole ring. (Figure 1) In this type of compounds, *gem*-phenyl-(1*H*-imidazol-1-ylmethyl) moiety (Figure 1) is thought to be responsible for the biological activity. [1]

In this study, we have investigated the reaction between imidazole (2) and various 2-bromo-1-arylethanone derivatives (1a-d) computationally. The extant literature contains reports on the reaction of imidazole with 2-bromoacetophenone, [2-20] 2-bromo-1-(4-chlorophenyl)ethan-1-one, [3-6, 8, 10, 14-16, 18-23] 2-bromo-1-(2,4-dichlorophenyl)ethan-1-one [5, 8, 14, 15, 18, 19, 21, 24-26] and 2-bromo-1-(furan-2-yl)ethan-1-one. [8, 27] We have carried out some DFT

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calculations on the reactants and products at B3LYP level of theory using 6-31G(d), 6-31G(d,p), 6-311G(d,p) and 6-311+G(2d,p) basis sets. We have compared the computationally obtained data with the experimental data.

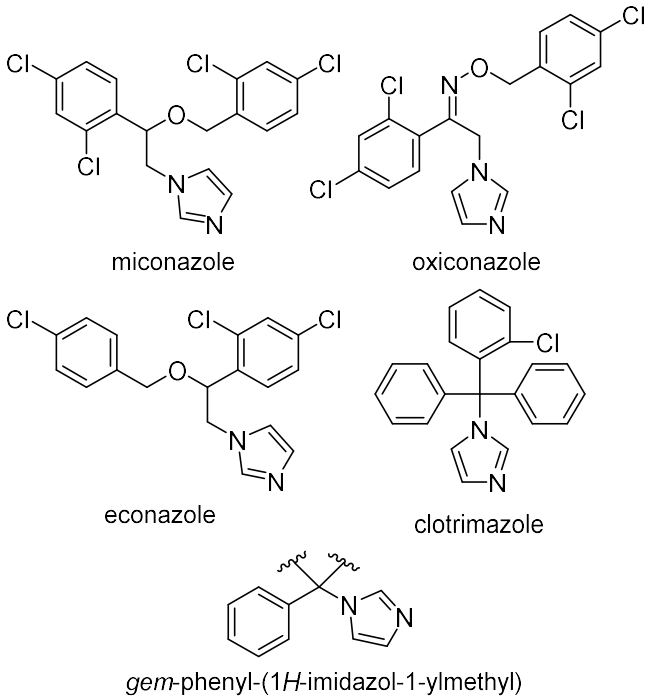

Figure 1. Some commercially available azole antifungals

All calculations have been carried out using Gaussian 09 Rev. D.01 Program Package [28], GaussView5 [29] and Avogadro 1.1.1. [30] Investigated reactions are given in Figure 2.

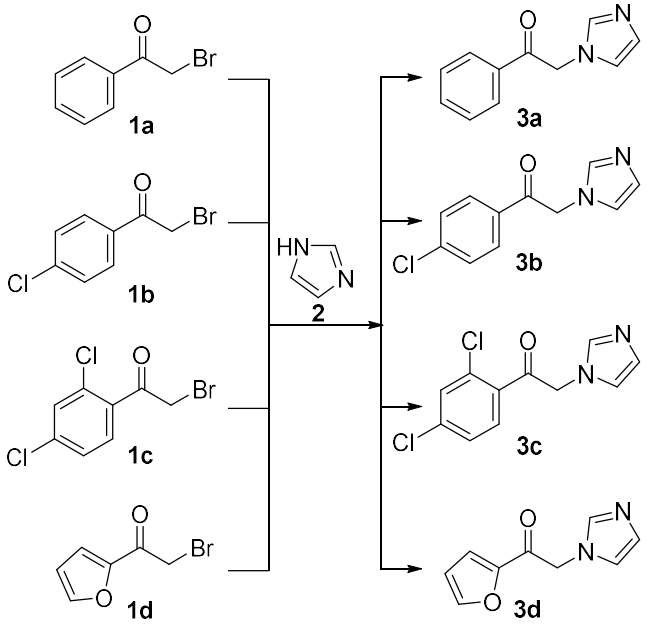

Figure 2. Investigated Reactions

2. THEORETICAL CALCULATIONS

2.1. Geometry Optimizations

Prior to geometry optimizations, a conformer search has been carried out and the most stable conformer was selected as the initial geometry. Optimizations and additionally a vibrational analysis have been carried out 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. Optimized structures of the reactants 1a-d are given in Figure 3. In Figure 4, optimized structures of the products are given.

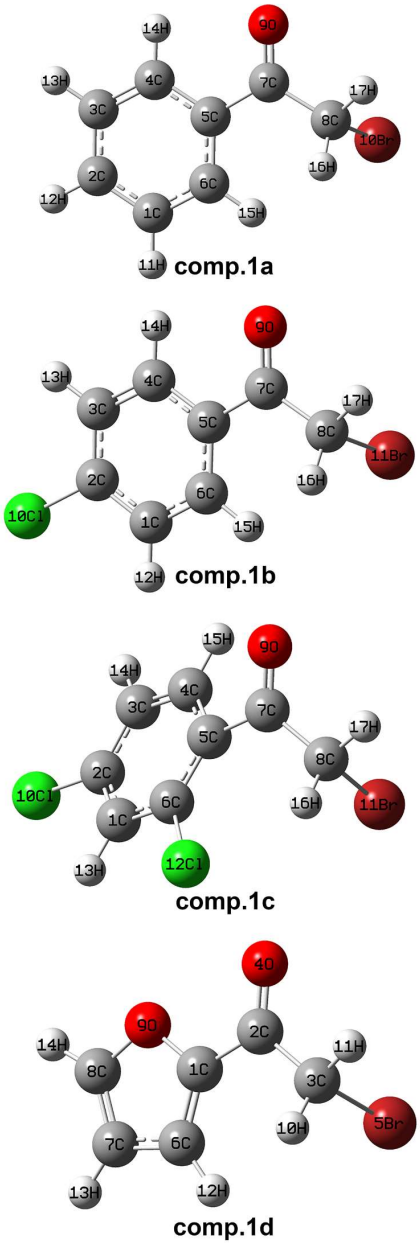

Figure 3. Optimized structures of the reactants (1a-d)

The optimized structures in Figures 3 and 4 have been obtained at B3LYP/6-311+G(2d,p) level of theory. Some selected geometric parameters for compound 3b are given in Table 1.

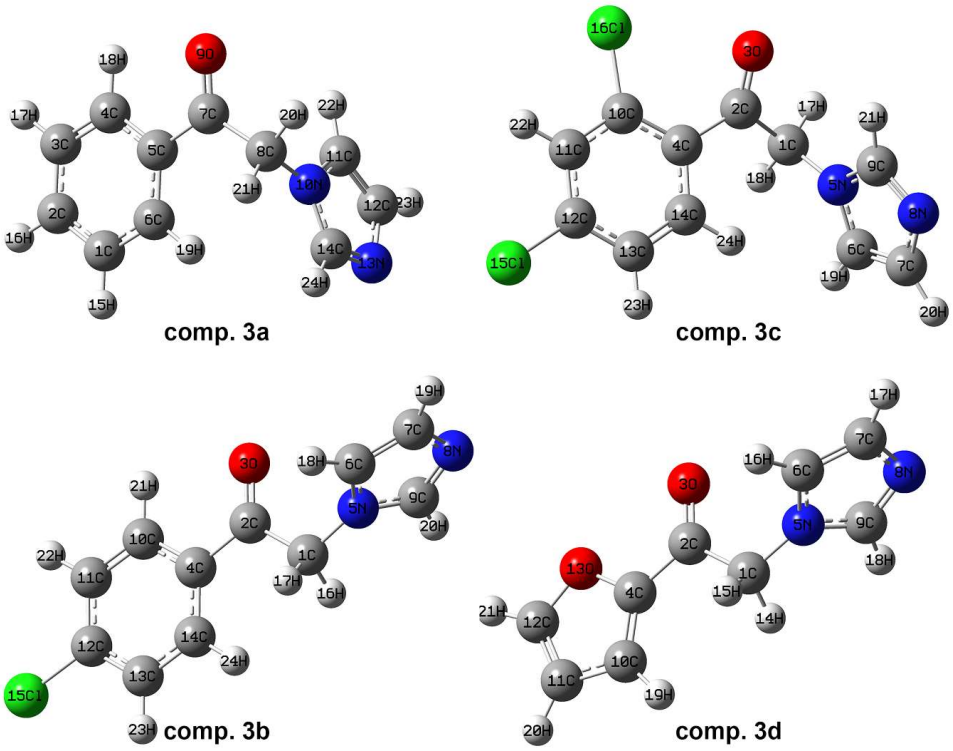

Figure 4. Optimized structures of the products (3a-d)

Table 1. Selected Geometric Parameters for Compound 3b

Atoms	Bond Lengths (Å)	Atoms	Bond Angles (°)	Atoms	Dihedral Angles (°)
1C-2C	1.539	2C-1C-5N	113.8	5N-1C-2C-3O	-0.8
1C-5N	1.440	1C-2C-3O	120.7	5N-1C-2C-4C	179.3
1C-16H	1.093	1C-2C-4C	117.7	2C-1C-5N-6C	77.7
2C-3O	1.210	3O-2C-4C	121.6	2C-1C-5N-9C	-100.4
2C-4C	1.495	2C-4C-10C	118.0	1C-2C-4C-10C	-179.8
4C-10C	1.400	2C-4C-14C	123.2	1C-2C-4C-14C	0.1
4C-14C	1.399	10C-4C-14C	118.8	3O-2C-4C-10C	0.3
5N-6C	1.379	1C-5N-6C	127.0	3O-2C-4C-14C	-179.8
5N-9C	1.367	1C-5N-9C	126.6	2C-4C-10C-11C	180.0
6C-7C	1.367	6C-5N-9C	106.4	14C-4C-10C-11C	0.0
7C-8N	1.375	5N-6C-7C	105.7	2C-4C-14C-13C	180.0
8N-9C	1.310	6C-7C-8N	110.4	10C-4C-14C-13C	-0.1
10C-11C	1.385	7C-8N-9C	105.3	1C-5N-6C-7C	-178.9
11C-12C	1.392	5N-9C-8N	112.1	9C-5N-6C-7C	-0.5
12C-13C	1.389	4C-10C-11C	120.9	1C-5N-9C-8N	179.0
12C-15Cl	1.750	10C-11C-12C	119.1	6C-5N-9C-8N	0.6
13C-14C	1.389	11C-12C-13C	121.2	5N-6C-7C-8N	0.2
		11C-12C-15Cl	119.4	6C-7C-8N-9C	0.1
		13C-12C-15Cl	119.4	7C-8N-9C-5N	-0.4
		12C-13C-14C	119.1	4C-10C-11C-12C	0.0
		4C-14C-13C	120.8	10C-11C-12C-13C	0.0
				10C-11C-12C-15Cl	180.0
				11C-12C-13C-14C	0.0
				15Cl-12C-13C-14C	180.0
				12C-13C-14C-4C	0.0

2.2. Single Point Energies (SPEs)

Single Point Energy calculations have been performed at B3LYP/6-31G(d), B3LYP/6-31G(d,p), B3LYP/6-311G(d,p) and B3LYP/6-311+G(2d,p) levels of theory. Computationally obtained values are given in Table 2. The results show that the bigger basis sets estimate lower SPE values for all compounds.

Table 2. Calculated single point energies for the investigated molecules

	opt1[a] (eV)	opt2[b] (eV)	opt3[c] (eV)	opt4[d] (eV)
1a	-80436.8	-80437.1	-80505.8	-80506.2
1b	-92943.0	-92943.3	-93012.8	-93013.2
1c	-105448.9	-105449.2	-105519.4	-105520.0
1d	-80376.2	-80376.4	-80445.3	-80445.7
2	-6155.6	-6155.9	-6155.9	-6157.3
3a	-16596.3	-16596.7	-16600.5	-16601.2
3b	-29102.5	-29102.9	-29107.4	-29108.2
3c	-41608.4	-41608.7	-41614.0	-41614.9
3d	-16535.8	-16536.1	-16540.0	-16540.8

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

2.3. Molecular Electrostatic Potential (MEP) Maps

For the determination of the electron rich and electron deficient parts of the investigated molecules, molecular electrostatic potential map calculations have been performed on the investigated molecules. The calculations have been carried out at B3LYP/6-31G(d), B3LYP/6-31G(d,p), B3LYP/6-311G(d,p) and B3LYP/6-311+G(2d,p) levels of theory. MEP maps for the investigated molecules, calculated at B3LYP/6-311+G(2d,p) level of theory, are given in Figures 5 and 6

2.4. Frontier Molecular Orbitals (FMOs) and Global Reactivity Descriptors

FMO calculations have also been carried out on the reactants and products at B3LYP/6-31G(d), B3LYP/6-31G(d,p), B3LYP/6-311G(d,p) and B3LYP/6-311+G(2d,p) levels of theory. Results for the reactants and products are given in Tables 3 and 4, respectively.

Table 3. Global reactivity descriptors for the reactants (1a-d and 2)

	1a	1b	1c	1d	2
LUMO	-2.454	-2.634	-2.560	-2.454	-0.232
HOMO	-7.385	-7.406	-7.442	-7.160	-6.541
Gap	4.931	4.773	4.862	4.706	6.309
I	7.385	7.406	7.442	7.160	6.541
A	2.454	2.634	2.580	2.454	0.232
χ	4.920	5.020	5.011	4.807	3.387
η	2.466	2.386	2.431	2.353	3.155
S	0.203	0.210	0.206	0.213	0.159
μ	-4.920	-5.020	-5.011	-4.807	-3.387
ω	4.908	5.280	5.164	4.910	1.818

Table 4. Global reactivity descriptors for products (3a-d)

	3a	3b	3c	3d
LUMO	-2.370	-2.532	-2.661	-2.304
HOMO	-6.580	-6.388	-6.746	-6.324
Gap	4.210	3.857	4.084	4.022
I	6.580	6.388	6.746	6.325
A	2.370	2.532	2.662	2.304
χ	4.475	4.460	4.704	4.315
η	2.105	1.928	2.042	2.010
S	0.238	0.259	0.245	0.249
μ	-4.475	-4.460	-4.704	-4.315
ω	4.756	5.157	5.417	4.630

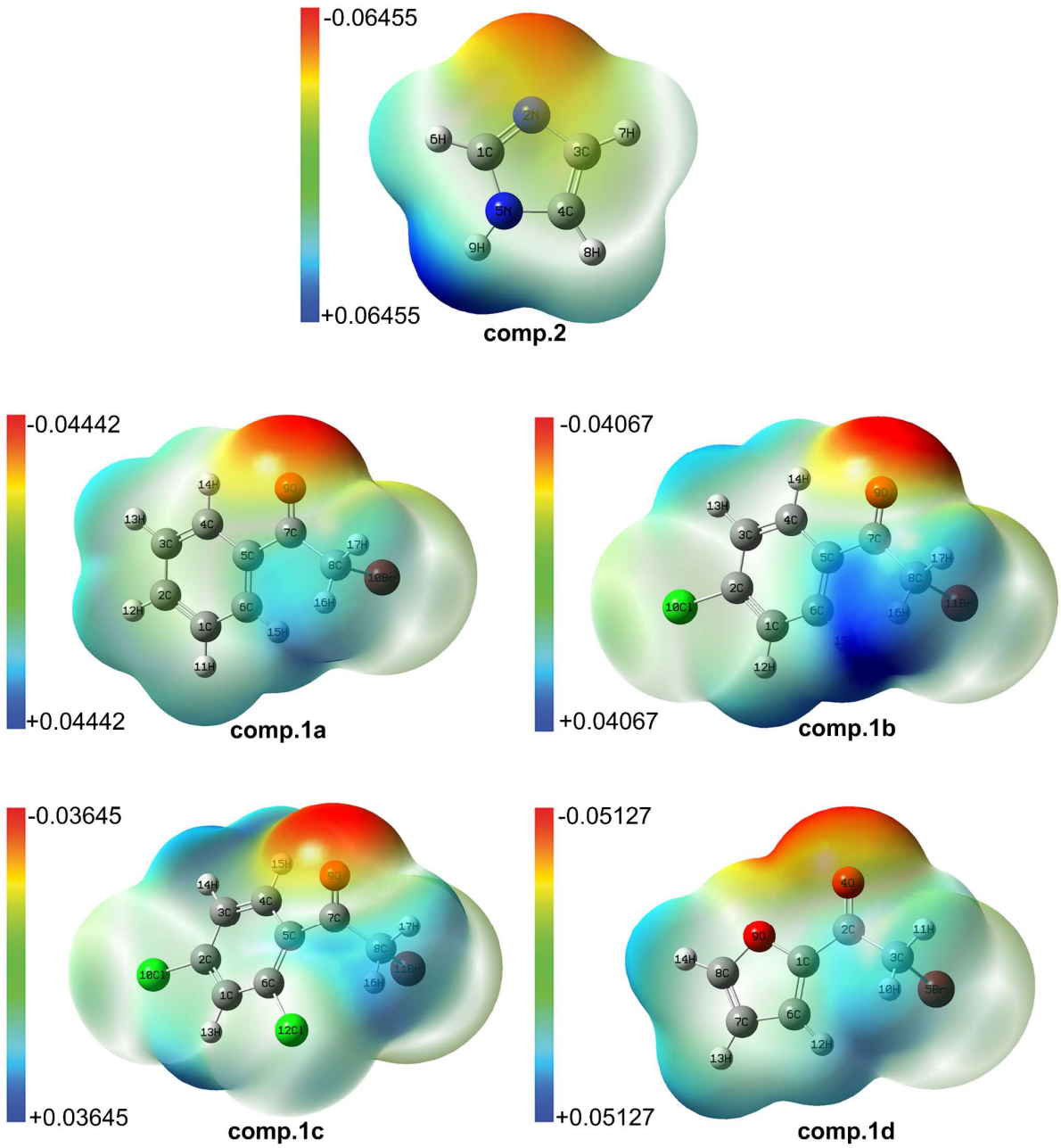

Figure 5. Molecular Electrostatic Potential Maps for the reactants (1a-d and 2)

Ionization potentials, electron affinities, electronegativities, chemical softness and chemical hardness values, electronic potentials and electrophilicity index have been calculated using Equations 1-7. [31-39]

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

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

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

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

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

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

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

As can be seen from Table 3, the electrophilicity order of the reactants is as follows: 1b>1c>1d>1a. Electrophilicity index value of the imidazole (2) is the smallest one as expected.

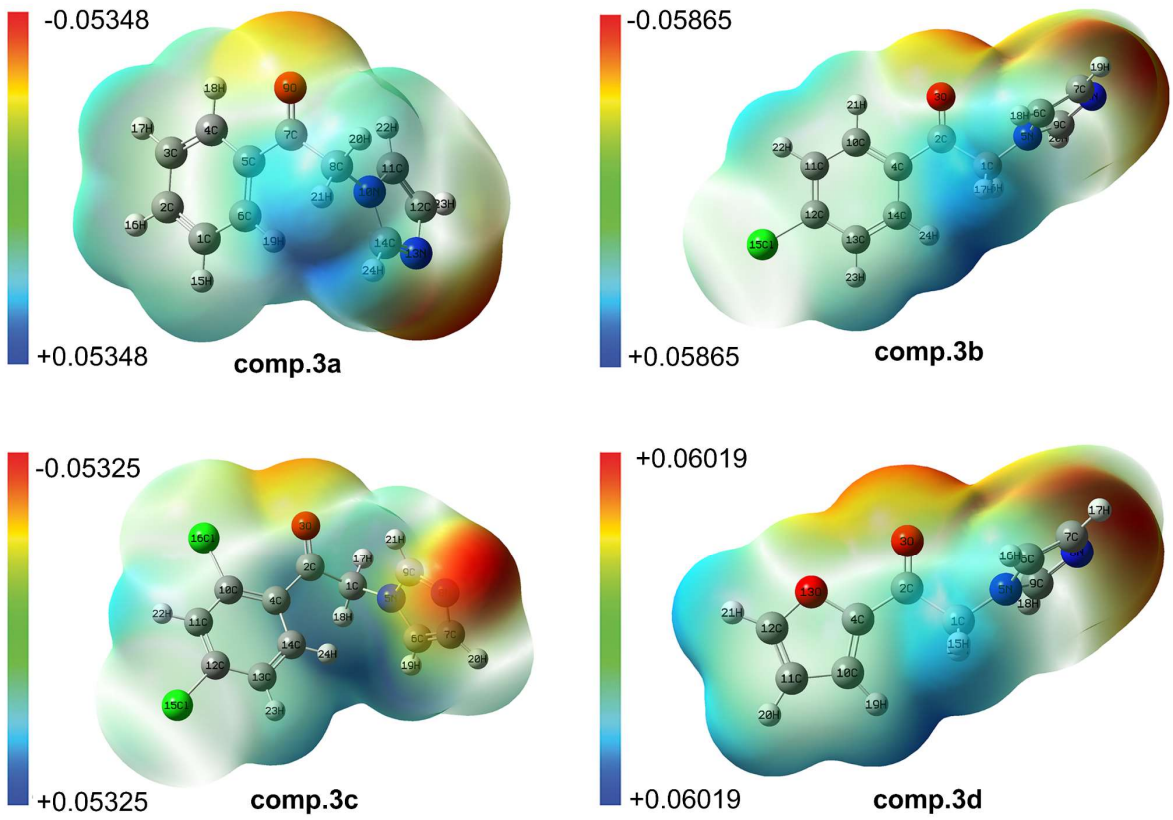

Figure 6. Molecular Electrostatic Potential Maps for the products (3a-d)

HOMO-LUMO gap values for the compounds 1a-d and 3a-d are given in Figures 7 and 8, respectively. It was observed that for compounds 1a-d, the HOMO-LUMO gaps are generally becoming smaller as the basis sets getting bigger. (Figure 7) It was also seen that this observation is not valid for compounds 3a-d. (Figure 8)

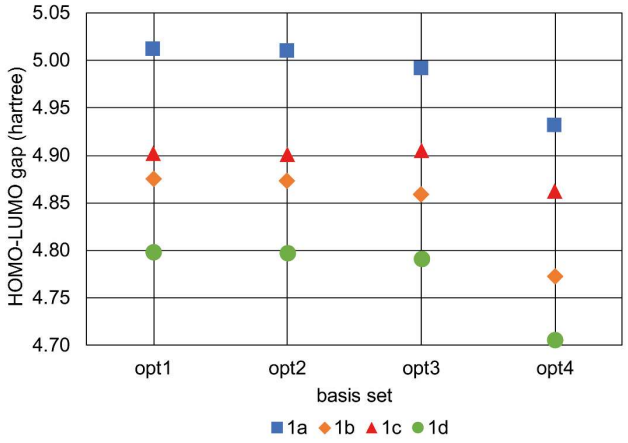

Figure 7. HOMO-LUMO gaps for reactants (1a-d)

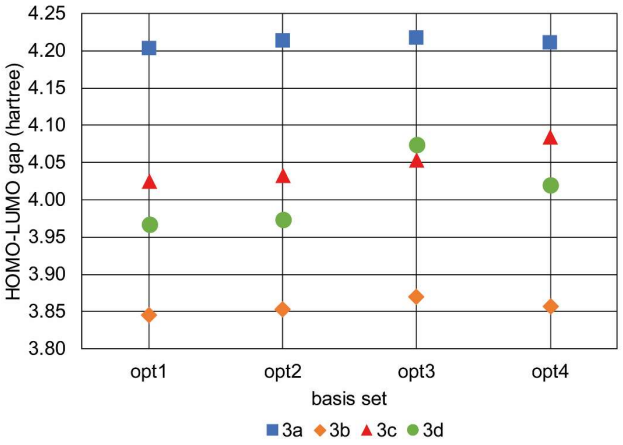

Figure 8. HOMO-LUMO gaps for products (3a-d)

The investigated reactions are take place through the $HOMO_2$-$LUMO_{1a-d}$ interactions. The energy differences between $HOMO_2$ and $LUMO_{1a-d}$ are represented in Figure 9. The order of the HOMO-LUMO gap values is as follows: $HOMO_2$-$LUMO_{1b}$<$HOMO_2$-$LUMO_{1c}$<$HOMO_2$-$LUMO_{1a}$=$HOMO_2$-$LUMO_{1d}$.

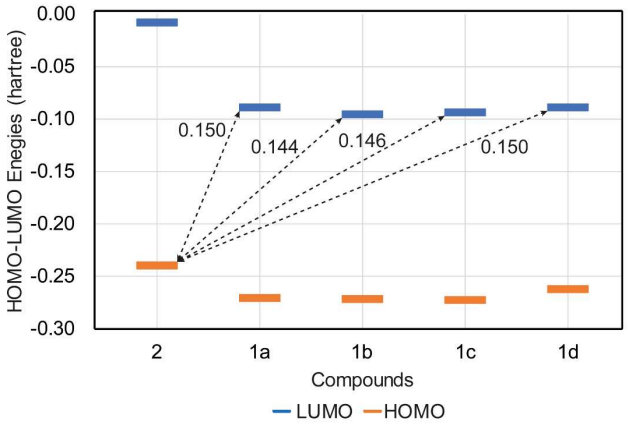

Figure 9. HOMO-LUMO interactions between the FMOs of the reactants.

HOMO and LUMOs of the reactants calculated at DFT B3LYP/6-311+G(2d,p) level of theory are given in Figure 10.

2.5. Nuclear Magnetic Shielding Tensors

These calculations have been performed at B3LYP/6-31G(d), B3LYP/6-31G(d,p), B3LYP/6-311G(d,p) and B3LYP/6-311+G(2d,p) levels of theory using both CSGT and GIAO methods. A comparison has also been performed between computationally obtained data and experimental data. Experimental data have been obtained from the literature. [8, 15]

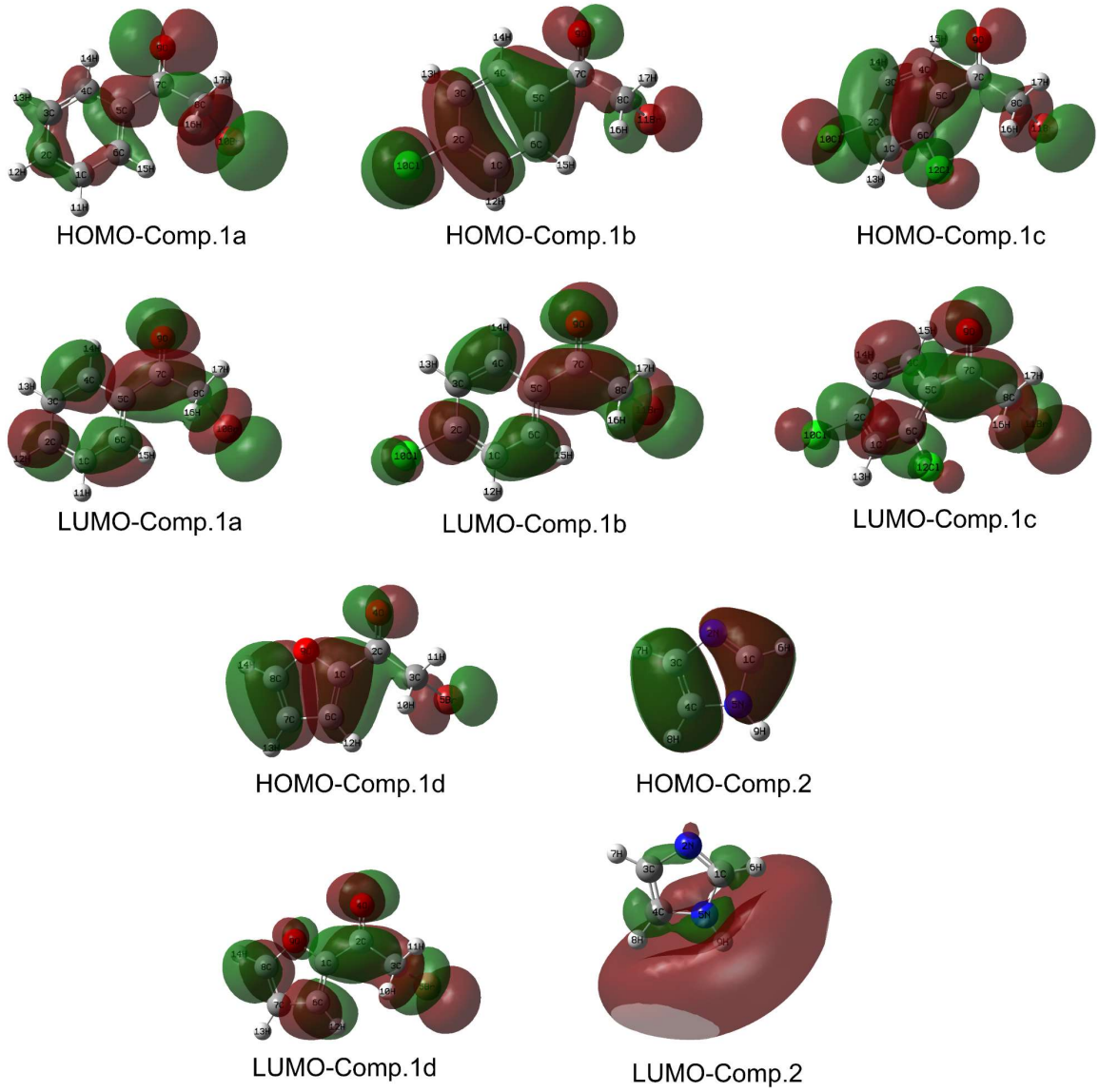

Figure 10. HOMO and LUMOs of the reactants 1a-d and 2.

Calculated ^{1}H NMR chemical shifts for the products (3a-d) are given in Tables 5, 6, 7 and 8. To emphasize the agreement between computational and experimental data, a color scale from green to red has been applied to Tables 5, 6, 7 and 8. Green colors represents the more successful results while red color represents the worse results. As can be seen from Tables 5, 6, 7 and 8, GIAO method is more successful than CSGT method.

Table 5. Experimental and computational ^{1}H NMR chemical shifts for compound 3a.

	EXP. [1]	CSGT1	CSGT2	CSGT3	CSGT4	GIAO1	GIAO2	GIAO3	GIAO4
20-H	6.04	2.47	2.93	3.64	4.78	4.66	4.76	4.87	5.06
21-H	6.04	2.47	2.93	3.64	4.78	4.66	4.76	4.87	5.06
22-H	7.55-7.68	3.74	4.52	5.87	6.65	6.57	6.88	6.85	6.87
23-H	7.55-7.68	3.84	4.57	5.89	6.88	6.79	7.07	7.12	7.20
15-H	7.55-7.68	4.75	5.30	6.44	7.31	7.26	7.45	7.54	7.61
17-H	7.55-7.68	4.75	5.30	6.44	7.31	7.26	7.45	7.54	7.61
24-H	8.98	3.70	4.62	6.26	7.30	7.04	7.35	7.44	7.62
16-H	7.69-7.78	4.83	5.37	6.49	7.45	7.35	7.53	7.63	7.74
18-H	8.05-8.15	5.13	5.69	6.87	7.97	7.95	8.20	8.25	8.37
19-H	8.05-8.15	5.13	5.69	6.87	7.97	7.95	8.20	8.25	8.37

Table 6. Experimental and computational ^{1}H NMR chemical shifts for compound 3b.

	EXP. [1]	CSGT1	CSGT2	CSGT3	CSGT4	GIAO1	GIAO2	GIAO3	GIAO4
16-H	5.37	2.61	3.03	3.78	5.06	4.84	4.96	5.02	5.35
17-H	5.37	2.61	3.03	3.78	5.06	4.84	4.96	5.02	5.35
18-H	6.93	3.52	4.31	5.60	6.60	6.41	6.73	6.71	6.86
20-H	7.13	3.46	4.32	6.04	6.98	6.76	7.05	7.16	7.31
19-H	7.47-7.58	3.88	4.61	5.91	7.03	6.87	7.14	7.25	7.35
22-H	7.47-7.58	3.90	4.58	5.84	7.24	7.17	7.39	7.51	7.70
23-H	7.47-7.58	3.90	4.58	5.84	7.24	7.17	7.39	7.51	7.70
21-H	7.9	4.65	5.29	6.47	7.85	7.80	8.05	8.08	8.28
24-H	7.9	4.65	5.29	6.47	7.85	7.80	8.05	8.08	8.28

Table 7. Experimental and computational ^{1}H NMR chemical shifts for compound 3c.

	EXP. [1]	CSGT1	CSGT2	CSGT3	CSGT4	GIAO1	GIAO2	GIAO3	GIAO4
17-H	6.02	2.12	2.58	3.33	4.52	4.51	4.60	4.62	4.80
18-H	6.02	2.12	2.58	3.33	4.52	4.51	4.60	4.62	4.80
19-H	7.68-7.77	3.19	4.08	5.53	6.73	6.33	6.68	6.76	6.94
23-H	7.68-7.77	3.46	4.14	5.34	6.78	6.79	7.00	7.07	7.32
20-H	7.68-7.77	3.82	4.58	5.91	7.08	6.89	7.18	7.29	7.43
21-H	7.86	3.97	4.83	6.40	7.34	7.27	7.55	7.54	7.75
24-H	8.12	4.30	5.00	6.11	7.27	7.41	7.69	7.61	7.76
22-H	9.19	3.11	3.90	5.27	7.11	7.03	7.28	7.37	7.78

Table 8. Experimental and computational ^{1}H NMR chemical shifts for compound 3d.

	EXP. [2]	CSGT1	CSGT2	CSGT3	CSGT4	GIAO1	GIAO2	GIAO3	GIAO4
14-H	5.25	2.37	2.80	3.70	4.85	4.55	4.68	4.83	5.07
15-H	5.25	2.37	2.80	3.70	4.85	4.55	4.68	4.83	5.07
20-H	6.63	3.49	4.21	5.25	6.36	6.22	6.53	6.57	6.67
16-H	6.97	3.97	4.74	5.72	6.65	6.88	7.18	6.77	6.90
19-H	7.13	3.63	4.41	5.58	6.96	6.72	7.04	7.07	7.21
18-H	7.29	3.41	4.28	6.03	6.96	6.73	7.03	7.13	7.26
17-H	7.55	3.88	4.61	5.92	7.02	6.84	7.12	7.22	7.32
21-H	7.67	4.30	5.17	6.54	7.50	7.45	7.72	7.69	7.83

Conclusions

In this study, substitution reactions between 2-bromo-1-arylethanones (1a-d) and imidazole (2) have been investigated computationally. All calculations have been performed at DFT B3LYP/6-31G(d), B3LYP/6-31G(d,p), B3LYP/6-311G(d,p) and B3LYP/6-311+G(2d,p) levels of theory.

In NMR calculations CSGT and GIAO methods were used. As can be seen from Tables 5, 6, 7 and 8, GIAO method is more successful than CSGT method for the estimation of chemical shifts. The performance of CSGT method is increasing with the use of bigger basis sets. For compound 3a (Table 5), the performance of 6-31G(d), 6-311G(d,p) and 6-311+G(2d,p) basis sets with GIAO method are similar and quite good. For compound 3b (Table 6) 6-311G(d,p) basis set with GIAO method is the best. For compound 3c (Table 7), 6-311+G(2d,p) basis set with GIAO method slightly better than the 6-311G(d,p) basis set. For compound 3d (Table 8), 6-311+G(2d,p) basis set is the best again. As can be seen from Tables 5, 6, 7 and 8, except some certain hydrogens, there is a good agreement between experimental and computationally obtained data. In our previous studies it was observed that CSGT methods with bigger basis sets also give satisfactory results. [40, 41]

HOMO-LUMO gaps for the reactants (1a-d) are given in Figure 7. It was observed that, bigger basis sets estimate lower energies for both HOMO and LUMOs. On the other hand, HOMO-LUMO energy gaps are becoming smaller as the basis sets getting bigger for compounds 1a-d. This correlation is not observed for the products 3a-d. With one exception the biggest HOMO-LUMO gaps have been obtained from the calculations at DFT B3LYP/6-311G(d,p) level of theory for products (3a-d). For compound 3c, the biggest HOMO-LUMO gap has been obtained with 6-311+G(2d,p) basis set.

In Figure 9, energy values for the interaction between HOMO of the imidazole and LUMO of the compounds 1a-d are given. As can be seen from Figure 9, the most effective interaction takes place between imidazole (2) and 2-bromo-1-(4-chlorophenyl)ethan-1-one (1c) and this is followed by 1b, 1a and 1d, respectively.

Acknowledgements

This work was supported by Kocaeli University Scientific Research Projects Unit. Project Numbers: 2011/062; 2017/38 HD. The author acknowledges Kocaeli University for the financial support.

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