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Density functional theory study of indole and highly substituted imidazole derivatives using isodesmic reactions

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Density functional theory studies have been performed on a series of highly substituted imidazole and indole derivatives. Heats of formation have been calculated using B3LYP functional with 6-31G basis sets by designing isodesmic reaction conditions. General trend which has been observed in the case of highly substituted imidazoles is that as substitution increases the heat of formation increases. The HOF of 1,2,4,5-tetraphenyl-1*H*-imidazole is the largest (131.28 kJ/mol) and the HOF of 2-(4-chlorophenyl)-1-benzyl-4,5-diphenyl-1*H*-imidazole (H) is the smallest (85.82 kJ/mol) at the B3LYP/6-31G level. The relative stability of the substituted imidazoles have been evaluated based on the calculated HOFs and the energy gap between the frontier molecular orbitals.

Keywords: Isodesmic reactions, imidazoles, indoles, heat of formation

Heterocyclic compounds containing nitrogen possess wide range of biological, industrial and high energy material applications[1-3]. Imidazoles are found to be better candidates for NLO active materials[4,5]. Imidazoles and their derivatives have profound application in OLED applications[6-8]. The imidazole ring is a constituent of several important natural products including purine, histamine, histidine and nucleic acids. Imidazole is an entity which explores different type of pharmacological and biological properties such as anti-bacterial, anti-fungal, anti-inflammatory, analgesic activities, anti-tubercular, anti-depressant, anti-viral and anti-cancer[9]. Furthermore, some of them have found application as florescent whitening agents. Different derivatives of imidazole were used as corrosion inhibitors on different metals[10]. In the field of explosive research, emphasis is given to high quality simple compounds with high energy, high density, heat resistance and low sensitivity. It is found that poly nitro imidazole derivatives which are quite insensitive, but with significant power and thus they can be used as high energetic materials[11]. Many compounds of industrial and technological importance contain imidazole derivatives. The thermodynamic parameter especially the enthalpies of formation have a crucial importance because they are needed to calculate the amount of energy involved in chemical reactions, to calculate other thermodynamic function to evaluate and interpret the stability of molecule. For stable compounds, calculation of heat formation is possible experimentally and is readily available in the literature. However, sometimes it is impractical or dangerous to measure HOFs experimentally, because certain energetic compounds are difficult to synthesize and some of them are highly unstable. Hence it would be useful to develop a reliable theoretical means to calculate the heat of formation of those demanding material.

Ab-initio methods have been selected to calculate the heat of formation for many years. However, these approaches need powerful calculation resources and can only be used for small to medium size molecule. Density functional theory (DFT) has emerged as a very reliable theoretical method to calculate geometries of molecules. Hence, it has been used to evaluate the heat of formation of interested molecule and the results indicate that DFT method is a reliable method. Now a days, the DFT methods, especially B3LYP hybrid DFT methods not only produces reliable geometries and energies but also requires less time and computer resources, have been widely employed and have become an important and economical tool to deal with complex electron correlation problems[12].

The indolic rings appear in a large number of compounds with biological and industrial importance.

The indole structure can be found in many organic compounds such as in the amino acid tryptophan and in a large number of alkaloids. Also they are found in drugs or drug candidates with interesting and promising therapeutic use[13]. Indole and its derivatives have occupied an inimitable place in the chemistry of nitrogen heterocyclic compounds. It has been found that several indole derivatives possess a wide range of biological activities. In industry they were used especially in dyes and have potential as corrosion inhibitors[14]. Auxins are one of the major classes of plant- produced hormone affecting plant growth including bud formation and root initiation. Indole-3-acetic acid (IAA) is the most common auxin found in plants. IAA and its analogues like indole-3- butyric acid (IBA) are used in the horticulture[15].

Imidazole is a five membered aromatic heterocyclic compound, having molecular formula $C_3N_2H_4$. The imidazole ring is a constituent of several important natural products including purine, histamine, histidine and nucleic acids. Imidazole is an entity which explores different type of pharmacological and biological properties such as anti-bacterial, anti-fungal, anti-inflammatory, analgesic activities, anti-tubercular, anti-depressant, anti-viral and anti-cancer activities[16].Furthermore, some of them have found application as florescent whitening agents. Different derivatives of imidazole were used as corrosion inhibitors on different metals[17]. In the field of explosive research, emphasis is given to high quality simple compounds with high energy, high density, heat resistance and low sensitivity. It is found that poly nitro imidazole derivatives which are quite insensitive, but with significant power and thus they can be used as high energetic materials[18]. Many compounds of industrial and technological importance contain imidazole derivatives.

In this work, HOFs of some indole and highly substituted imidazoles are calculated making use of isodesmic reaction conditions. Energies of frontier molecular orbitals and electrostatic potentials of the compounds are calculated and reported.

Computational methods

Isodesmic reactions were designed to determine HOFs. Computations were performed *via* the Gaussian 09 packages for computing thermochemical properties. The standard split valence basis set 6-31G(d) has been used[19].The heat of formation of a compound is an important thermodynamic quantity, there are two important approaches to determine HOF at 298 K - the atomization approach and isodesmic method. Atomization approach make use of heat of formation of atomic elements in calculating heats of formation, but there is no cancellation of bond energy across the work reaction, which leads to relatively large systematic bonding errors. However, the isodesmic reaction methods found to be very successful in determining HOF for molecular species. Isodesmic reaction is a kind of process where the number of each kind formal bond is preserved on both sides of the reaction[20-23]. This method leads to cancellation of systematic errors resulting from the bond environments, spin contamination, basis set super position and other non-random factors. The accuracy of heat of formation depends on the reliability of HOFs of the reference compounds and the choice of working chemical reaction used in the calculation.

For isodesmic reactions, the heat of reaction ΔH_{298} can be calculated through reaction enthalpies.

$$\Delta H_{298\,K} = \sum \Delta H_f^0{}_{\text{products}} - \sum \Delta H_f^0{}_{\text{reactants}}$$

where, $\sum \Delta H_f^0{}_{\text{products}}$ and $\sum \Delta H_f^0{}_{\text{reactants}}$ are the sums of the heat of formation of products and reactants in gas at 298 K, since HOF of reference compounds are available from experiment, the HOF of title compound can be obtained, if heat of reaction at 298 K are known.

$$\Delta H_{298\,K} = \Delta E_{298\,K} + \Delta(PV)$$

$$\Delta H_{298\,K} = \Delta E_e + \Delta\, ZPE + \Delta\, H_T + \Delta\, nRT$$

where, ΔE_e and ΔZPE are the electronic energy difference and the zero-point energy difference between products and reactants at 0 K respectively. ΔH is the changes in the thermal correction to enthalpies between reactant and product. $\Delta(PV)$ equals ΔnRT for reaction in gas phase. For isodesmic reaction $\Delta n = 0$[24].

For calculation of heat of formation, geometry optimization and frequency analysis were performed to obtain the structures and evaluate ZPE's and H_T at B3LYP level with 6-31G(d) and 6-31G(d,p) basis sets, which was shown to yield quite reliable geometries for this class of compounds.

Results and Discussion

Heat of Formation of Indole Derivatives

The isodesmic reactions were adopted for the prediction of HOFs and are depicted in Fig. 1. To further improve accuracy for ring containing molecule, it is also desirable to use an additional guide line of ring conservation[25]. On basis of such considerations, within constraints of availability of measured reference data for the best accuracy of HOF predicts, we select the following set of isodesmic reactions for the indole, 4-methyl 1-H indole, 4- chloro 1-H indole, 1 –H indol-4-ol, 1-H-indol -4-ylamine,4 Nitro 1-H indole.

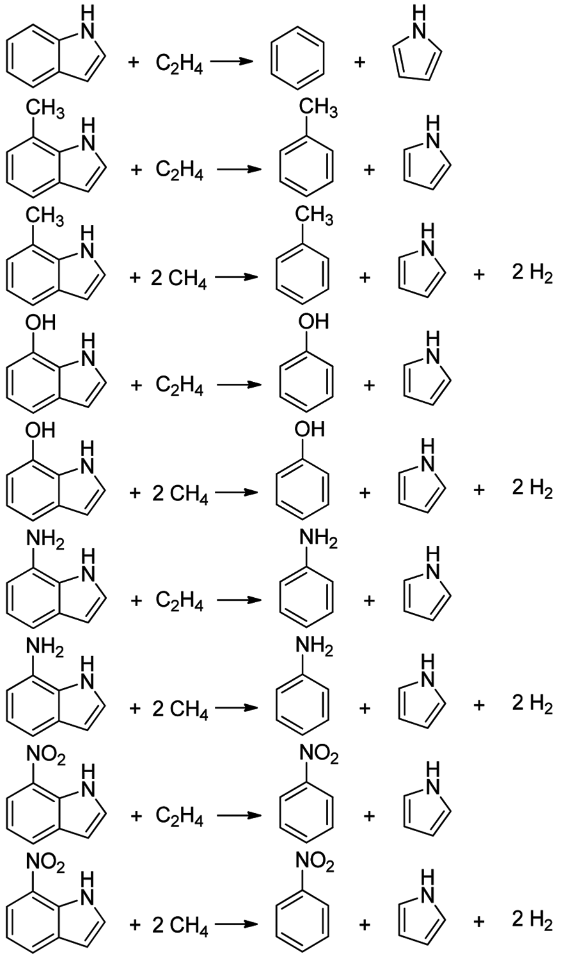


Fig. 1 — Isodesmic reaction scheme for various indole derivatives

Table 1 gives the experimental heats of formation for the reference species.

The calculated heat of formation values and working chemical reactions are included in Table 2. In order to reduce the errors from choice of reactions, more than one work reactions have been performed for the title compounds and calculated HOF from these work reactions have been averaged.

It can be seen that from Table 2 that, the predicted HOFs values based on various reactions are nearly same for each of the title compounds, with the difference of 3.38 kcal mol^{-1}, which further shows the reliability of the method. Based on these reactions and B3LYP/6-31G(d p) calculation level, the recommended average value for HOF are 37.2, 29.09,29.33, −5.55,32.57,33.4 kcal mol^{-1} for indole, 4-methyl 1-H indole, 4- chloro 1-H indole, 1 –H indol-4-ol, ,4 Nitro 1-H indole1-H-indol -4-ylamine, respectively.

Using the basis set B3LYP/6-31G (d,p) the obtained HOF values are 37.5, 29.5, 29.7, −5.1, 28.3, 33.43 kcal mol^{-1} for indole, 4-methyl 1-H indole, 4-chloro 1-H indole, 1 –H indol-4-ol, 4 Nitro 1-H indole,1-H-indol -4-ylamine, respectively. The results obtained by the two computational levels are found to be almost comparable.

Heat of Formation of highly substituted Imidazole derivatives

In order to calculate the heat of formation it is necessary to properly select the isodesmic reaction of the molecule under consideration. The isodesmic reactions (Fig. 2) are selected for various imidazole derivatives 1,2,4,5 tetraphenyl 1-H imidazole, 2-(4-chlorophenyl)- 1,4,5 triphenyl 1 H imidazole,1-methyl-2,4,5- triphenyl -1H imidazole, , 2-(4-

Table 1 — Experimental gas- phase standard heat of formation (ΔH_f^0 /kcal mol^{-1}) for reference species (EtBen: ethylbenzene, NitroBen: Nitrobenzene, ChloroBen: chlorobenzene)[23]

Compound	ΔH_f^0	Compound	ΔH_f^0
NH_3	-11.0	Imidazole	31.8±0.1
H_2	0	Benzene	19.8±0.1
CH_4	−17.9±0.1	Toluene	12.0±0.02
$CH_3CH_2NH_2$	−11.35	$CH_3CH_2CH_3$	−25.02±0.12
CH_3CH_3	−20.0±0.1	EtBen	7.10±0.20
CH_3NH_2	−19.3±0.3	C_2H_4	12.54±0.12
Pyrrole	25.86±0.12	ChloroBen	12.43
Phenol	−23.04	NitroBen	16.38±0.16
Aniline	20.8±0.2	CH_3NO_2	−19.3±0.3

Table 2 — Working chemical reactions and calculated heats of formation (ΔH_f^0) for indole and its derivatives

Compound	Reactions	ΔH_f^0 6-31G(d)	ΔH_f^0 6-31G(d,p)
Indole	IND + $C_2H_4 \longrightarrow$ Benzene + pyrrole	38.84	39.01
	IND + 2 $CH_4 \longrightarrow$ Benzene + pyrrole + 2 H_2	35.47	36.18
4–Methylindole	4 MeIND + $C_2H_4 \longrightarrow$ Toluene + pyrrole	30.78	30.9
	4 MeIND + 2 $CH_4 \longrightarrow$ Toluene + pyrrole + 2 H_2	27.4	28.1
4- Chloroindole	4 ChloroIND + $C_2H_4 \longrightarrow$ ChloroBen + pyrrole	31.02	31.17
	4 ChloroIND + 2 $CH_4 \longrightarrow$ ChloroBen+pyrrole+2H_2	27.64	28.34
4-Hydroxyindole	4 HydroxyIND + $C_2H_4 \longrightarrow$ Phenol + pyrrole	−3.86	−3.7
	4 HydroxyIND + 2 $CH_4 \longrightarrow$ Phenol + pyrrole + 2 H_2	−7.24	−6.53
4- Nitroindole	4 NitroIND + $C_2H_4 \longrightarrow$ NitroBen + pyrrole	34.26	31.74
	4 NitroIND + 2 $CH_4 \longrightarrow$ NitroBen+ pyrrole+ 2 H_2	30.88	24.82
4 – Aminoindole	4 AminoIND + $C_2H_4 \longrightarrow$ Aniline + pyrrole	35.09	35.12
	4 AminoIND + 2 $CH_4 \longrightarrow$ Aniline + pyrrole + 2 H_2	31.71	31.74

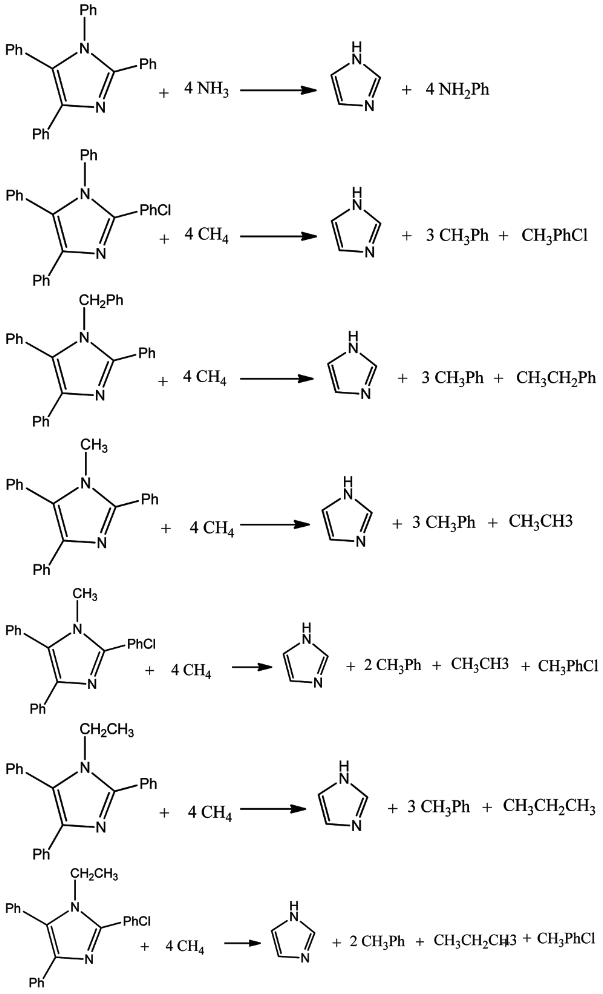


Fig. 2 — Isodesmic reaction scheme for various imidazole derivatives

chlorophenyl)- 1- methyl-4,5- diphenyl -1H imidazole, 1- ethyl-2,4,5- tri phenyl -1H imidazole, 2-(4-chlorophenyl)-1- ethyl-4,5- diphenyl -1H imidazole,1- benzyl-2,4,5- triphenyl -1H imidazole, 2-(4-chlorophenyl)- 1- benzyl-4,5- diphenyl -1H imidazole in order to calculate the heat of formation.

The calculated heat of formation values for imidazole derivatives are listed in the Table 3.

It is clear from the Table 3 that the calculated HOF of various phenyl substituted imidazole 1,2,4,5 tetra phenyl imidazole have the highest values of heat of formation. When one of the phenyl rings is substituted by chlorine atom on *para* position, the value of HOF decreases. A similar trend is observed when substituent on N-1 changes to methyl and ethyl group.

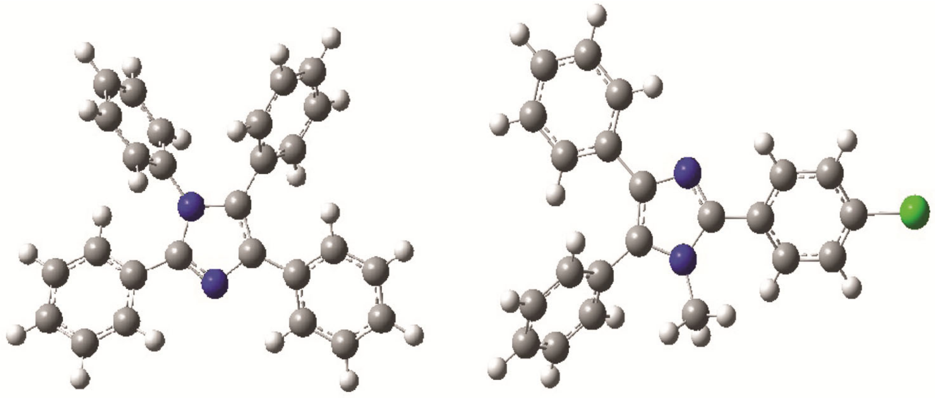
Energies of frontier molecular orbitals of highly substituted imidazoles

The optimised structure of highly substituted molecules is shown in Fig. 3. All the molecules are coplanar and deviation from coplanarity may be ascribed to the steric effect of bulkier group. HOMO-LUMO energy gap is used to evaluate the efficiency of chemical reaction process and also the ease of excitation of a molecule. If the energy gap is small, excitation is easier. Energies of molecular orbitals and the band gaps at B3LYP/6-31G levels are given in Table 4. It is observed that energy is maximum for 2-(4-chlorophenyl)- 1- benzyl-4,5- diphenyl-1*H*-imidazole and minimum for 1- benzyl-2,4,5- triphenyl -1*H*-imidazole. All the selected molecules showed lower energy gap than most of the imidazole based energetic molecules, which indicates that these molecules were easily excited than most of the imidazole based energetic molecules in chemical reaction process.

Sensitivity of molecules can be studied by calculating electrostatic potential and this will help in

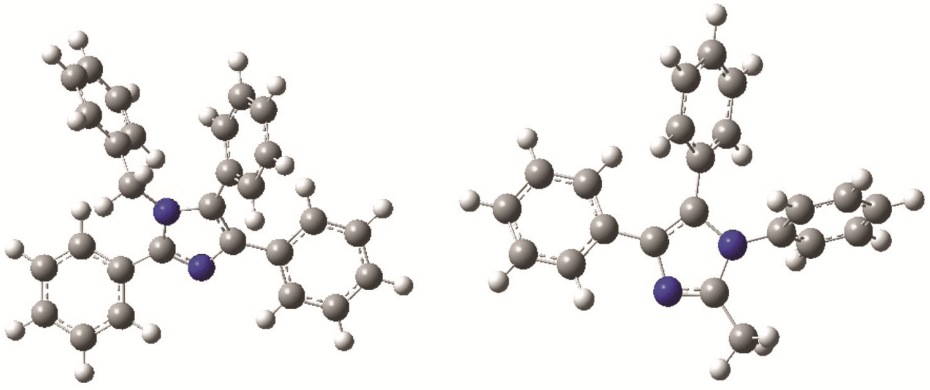
Table 3 — Calculated heat of formation values for imidazole derivatives

Compound	Reactions	HOF	
		B3LYP/6-31G(d)	B3LYP/6-311G(2d 2p)
1,2,4,5 tetraphenyl 1-H imidazole (A)	$A + 4\ CH_4 \longrightarrow IMI + 4\ CH_3Ph$	128.3	125.2
	$A + 4\ NH_3 \longrightarrow IMI + 4\ PhNH_2$	131.28	126.4
2-(4-chlorophenyl)- 1,4,5 triphenyl 1H imidazole (B)	$B + 4\ CH_4 \longrightarrow IMI + 3\ CH_3Ph + CH_3PhCl$	121.38	120.6
1- benzyl-2,4,5- triphenyl -1H imidazole, (C)	$C + 4\ CH_4 \longrightarrow IMI + 3\ CH_3Ph + CH_3CH_2Ph$	125.52	121.4
2-(4-chlorophenyl)- 1- benzyl-4,5- diphenyl -1H imidazole (D)	$D + 4CH_4 \longrightarrow IMI + 2CH_3Ph + CH_3CH_2Ph + p\text{-}Cl\ PhCH_3$	118.73	114.8
1- methyl-2,4,5- triphenyl -1H imidazole (E)	$E + 4\ CH_4 \longrightarrow IMI + CH_3\text{-}CH_3 + 3\ CH_3Ph$	97.46	96.32
2-(4-chlorophenyl)- 1- methyl-4,5- diphenyl -1H imidazole (F)	$F + 4\ CH_4 \longrightarrow IMI + CH_3\text{-}CH_3 + Cl\ PhCH_3 + 2\ CH_3Ph$	90.76	90.24
1- ethyl-2,4,5- tri phenyl -1H imidazole (G)	$G + 4\ CH_4 \longrightarrow IMI + 3\ CH_3Ph + CH_3CH_2CH_3$	91.78	88.62



1,2,4,5-tetraphenyl-1*H*-imidazole (A)

2-(4-chlorophenyl)-1-methyl-4,5-diphenyl-1*H*-imidazole (F)



1-benzyl-2,4,5-triphenyl-1*H*-imidazole (G)

1-methyl-2,4,5-triphenyl-1*H*-imidazole (E)

Fig. 3 — Optimized structure of selected compounds

predicting electrophilic and nucleophilic sites of molecules[27]. In order to identify the reactive sites in the molecule, MEP calculations were done at the B3LYP/6-31G level. Electrostatic potential of the designed molecules are shown in Fig. 4. Positive electrostatic potentials are marked in blue while negative electrostatic potentials in red. Positive electrostatic potentials of the selected molecules were concentrated mainly in the outer region and negative electrostatic potentials are concentrated on the central part of the rings. The maximum positive electrostatic potential is shown by 1- benzyl-2,4,5- triphenyl -1H imidazole 96.6 kcalmol^{-1} whereas minimum electrostatic potential of 55.4 kcalmol^{-1} is shown by

Table 4 — HOMO-LUMO energy of substituted imidazole molecules

Compound	HOMO (eV)	LUMO (eV)	ET (eV)
A	−0.2034	−0.0408	4.424
B	−0.1996	−0.0409	4.325
C	−0.1939	−0.03028	4.452
D	−0.2146	−0.0339	4.933
E	−0.1935	−0.0328	4.373
F	−0.1996	−0.0418	4.292
G	−0.2139	−0.0156	5.396

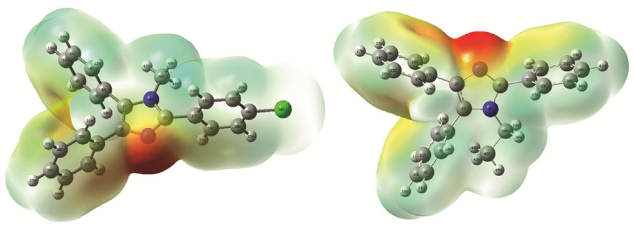

1-methyl-2,4,5-triphenyl-1*H*-imidazole 1-ethyl-2,4,5-triphenyl-1*H*-imidazole

Fig. 4 — Electrostatic potential of the designed molecules

2-(4-chlorophenyl)- 1- benzyl-4,5- diphenyl -1H imidazole kcalmol^{-1}. Sensitivity increases with increase in positive electrostatic potential. Presence of alkyl group decreases the electrostatic potential. 1,2,4,5-tetraphenyl 1-H imidazole molecule showed maximum positive potential indicating the higher sensitivity and 1-benzyl 2,4,5-triphenyl-1H imidazole showed minimum electrostatic potential.

Conclusions

The thermodynamic parameter, especially the enthalpies of formation have a crucial importance in many applications. In this work, density functional theory is used to study the heat of formation of indole and substituted imidazoles. The conclusions of the work are follows:

i. Standard heats of formation are determined using working chemical reactions at B3LYP/6-31G(d) level. First, using nitro aromatic compounds with experimentally well-established HOFs as test system. The performance of employed theoretical level and reactions for heat of formation was verified to be accurate. Then heat of formation were estimated to be 37.2, 29.09, 29.33, −5.55, 32.57, and 33.4 kcal mol^{-1} for indole, 4-methylindole, 4- chloroindole, 4-hydroxyindole,4-nitroindole,4-aminoindole respectively.

ii. The HOF studies are also conducted with a different basis set 6-31G (d, p) level. Using the basis set B3LYP/6-31G (d, p), the obtained HOF values are 37.5, 29.5, 29.7, −5.1, 28.3, and 33.43 kcal mol^{-1} for indole, 4-methyl 1-H indole, 4- chloro 1-H indole, 1 – H indol-4-ol, 4 Nitro 1-H indole,1-H-indol -4-ylamine, respectively. The results obtained by the two computational levels are found to be almost comparable.

iii. The heat of formation values is estimated for different phenyl substituted imidazole derivatives. It is found that 1,2,4,5 tetra phenyl imidazole have the highest value of heat of formation. When one of the phenyl rings is substituted by chlorine atom on *para* position the value of HOF decreases. A similar trend is observed when substituent on N-1 changes to methyl, ethyl and benzyl group.

iv. Energies of molecular orbitals were calculated to evaluate the efficiency of chemical reaction process and also the ease of excitation of molecules.

v. Molecular electrostatic potential of imidazole molecules is calculated to evaluate the sensitivity of the designed molecules.

References

1 Koch P, Bäuerlein C, Jank H & Laufer S, *J Med Chem*, 51 (2008) 5630.
2 Pandeya S N, *A Text Book of Medicinal Chemistry*, (SG Publisher) 2004, p 2.
3 Kerru N, Gummidi L, Maddila S, Gangu K K & Jonnalagadda S B, *Molecules*, 25 (2020) 1909.
4 Kannan V, Sreekumar K & Ullahannan R T, *J Mol Struc*, 1166 (2018) 31.
5 Ullahannan R T, Kannan V, Vidhya V & Sreekumar K, *J Mol Struc*, 1199 (2020) 127004.
6 Chen W C, Zhu Z L & Lee C S, *Adv Optical Mater*, 1800258 (2018) 1.
7 Kothavale S, Lee K H, Lee J Y, *Chem A Eur J*, 26(2020)845.
8 Zhu J J, Chen Y, Xiao Y H, Lian X, Yang G X, Tang S S, Ma D, Wang Y & Tong *Q X, J Mater Chem C,8 (2020)2975.*
9 Manocha P, Wakode S R, Kaur A, Anand K & Kumar H A, Int J Pharma Sci Res, 1 (2016) 12.
10 Jinchang W, Ambrish S, Mohd T, *Int J Electrochem Sci,* 13 (2018) 11539.
11 Su X, Cheng X & Ge S, *J Mol Struct*, 895 (2009) 44.
12 Muz I, Kurban M & Dalkilic M, *J Comp Ele*, 19 (2020) 895.
13 Kübra S, Gülbin K, Fatma S & Mustafa G, *J Compt*, 1201 (2021) 113275.
14 Li Y F, Fan X W, Wang Z Y & Ju X H, *J Mol Struc,* 896 (2009) 96.
15 Silva M A D, Cabral J I & Gomes J R, *J Phys Chem A*, 112 (2008) 12263.
16 Simon S & Petrasek P, *Plant Science*, 180 (2011) 454.
17 Jinchang W, Ambrish S & Mohd T, *Int J Electrochem Sci*, 13 (2018) 11539.
18 Li X, Zhang R & Zhang X, *J Haz Mat*, 183 (2010) 622-631.
19 Frisch M J, Trucks G W, Schlegel H B, Scuseria G E, Robb M A, Cheeseman J R, Scalmani G, Barone V, Mennucci B, Petersson G A, Nakatsuji H, Caricato V, Li X, Hratchian H P, Izmaylov A F, Bloino J, Zheng G, Sonnenberg J L,

Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery J A, Peralta J E, Ogliaro F, Bearpark, M, Heyd J J, Brothers E, Kudin K N, Staroverov V N, Keith T, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant J C, Iyengar S S, Tomasi J, Cossi M, Rega N, Millam J M, Klene M, Knox J E, Cross J B, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann R E, Yazyev O, Austin A J, Cammi R, Pomelli C, Ochterski J W, Martin R L, Morokuma K , Zakrzewski V G, Voth G A , Salvador J J , Dannenberg, P, Dapprich S, Daniels A D, Farkas O, Foresman J B, Ortiz J V, Cioslowski J & Fox D J, *Gaussian 09, Revision B.01*, (Gaussian, Inc., Wallingford CT) 2010.

20 Ju X H, Wang X & Bei F L, *J Comp Chem*, 26 (2005) 1263.

21 Ponomarev D A & Takhistove V V, *J Chem Educ*, 74 (1997) 201.

22 Lories X, Vandooren J, Peeters D, *J Comput Theor Chem*, 966 (2011) 244.

23 Pedley J B, Naylor R D & Kirby S P, *Thermochemistry of Organic Compounds*, 2nd ed., (Chapman and Hall, New York) 1986.

24 Su X, Cheng X & Ge S, *J Mol Struct*, 895 (2009) 44.

25 Sivaramakrishnan R, Tranter R S & Brezinsky K, *J Phys Chem A*, 109 (2005) 1621.

26 Luque F J, Lopez J M & Orozco M, *Theor Chem Acc*, 103 (2000) 343.