

DFT STUDIES ON THE MECHANISM OF BASE-CATALYZED HYDROCYANATION OF ALPHA, BETA-UNSATURATED KETONES

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Abstract

When creating new carbon-carbon bonds during the hydrocyanation of α , β -unsaturated ketones, catalytic Michael addition reactions are extremely effective tools. A simple method for converting α , β -unsaturated ketone to its hydrocyanic form involves using cyanohydrin acetone with a mild base and a phase transfer catalyst. This reaction stoichiometry produced a high-quality product with a high yield on the gram scale. Density functional theory (DFT) calculations have been used in a comprehensive theoretical investigation to elucidate the mechanism of base-catalyzed hydrocyanation reaction of enolisable α , β -unsaturated ketone. B3LYP-D3(BJ)/6-311+G**//B3LYP-D3(BJ)/6-311G** was used to study the genesis and reaction mechanism of asymmetric induction for conjugate addition of cyanide to the C=C bond of α , β -unsaturated ketone. Additionally taken into account are the relative stability of the investigated compounds as well as their atomic charges, electron densities, energetic characteristics, chemical thermodynamics, dipole moments, etc. The final charge transfer interaction within the investigated molecule is suggested by the narrow frontier orbital gap, which also demonstrated significant chemical reactivity. Lastly, to visualize the charge transfer between the localised bonds and lone pairs, natural bond orbital analysis is done. The current study's mechanistic insights should be helpful in the logical design of efficient catalysts with high selectivity and yield for this type of reaction.

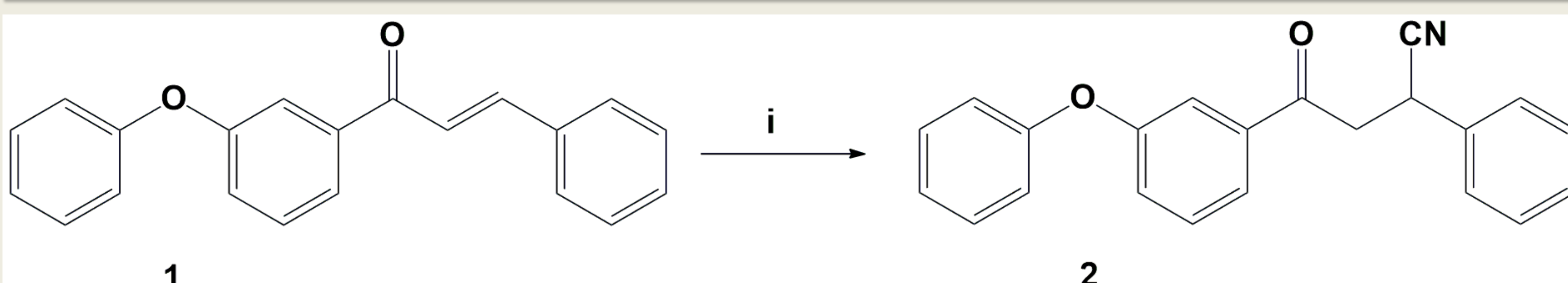
Keywords: DFT; Frontier orbital gap; Hydrocyanation; α , β -unsaturated ketones.

Introduction

Hydrocyanation of α , β -unsaturated ketone is a popular Michael addition reaction widely used to prepare several pharmacologically active compounds. Application of commonly used NaCN/KCN for the hydrocyanation of enone is not a facile synthetic route. Hence it is envisaged to use cyanohydrin acetone in place of NaCN/KCN in the presence of a mild base and phase transfer catalyst to improve the yield and for user-friendly synthesis. Currently, DFT simulations are most frequently used to calculate the gas-phase proton affinities of molecules, various spectroscopic characteristics of compounds, and molecular structural features. To understand the reactivity, experimental results and electrical characteristics of the enone and hydrocyanated product, the use of density functional theory (DFT) in the ground state was further investigated.

Experimentals

Synthesis of compound 2 was done by conventional method using AR/LR grade reagents. Progress of the reaction was monitored by TLC using hexane and ethyl acetate (8:2) as the mobile phase. Formation of the desired product was confirmed by m.p., UV, FTIR, 1H and 13C NMR and ESI MS. Computational study was carried out on an Intel Core i5-based system with Windows 10. Structure preparation was done using Chemdraw Ultra 19.0. The structures were 'cleaned' w.r.t. geometries, atom types, and charges were computed using ANTICHAMBER (Gasteiger method) in chimera. The DFT investigations were carried out using Gaussian 9.5 F.



Reagents and conditions: (i). Cyanohydrin acetone, $\text{Bu}_3(\text{Me})\text{N}+\text{OH}$, K_2CO_3 , Me_2CO , 14 h, 93%.

Fig. 1. Synthesis of 4-oxo-4-(3-phenoxyphenyl)-2-arylbutanenitrile (2)

Result and Discussion

Table 1. Reagents, reactions conditions and % yield of synthesis of compound 2

Compound 1	Cyanohydrin acetone	Potassium carbonate	Tributyl methyl ammonium hydroxide	Acetone + water	Temperature	Time	Yield
0.33 mM	0.33 mM	0.33 mM	0.165 mM	15:1 (16 mL)	57–58 °C	14h	93%

Table 2. Calculated Global Reactivity Descriptors by B3LYP/6-31++G (d, p) Basis Set at DFT Level of Theory

Compounds	HOMO	LUMO	HOMO-LUMO Gap KCal	Hardness (η)	Softness (S)	Electrophilicity Index	Nucleophilicity Index	Ionisation Potential	Chemical Potential
1	-6.09	-2.272	3.818	1.909	0.523	4.57	0.21	6.09	-4.181
2	-6.339	-2.024	4.315	2.157	0.463	4.05	0.24	6.339	-4.181

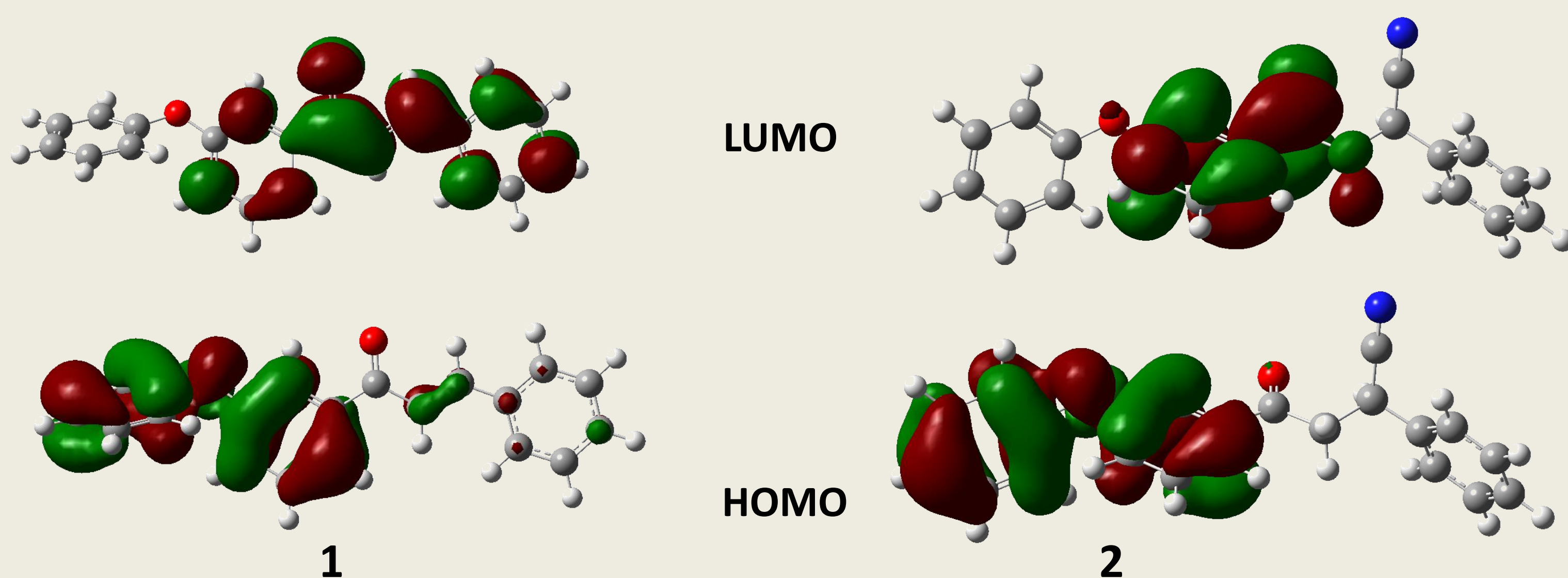


Fig 1. HOMO and LUMO orbitals of compounds 1 and 2. Green and Maroon colours: different phases.

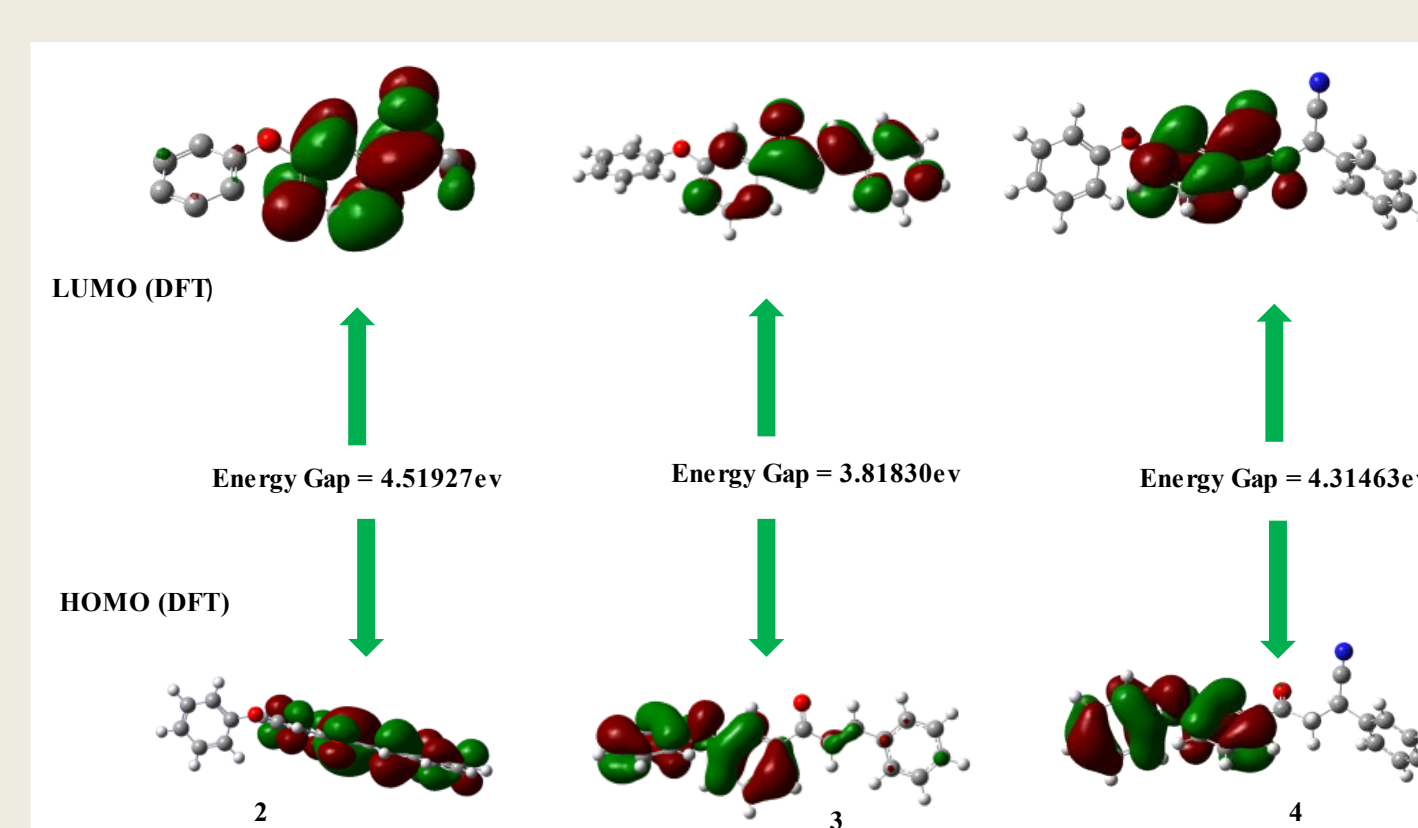
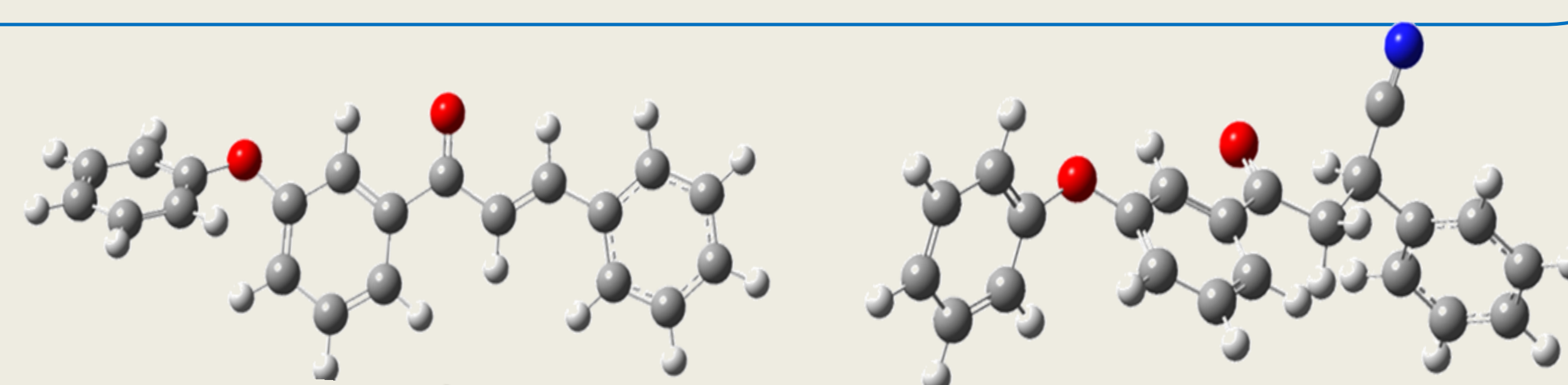


Fig 2. Important electronic transitions were obtained at the B3LYP/6-311++G (d, p) (isovalue:0.02) level of theory for chalcone derivatives.

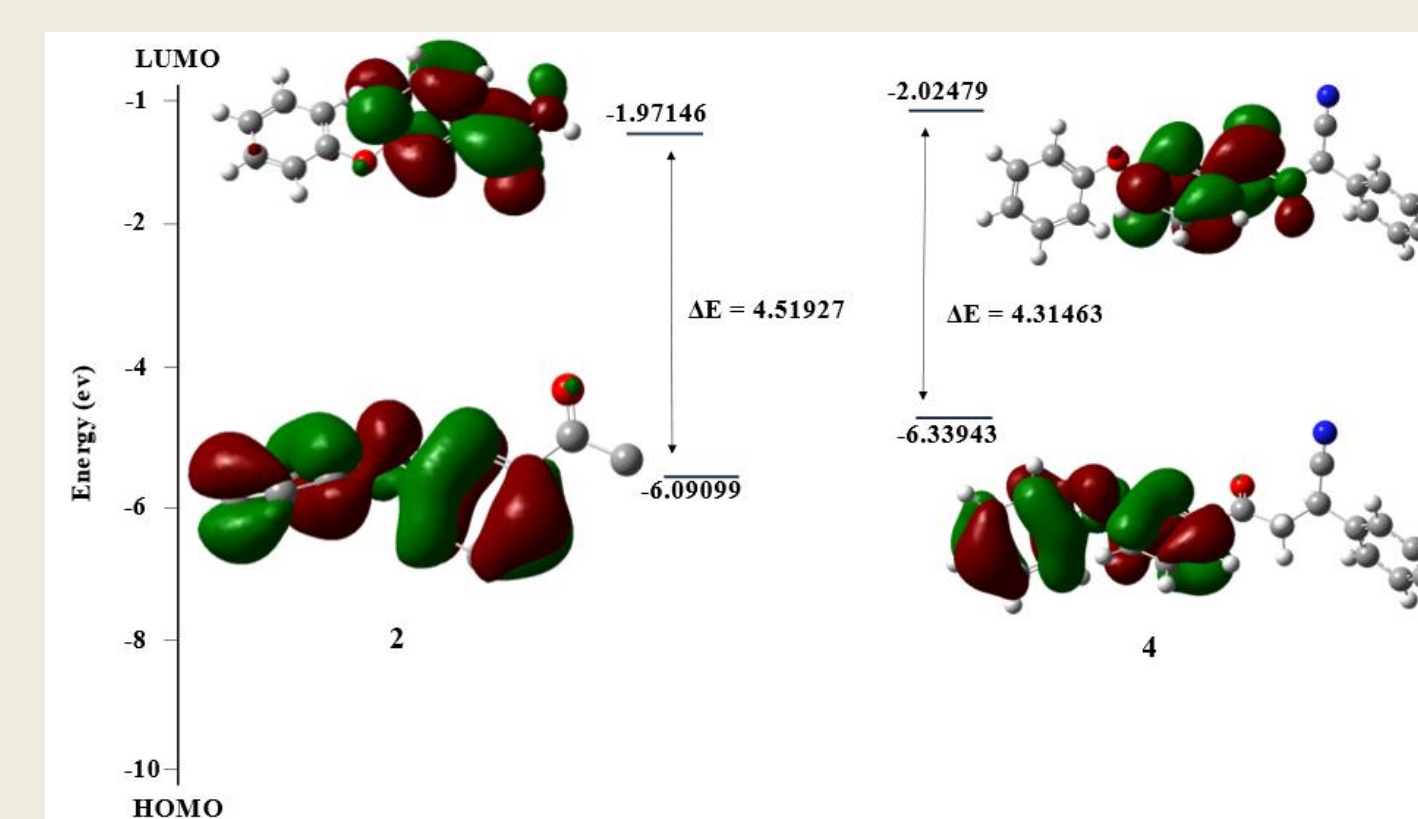


Fig 3. FMO orbitals (isovalue: 0.02 [e bohr⁻³]/2oftrans-DZ generated from TD/DFT calculation). Green and Maroon colors depict different phases.

Orbitals	1	2
HOMO	-6.09	-6.339
LUMO	-2.272	-2.024
[HOMO-LUMO]	3.818	4.315
HOMO -1	-6.408	-6.901
LUMO +1	-0.752	-0.499
[(HOMO-1) - (LUMO+1)]	5.656	6.402
HOMO -2	-6.741	-7.126
LUMO +2	-0.259	-0.379
[(HOMO-2) - (LUMO+2)]	6.482	6.747

Conclusion

In this study, we report DFT calculation of a new chalcone derivative, A computational study Using DFT techniques at the B3LYP/6-311+G (d,p) and DFT computational levels, the molecular mechanisms of the likely hydrocyanation reactions of (E)-1-(3-phenoxy phenyl)-3-phenylprop-2-en-1-one with acetone cyanohydrin to 4-oxo-4-(3-phenoxy phenyl)-2-phenylbutane nitrile were examined. The spontaneity of the reaction may be seen by analyzing the energy of HOMO and LUMO, as well as the energy gap value. The pace of reaction is determined by the species whose most electrophilic center corresponds to the hardness or softness value of the compound.

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