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 narrow frontier orbital gap suggests the final charge transfer interaction within the investigated molecule, which also demonstrated significant chemical reactivity. Lastly, to visualise 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:

Chalcones are carbonyl compounds with α -and β-unsaturation, and two phenyl rings linked to the carbonyl and -carbon, respectively. Synthetic methods for producing chalcones have been outlined in several reviews. They are the main constituents of natural products and are significant precursors for synthesis. As double bonds are present in conjugation with carbonyl groups, chalcones and their derivatives exhibit substantial biological actions that are crucial for drug creation. Chalcones can be easily produced using Claisen-Schmidt condensation, and chalcone compounds are extremely physiologically active chemicals. The α and β unsaturation is responsible for the pharmacological properties of chalcones with significant therapeutic applications, including electrochromic, fluorescence, dielectric, antimicrobial, anti-HIV, antibacterial, anti-inflammatory, anticancer, DNA-binding, and enzyme inhibition properties. They have been used as intermediates in numerous chemical reactions, including the synthesis of flavonoids and isoflavonoids, owing to their high solubilities. Chalcone derivatives are potent free-radical scavengers. In the most recent research publications, density functional theory (DFT), a computational technique to enhance the chemical and physical characteristics of synthesized substances, has been published and proven to be an important tool based on quantum mechanics. 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 enhance the experimental results and the electrical characteristics of the chalcone derivatives, the use of density functional theory (DFT) in the ground state was further investigated. [1]

Material and methods:

Materials:

The silica gel used for column chromatography has a mesh size of 100–200. The development of silica gel 60 F24 sheets with an aluminium backing was monitored using thin-layer chromatography (TLC; EMD Millipore). Melting points were measured using a melting point

instrument in a lab and recorded as uncorrected values. The 1 H NMR and 13C NMR spectra were recorded using an NMR spectrometer (AV400-400 MHz High-Resolution Multinuclear FT-NMR Spectrometer; Bruker India Scientific Pvt. Ltd., Bangalore, India) and dimethyl sulfoxide (DMSO)-d6 as the solvent. Gas chromatography-MS (Shimadzu GC-17A, GCMS-QP5050A; Shimadzu Analytical (India) Pvt. Ltd., Mumbai, India) and liquid chromatography-MS (Agilent 6520 series Q-TOF LC/MS; Agilent Technologies, Santa Clara, CA, USA) were used to collect the mass spectrometry (MS) data. Ultra-fast liquid chromatography (UFLC), reverse-phase high-performance liquid chromatography (HPLC), and Shimadzu) was used to evaluate the finished chemicals' purity, and it was discovered that they were 95% pure. Methanol and a pH 7.4 buffer were employed as the solvent systems.[2]

Synthesis of chalcone derivatives 1-(3-phenoxy-phenyl)- ethanone:

The following ingredients were successively added to the stirred mixture of 3-hydroxy acetophenone (3 g, 22.02 mmol) in anhydrous dichloromethane (120 mL): activated molecular sieves (4, 3 g), phenylboronic acid (4.02 g, 33.18 mmol), copper (II) acetate (7.98 g, 44.04 mmol), and anhydrous pyridine (3. At 25–27 °C, the resultant suspension was agitated. TLC was used to track the reaction's development while using hexane: ethyl acetate (9:1 v/v). Following the reaction's 72-hour conclusion, the reaction mixture was diluted with 100 mL of dichloromethane and filtered under reduced pressure. The filtrate was then dried over anhydrous MgSO4 and evaporated under reduced pressure after being washed with diluted hydrochloric acid (2 M, 75 mL) and water (75 mL). To acquire the target molecule, the crude chemical was purified using column chromatography on silica (100–200 mesh) using hexane: ethyl acetate (9:1) as the mobile phase.[2]

Yield =2.25 g (48%); Rf =0.95 (hexane: ethyl acetate = 9:1); λ_{max} =301 nm (MeOH); 1 H NMR (400 MHz, (DMSO)-d6) δ ppm: 7.77–7.72 (m, 1H), 7.55–7.51 (m, 1H), 7.47–7.46 (m, 1H), 7.43–7.39 (m, 2H), 7.28–7.26 (ddd, J=8.0, 2.8, and 0.8 Hz, 1H), 7.20–7.16 (m, 1H), 7.06–7.03 (m, 2H), 2.55 (s, 3H); calculated for C14H12O2 [M+]: 212.24, found GC–MS (EI, m/z): 212 (M)+ , 197 (M-CH_3) + , 169 (M-$COCH_3$) $^+$.[2]

General method for the synthesis of 3-(3-phenoxyphenyl)-1-aryl prop-2-en-1-one:

At 25–27 °C, aryl acetophenones (1 g, 4.711 mmol) in pure alcohol (25 mL) and KOH (0.527 g, 9.423 mmol) solutions were added to a solution of compound 2 (1 g, 4.711 mmol). At room temperature, the reaction mixture was then agitated. Hexane: Ethyl Acetate (8:2 v/v) was used in TLC to track the reaction's development. Following the reaction's 14-hour conclusion, the reaction mixture was emptied into 100 mL of ice-cold water, and the leftover material was extracted using 350 mL of ethyl acetate. After being dried over anhydrous MgSO4, the mixed organic layers were washed with water and brine and evaporated under reduced pressure. To extract the target molecule, the crude chemical was purified using column chromatography over silica (100–200 mesh) with hexane: ethyl acetate (8:2) mobile phase.[2]

1-(3-Phenoxyphenyl)-3-phenyl prop-2-en-1-one (3)

Yield =1.1 g (78%); MP =72°C–74°C; *Rf*=0.66 (hexane: ethyl acetate =8:2); λ_{max} =309.80 nm (MeOH); 1H NMR (400 MHz, (DMSO)-*d*6) δ ppm: 7.96–7.94 (dd, *J*=8.0 and 1.2 Hz, 2H), 7.83 (d, *J*=15.6 Hz, 1H), 7.77–7.72 (m, 3H), 7.65 (d, *J*=8.0 Hz, 2H), 7.48–7.45 (m, 2H), 7.37 (d, *J*=7.8 Hz, 1H), 7.32–7.25 (m, 1H), 7.23 (t, *J*=7.6 Hz, 1H), 7.16–7.14 (m, 2H), 7.12–7.08 (m, 1H); calculated for C21H16O2 [M+]: 300.35, found LC–MS (+ESI, *m*/*z*): 301.1069 $(M+H)^+$.[2]

General method for the synthesis of 4-oxo-4-(3-phenoxy phenyl)-2-aryl butane nitrile –

4-Oxo-4-(3-phenoxy phenyl)-2-phenyl-butane nitrile (4) –

Yield =0.32 g (84%); MP =62°C–64°C; *Rf*=0.47 (hexane: ethyl acetate =8:2); λ_{max} =224.4 nm (MeOH); 1H NMR (400 MHz, (DMSO)-*d*6) δ ppm: 8.02–7.98 (td, *J*=9.2, 2.2, and 2.4 Hz, 2H), 7.61–7.57 (td, *J*=9.2, 2.2, and 2.4 Hz, 2H), 7.42–7.36 (m, 3H), 7.28 (d, *J*=7.6 Hz, 1H), 7.16 (t, *J*=1.0 Hz, 1H), 7.17–7.12 (m, 2H), 7.02–6.94 (m, 2H), 6.92–6.91 (dd, *J*=2.4 and 1.2 Hz, 1H), 4.62–4.59 (dd, *J*=8.8 and 5.2 Hz, 1H), 4.01–3.95 (dd, *J*=18.4 and 8.8 Hz, 1H), 3.74–3.68 (dd, *J*=18.4 and 4.8 Hz, 1H); calculated for C22H17NO2 [M+]: 327.38, found LC–MS (+ESI, *m*/*z*): 328.1341 (M)+.[2]

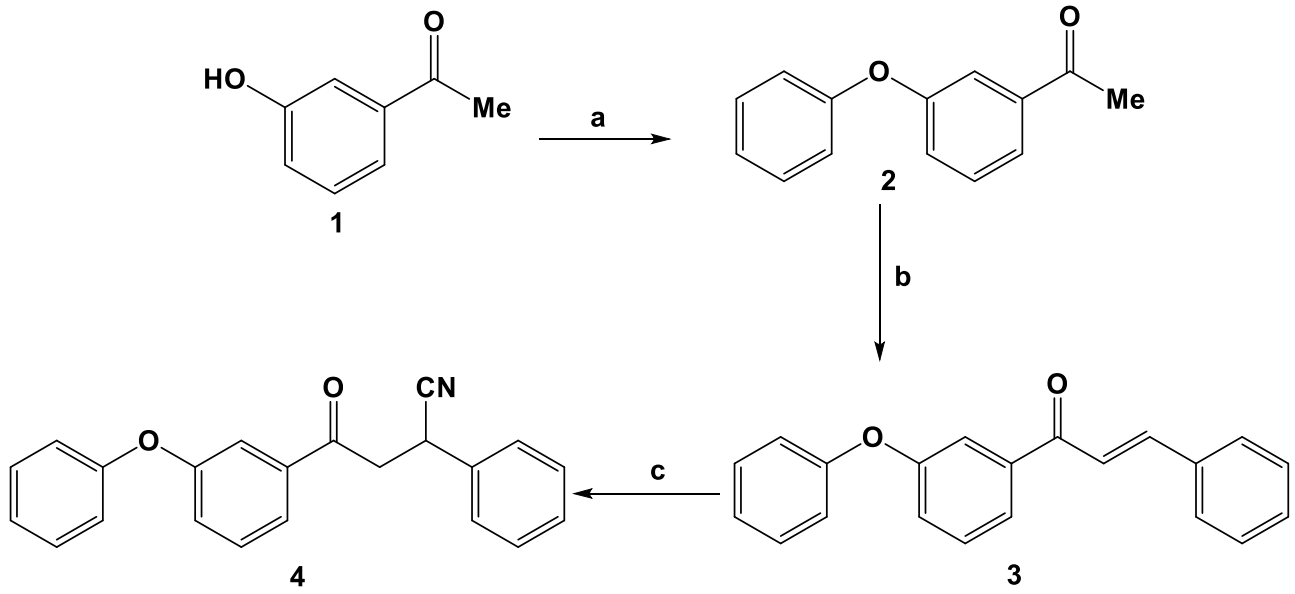

Fig 1. The general synthetic route for compound 4.

Notes: Reagents and Conditions: (a) $PhB(OH)_2$, $Cu(OAc)_2$, C_5H_5N, CH_2Cl_2, 25Â°C–27Â°C, 72 hours, 48%;
(b) ArCHO, KOH, EtOH, 25Â°C–27Â°C, 24 hours, 67%–78%;
(c) cyanohydrin acetone, $Bu_3(Me)N^+OH^-$, K_2CO_3, Me_2CO, H_2O, 55Â°C–27Â°C, 14 hours, 80%–93%

Methods of calculation –

Computational details:

Density Functional Theory (DFT) calculations –

For this work, a DFT suite called Gaussian 09W is utilized. Conjugation using the DFT approach was done using the fundamental set. Density functional theory employing the 6-311++G (d, p) basis set and the B3LYP (Becke-3-Lee-Yang-Parr) functional. To analyze such molecular properties in a crystalline environment, we therefore choose the 6-311 ++ G (d, p) basis set as a trade-off between cost and precision. The MMFF molecular mechanism is used by the free software Avogadro. To undertake conformational characterization of the synthesized molecule, the

field was used. The theory called for the B3LYP/6-311++G (d, p) conformer to perform the lowest energy conformer. [3]

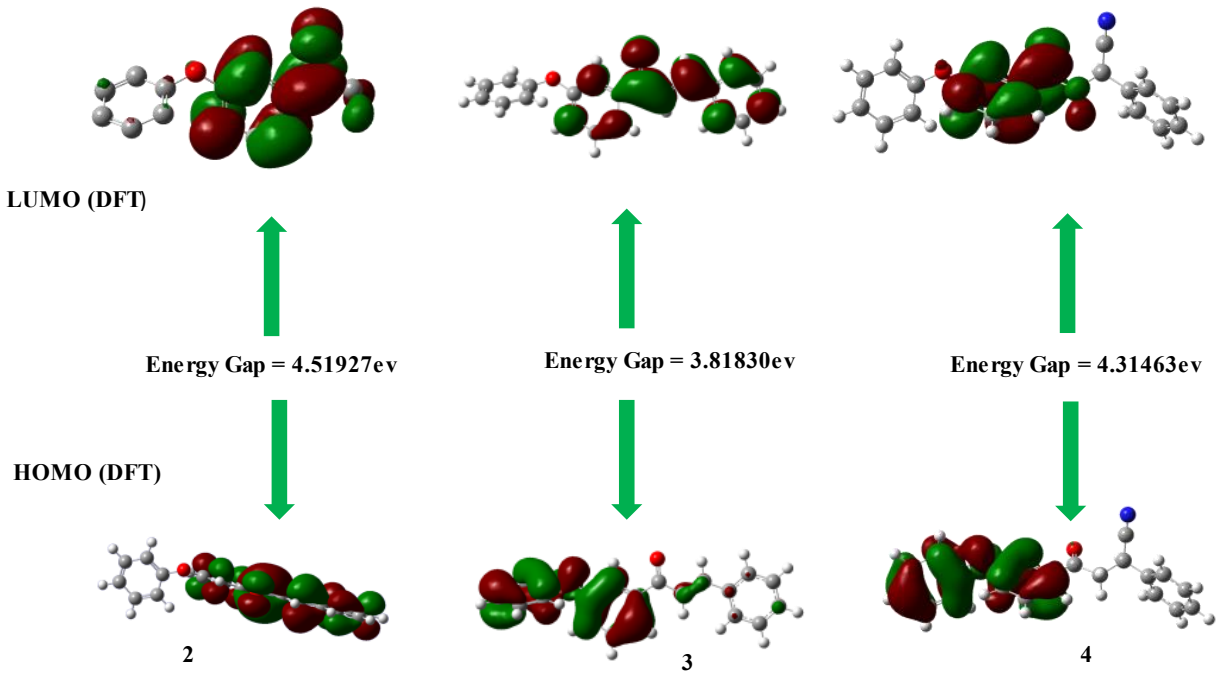

Fig 3. Important electronic transitions were obtained at the B3LYP/6-311++G (d, p) (isovalue:0.02) level of theory for chalcone derivatives.

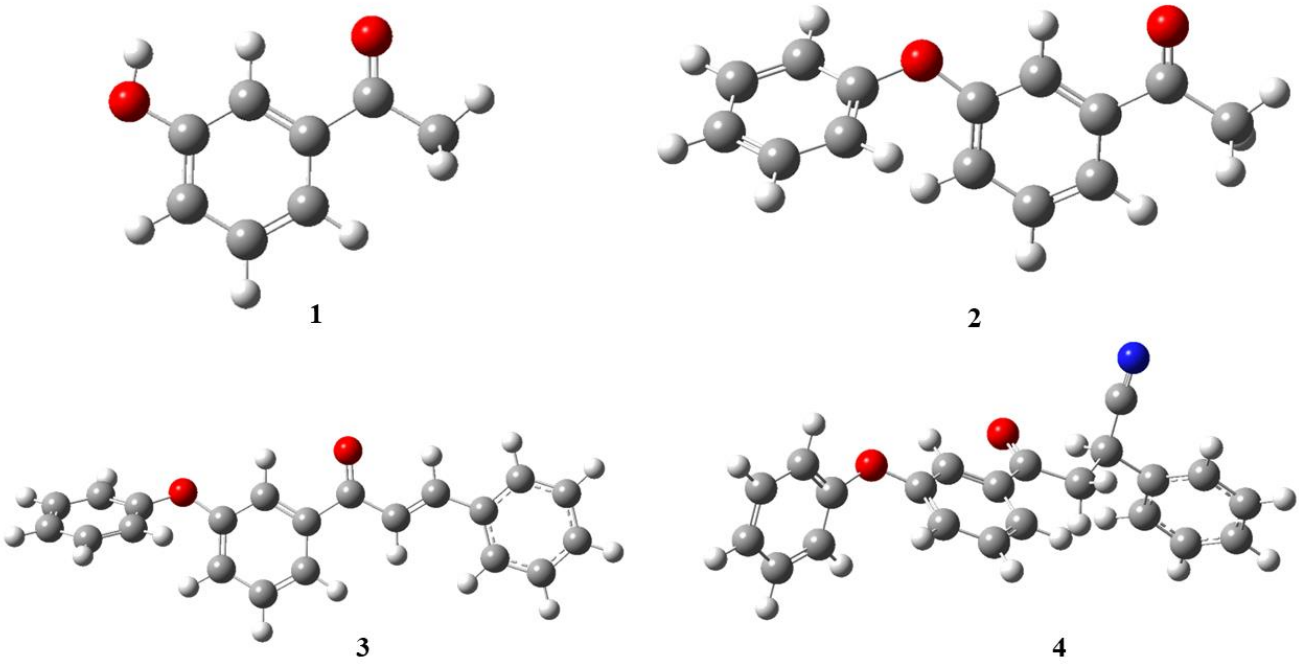

Figure 2 Optimized geometries B3LYP/6-311++G (d, p) method.

Deep blue: N, Red: O.

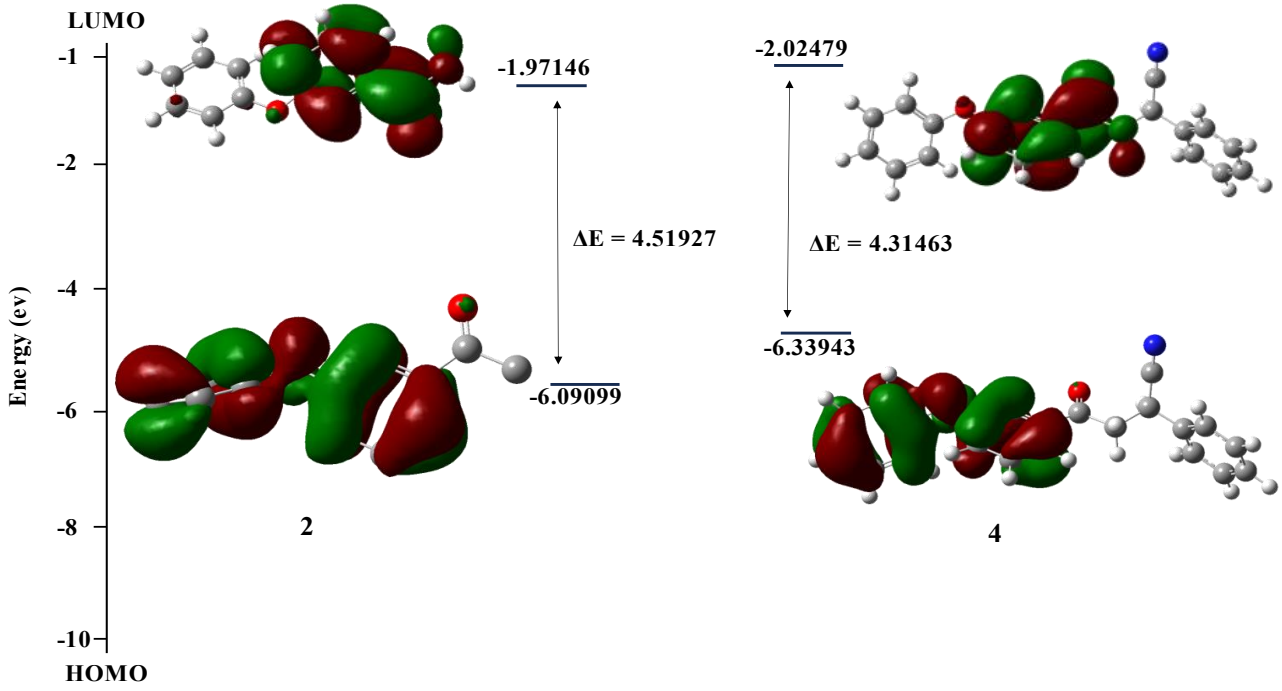

Fig 4. FMO orbitals (isovalue: 0.02 [e bohr−3]1/2oftrans-DZgenerated from TD/DFT calculation). Green and Maroon colors depict different phases.

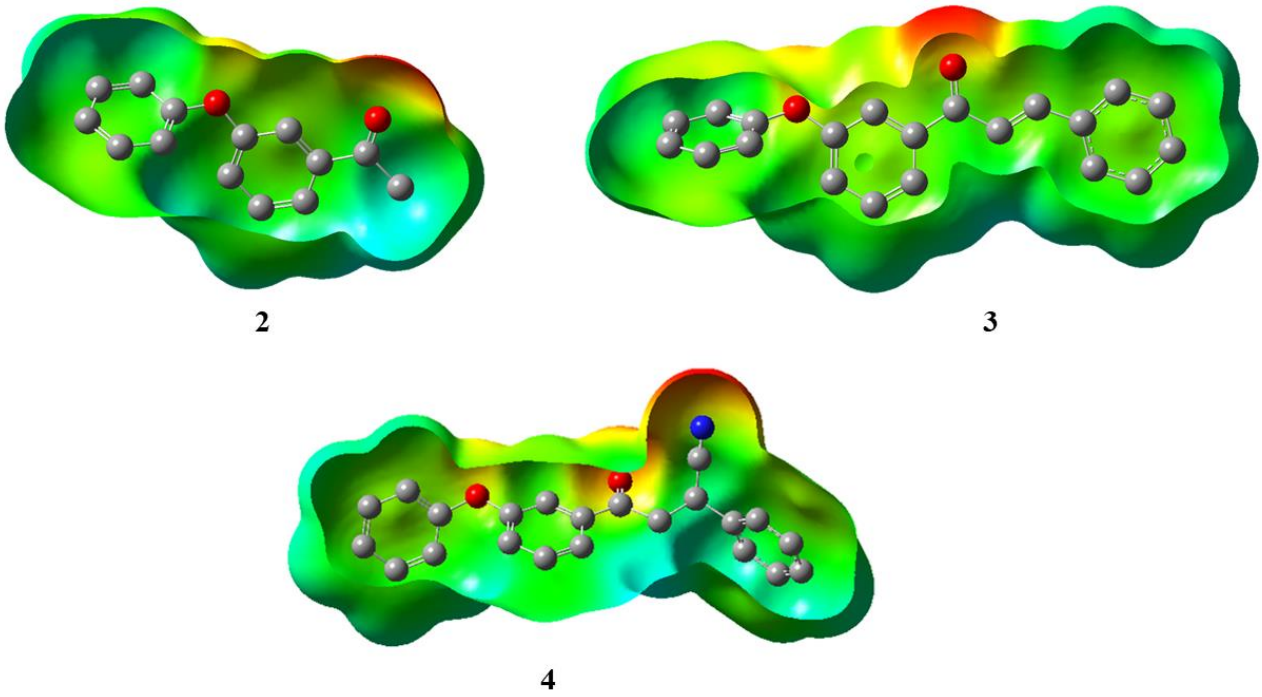

Fig 5. MEP Surfaces Of 2-4 Compound

Compounds	HOMO	LUMO	Energy Gap	Hardness (ή)	Softness (S)
2	-6.49	-1.971	4.519	2.259	0.442
3	-6.09	-2.272	3.818	1.909	0.523
4	-6.339	-2.024	4.315	2.157	0.463

Compounds	Ionisation Potential	Electronegativity(χ)	Electron Affinity
2	6.49	6.49	6.49
3	6.09	6.09	6.09
4	6.339	6.339	6.339

Orbitals	2	3	4
HOMO	-6.49	-6.09	-6.339
LUMO	-1.971	-2.272	-2.024
Eg [HOMO-LUMO]	4.519	3.818	4.315
HOMO -1	-7.153	-6.408	-6.901
LUMO +1	-0.838	-0.752	-0.499
Eg [(HOMO-1) - (LUMO+1)]	6.315	5.656	6.402
HOMO -2	-7.281	-6.741	-7.126
LUMO +2	-0.707	-0.259	-0.379
Eg [(HOMO-2) – (LUMO+2)]	6.574	6.482	6.747
HOMO -3	-7.34	-6.96	-7.152
LUMO +3	-0.405	-0.245	-0.329
Eg [(HOMO-3) – (LUMO+3)]	6.935	6.245	6.823

Compounds	Electrophilicity Index	Nucleophilicity Index	Chemical Potential
2	3.96	0.25	-4.23
3	4.57	0.21	-4.181
4	4.05	0.24	-4.181

Table 1,2,3.4 Calculated Global Reactivity Descriptors by B3LYP/6-31++G (d, p) Basis Set at DFT Level of Theory

Results and Discussion:

Methodology:

First, 3-phenoxy acetophenone (2) was prepared using Cu $(OAc)_2$ and the Chan-Lam coupling process. Chalcones (3) were synthesized by reacting 3-phenoxy acetophenone (2) with various aryl aldehydes (Figure 1). Continue with (4), which uses acetone cyanohydrin to synthesize compound 2 (Figure 1).

Computational Study:

Since the 6311++G (d, p) has included polarization function for hydrogen atoms in addition to the normal 6-31G basis set, it is more appropriate for modern proton transfer and prototrophic tautomerism. The initial structure of the compound was drawn by chem draw.

Quantum mechanical calculation:

Single point energy calculations are performed using the DFT method and the 6311-G (d, p) basis set to determine the frontier molecular orbital FMO. The following equations were used to estimate fundamental quantum parameters; energy gap ($\Delta E = E_{LUMO} - E_{HOMO}$), absolute electronegativity ($\chi = -E_{HUMO}+E_{LUMO}/2$), hardness ($ή = E_{LUMO}-E_{HOMO}/2$), softness ($\sigma = 1/ή$), chemical potential ($\mu = -\chi$), electrophilicity ($ώ = \chi 2/2ή$) and nucleophilicity ($1/ώ$).

Frontier molecular orbitals (FMOs) parameters:

The nucleophilicity (electron donation) and electrophilicity (electron acceptance), of a molecule are displayed by the HOMO and LUMO states, respectively. The energy of the orbitals was determined using the DFT technique at the ground state. The HOMO and LUMO charge densities are seen to be uniformly distributed throughout the molecule. This provides an overview of the quantum chemical descriptor. The DFT/HOMO value of compound 4 is -6.339 eV, respectively while the value of LUMO orbitals is -2.024 eV.

The computational factors used to characterize a molecule include its chemical hardness, chemical softness, electronegativity and chemical potential, all of which are calculated using the energy gap (ΔE) between the HOMO and LUMO.

Conclusion:

In this study, we report DFT calculation of a new chalcone derivative, A computational study of the conversion of 3-(3-phenoxy phenyl)-1-aryl prop-2-en-1-one into 4-Oxo-4-(3-phenoxy phenyl)-2-phenyl-butane nitrile using density functional theory (DFT) calculations was performed. 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-phenyl-butane 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 centre corresponds to the hardness or softness value of the compound.

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