

Quantum Chemical Insights into 2-[2-(Benzyloxy)benzylidene] malononitrile: DFT Analysis, MEP Surface Mapping, and HOMO-LUMO Energies

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Abstract – Malononitriles and their benzylidene derivatives stand out as a versatile class of organic compounds acclaimed for their wide-ranging pharmacological activities. Their crucial involvement in condensation reactions, driven by the reactivity of the active nucleophilic methylene group, holds profound significance across diverse industries, including medicine, industry, and agriculture. As computational methods have become integral for unraveling molecular-level behavior, this study delves into the theoretical calculations of the compound 2-[2-(benzyloxy)benzylidene] malononitrile. Utilizing Density Functional Theory (DFT) and Lee-Yang-Parr (LYP) with the B3LYP model, a 3-parameter Becke mixed model with correlation energy, and the 6-311G(d,p) basis set, the theoretical framework unfolds. The optimization process seeks the molecular system's solution, bringing it closest to the real system and reaching its most stable state. Post-optimization, the electrophilic and nucleophilic properties, derived from energy, are unveiled through local and global chemical activity calculations. Global chemical activity data, integrating hardness and softness parameters derived from the HOMO and LUMO energies (the primary molecular orbitals), offer insights into the overall reactivity. Concurrently, local chemical activity data, obtained through molecular electrostatic potential map analysis, provide a nuanced understanding of electrophilic and nucleophilic tendencies within the structure. This comprehensive computational approach elucidates the molecular behavior of 2-[2-(benzyloxy)benzylidene] malononitrile, contributing valuable insights for potential applications in various fields.

Keywords – Malononitrile, Benzylidene Derivative, DFT, MEP, HOMO-LUMO

I. INTRODUCTION

Malononitriles and their benzylidene derivatives constitute a diverse group of organic compounds acknowledged for their intricate pharmacological activities, as documented in the literature [1-3]. These substances have exhibited notable effects, including the inhibition of epidermal growth factor protein tyrosine kinase and the modulation of pro-inflammatory agents such as iNOS and COX-2. Benzylidenemalononitrile analogs, recognized for their free radical scavenging and anti-inflammatory attributes, particularly in suppressing TNF α release, fall within this compound class. The

reactivity inherent in these compounds, particularly attributable to the reactive methylene group, positions them as active nucleophiles in condensation reactions. Their role in synthesizing both carbo- and heterocyclic products underscores their significance across medical, industrial, and agricultural domains. Significantly, the documented antithyroid effects of malononitriles, observed through in vivo experiments on both rats and humans, emphasize their potential applicability in biological contexts [4-7].

Furthermore, malononitriles manifest a spectrum of biological activities, including the augmentation of nucleoproteins in cells, the regulation of RNA synthesis in neurons and nerve tissues, the promotion of nerve tissue regeneration, the stimulation of acetylcholine (ACh) biosynthesis, the modulation of learning and memory processes, and the amelioration of amnesia following electric shock. The multifaceted nature of these properties and biological activities underscores the significance and diverse applications of malononitriles, extending from pharmaceuticals to neuroscience [8-10].

Density Functional Theory (DFT) has become a prominent methodology in the field of chemistry due to its ability to accurately predict a wide range of molecular properties, including electronic structure, bond lengths, bond angles, and vibrational frequencies. This comprehensive suite of information provides researchers with a robust toolkit for exploring and understanding molecular reactions, as well as for the deliberate design of novel compounds with specified characteristics. In the context of the present investigation, a computational research initiative was conducted concerning the 2-[2-(benzyloxy)benzylidene] malononitrile compound, facilitating the acquisition of crucial data related to the Highest Occupied Molecular Orbitals (HOMOs), Lowest Unoccupied Molecular Orbitals (LUMOs), and a Molecular Electrostatic Potential (MEP) map. All of these parameters were derived through the application of the DFT method.

II. MATERIALS AND METHOD

Within this investigation, the Density Functional Theory (DFT) methodology was applied, utilizing the B3LYP/6-311G(d,p) basis set endowed with three parameters [11-13]. DFT computations, typically reliant on specialized software, such as Gaussian, necessitate substantial computational resources. In this study, the Gaussian 09W [14] and GaussView 5.0 [15] programs were employed for computational analyses. The primary focus of this research pertained to the determination of pivotal chemical descriptors, specifically the parameters of chemical hardness and softness, providing valuable insights into the stability of the examined compound. These descriptors were deduced from the energy values associated with the Highest

Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO).

Furthermore, the inquiry extended to the delineation of nucleophilic and electrophilic regions within the compound. This mapping was executed through the generation of a Molecular Electrostatic Potential (MEP) map, serving as a valuable instrument for characterizing electron density distribution and electrostatic interactions within the molecular framework. Selected geometric parameters are presented in Table 1, contributing to the comprehensive analysis of the compound's structural attributes.



Fig. 1 The optimized structure of $C_{17}H_{12}ON_2$.

Table 1. Some selected geometric parameters of $C_{17}H_{12}ON_2$

Bond lengths (Å)		Bond angles (°)	
C31-N2	1.1643	C15-O1-C18	118.82
C32-N3	1.1638	C19-C18-O1	123.76
C15-O1	1.4418	C14-C15-O1	109.28
C18-O1	1.3562	C4-C14-C15	121.64
C14-C15	1.5042	C12-C14-C15	119.67
C27-C28	1.4478	C27-C28-C30	130.76
C28-C30	1.3691	C28-C30-C31	125.62
C30-C31	1.4315	C31-C30-C32	114.86

III. RESULTS AND DISCUSSION

A. The Frontier Orbitals

The utilization of DFT-based quantum chemical descriptors has proven invaluable in furnishing essential insights into the chemical behavior of key biochemical molecules. These descriptors not only elucidate the chemical activity patterns but also contribute significantly to the rational design of novel agents and drugs employed in cancer treatment. One such compound subjected to DFT calculations is 2-[2-(benzyloxy)benzylidene] malononitrile, and the computations were conducted using the B3LYP functional and the 6-311 G(d,p) basis set.

In Figure 1, the optimized structure of the $C_{17}H_{12}ON_2$ compound is depicted, and the corresponding bond lengths and bond angles are detailed in Table 1. Moving further, Table 2 provides a comprehensive overview of calculated global descriptors, including ΔE (energy gap), μ (chemical potential), η (hardness), ω (electrophilicity index), and ΔN_{\max} (maximum charge difference), exclusively for the 6-311 G(d,p) basis set.

It's worth noting that the HOMO-LUMO (Highest Occupied Molecular Orbital - Lowest Unoccupied Molecular Orbital) energy gap, represented by ΔE , plays a crucial role in understanding the electronic transitions and reactivity of the compound [16-17]. A smaller ΔE often indicates enhanced electronic delocalization and a potentially higher reactivity, while a larger ΔE signifies greater stability. These HOMO-LUMO insights contribute significantly to unraveling the electronic structure and reactivity of the studied compound, offering valuable information for drug design and cancer treatment applications.

The energy levels and spatial distributions of the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) of the investigated molecule are illustrated in Figure 2. Calculated HOMO and LUMO energies reveal values of -6.49 eV and -2.64 eV, respectively, resulting in an energy gap (ΔE) of 3.85 eV. This gap serves as a metric for the molecule's stability. Further analysis yields a hardness value of 1.92 eV and a softness value of 0.26 (eV)^{-1} .

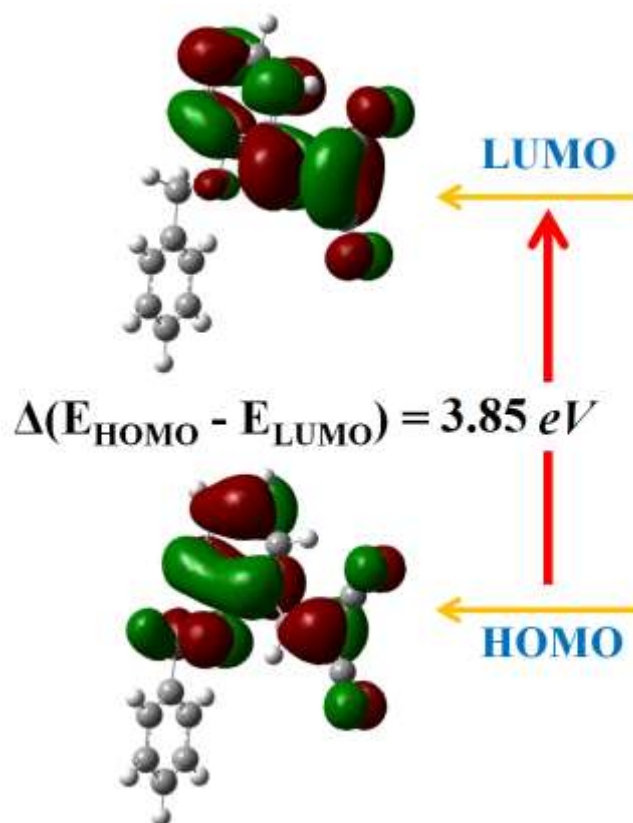


Fig. 2 HOMO-LUMO energy gap of $C_{17}H_{12}ON_2$.

Hardness, indicative of a molecule's resistance to electron transfer, stands in contrast to softness, which represents the opposite characteristic. A higher hardness value implies a reduced likelihood of intramolecular charge transfer. With a notably high energy gap, elevated hardness, and low softness values, the studied molecule is identified as stable and hard, signifying low chemical reactivity and heightened kinetic stability.

Table 2. HOMO-LUMO energy parameters of $C_{17}H_{12}ON_2$

Parameters	
E_{LUMO} (eV)	-2.64
E_{HOMO} (eV)	-6.49
Energy bandgap $ E_{HOMO}-E_{LUMO} $	3.85
Ionization potential ($I = -E_{HOMO}$)	6.49
Electron affinity ($A = -E_{LUMO}$)	2.64
Chemical hardness ($\eta = (I-A)/2$)	1.92
Chemical softness ($S = 1/2\eta$)	0.26
Electronegativity ($\chi = (I+A)/2$)	4.56
Chemical potential ($\mu = -(I+A)/2$)	-4.56
Electrophilicity index ($\omega = \mu^2/2\eta$)	5.42
Max. charge transfer index ($\Delta N_{\max} = -\mu/\eta$)	2.38

B. The Molecular Electrostatic Potentials

In the context of molecular orbitals and chemical reactivity, the terms "positive-negative potential" and "electrophilic-nucleophilic attacks" are closely related. Generally, negative potential is often associated with colors like red or yellow, while positive potential is associated with blue or green. These color assignments are used in visual representations to highlight regions of positive and negative electrostatic potential on molecular surfaces. Positive potential typically indicates regions where electron density is relatively low, and there is a tendency to attract electrons. Conversely, negative potential regions tend to have higher electron density. Electrophilic attacks involve electron-seeking species (electrophiles), while nucleophilic attacks involve electron-donating species (nucleophiles). These attacks play a crucial role in chemical reactions, with electrophiles and nucleophiles interacting to form new chemical bonds [18-21].

Molecular Electrostatic Potential (MEP) analysis is a valuable technique employed to visualize the electron density distribution within a molecule, offering insights into its electron-rich and electron-poor regions. MEP surfaces are systematically color-coded, where blue denotes electron-poor regions, and red signifies electron-rich areas.

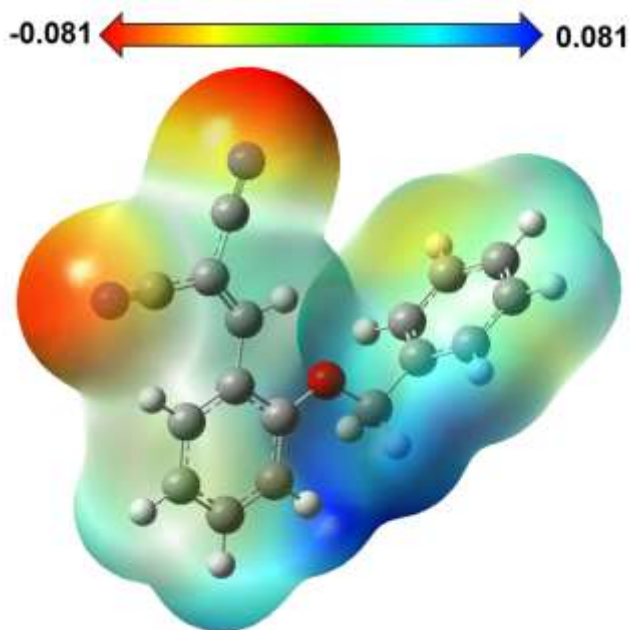


Fig. 3 The MEP surface of $C_{17}H_{12}ON_2$.

In the $C_{17}H_{12}ON_2$ molecule under investigation, the MEP analysis highlights the nitrogen atoms as

possessing the most negative potential, indicative of a highly electron-rich environment. Conversely, the hydrogen atoms exhibit the most positive MEP, signaling electron deficiency. As seen in Figure 3, the most negative regions are located on nitrogen atoms, while the most positive regions are located on hydrogen atoms. While the electrophilic dominant regions of the structure are on the most negative regions, the regions prone to nucleophilic attack are concentrated on hydrogen atoms.

IV. CONCLUSION

All theoretical calculations for the investigated structure were conducted using density functional theory with the B3LYP functional and 6-311G(d,p) basis set. The selection of the method followed optimization and thorough testing of the basis set's reliability. Subsequently, various molecular properties were derived from the energy calculations.

Detailed analysis of the molecular and chemical structure included the examination of local and global chemical activity, as well as the determination of charge transfer, which is not attainable through experimental means. With Molecular Electrostatic Potential (MEP) analyses based on global activity data, revealed an electrophilic dominance localized on N2 and N3 atoms within the structure. The computation of global chemical activity parameters indicated a structure with a very high energy range, characterized by high hardness ($\eta = 1.92$ eV) and a low softness parameter ($S = 0.26$ eV⁻¹). These findings signify low chemical activity and high kinetic stability, suggesting that the molecule under study is in a highly stable state.

REFERENCES

- [1] A. W. Erian, "The chemistry of beta-enaminonitriles as versatile reagents in heterocyclic synthesis," *Chem. Rev.*, vol. 93 (6), pp. 1991–2005, 1993.
- [2] F. Freeman, "Chemistry of malononitrile," *Chem. Rev.*, vol. 69 (5), pp. 591–624, 1969.
- [3] K. S. Dhindsa, "Histological changes in the thyroid gland of the mouse following treatment with 1, 1, 3-tricyano-2-amino-1-propene," *Cells Tissues Organs*, vol. 106 (4), pp. 468–472, 1980.
- [4] P. T. Francis, A. M. Palmer, M. Snape, and G. K. Wilcock, "The cholinergic hypothesis of Alzheimer's disease: a review of progress," *J. Neurol. Neurosurg. Psychiatry*, vol. 66(2), pp. 137–147, 1999.
- [5] T. H. Ferreira-Vieira, I. M. Guimaraes, F. R. Silva, and F. M. Ribeiro, "Alzheimer's disease: targeting the cholinergic system," *Curr. Neuropharmacol.*, vol. 14 (1), pp. 101–115, 2016.
- [6] C. N. Pope, and S.

- Brimijoin, "Cholinesterases and the fine line between poison and remedy," *Biochem. Pharmacol.*, vol. 153, pp. 205–216, 2018.
- [6] P. Güller, Z. Dağalan, U. Güller, U. Çalışır, and B. Nişancı, "Enzymes inhibition profiles and antibacterial activities of benzylidenemalononitrile derivatives," *J. Mol. Struct.*, vol. 1239, pp. 130498, 2021.
- [7] S. H. Ingbar, "The action of 1, 1, 3-tricyano-2-amino-1-propene (U-9189) on the thyroid gland of the rat and its effects in human thyrotoxicosis," *J. Clin. Endocrinol. Metab.*, vol. 21 (2), pp. 128–139, 1961.
- [8] J. W. Paul, and J. P. DaVanzo, "1, 1, 3 Tricyano-2- amino-1-propene (Triap) stimulates choline acetyltransferase activity in vitro and in vivo," *Dev. Brain Res.*, vol. 67 (2), pp. 113–120, 1992.
- [9] A. Blokland, "Acetylcholine: a neurotransmitter for learning and memory?" *Brain Res. Rev.*, vol. 21 (3), pp. 285–300, (1995).
- [10] A. D. Becke, "Density-functional exchange-energy approximation with correct asymptotic behavior," *Phys. Rev. A*, vol. 38(6), pp. 3098, 1988.
- [11] A. D. Becke, "A new mixing of Hartree–Fock and local density-functional theories," *J. Chem. Phys.*, vol. 98(2), pp. 1372-1377, 1993.
- [12] A. D. Becke, "Density-functional thermochemistry. I. The effect of the exchange-only gradient correction," *J. Chem. Phys.*, vol. 96(3), pp. 2155-2160, 1992.
- [13] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, *Gaussian 09, Revision A.02*, Gaussian, Inc., Wallingford CT, 2016.
- [14] R. D. Dennington, T. A. Keith, and J. M. Millam, *GaussView 5.0.8*. Gaussian Inc. Wallingford CT, 2008.
- [15] Y. Oueslati, S. Kansız, N. Dege, C. de la Torre Paredes, A. Llopis-Lorente, R. Martínez-Mañez, and W. S. Sta, "Growth, crystal structure, Hirshfeld surface analysis, DFT studies, physicochemical characterization, and cytotoxicity assays of novel organic triphosphate," *J. Mol. Model.*, vol. 28(3), pp. 65, 2022.
- [16] D. M. Al-thamili, A. I. Almansour, N. Arumugam, S. Kansız, N. Dege, S. M. Soliman, M. Azam, and R. S. Kumar, "Highly functionalized N-1-(2-pyridinylmethyl)-3, 5-bis[(E)-arylmethylidene] tetrahydro-4 (1H)-pyridinones: Synthesis, characterization, crystal structure and DFT studies," *J. Mol. Struct.*, vol. 1222, pp. 128940, 2020.
- [17] M. R. Albayati, S. Kansız, H. Lgaz, S. Kaya, N. Dege, I. H. Ali, R. Salghi, and I. M. Chung, "Synthesis, experimental and theoretical characterization of (E)-2-((2,3-dimethylphenyl) amino)-N'-(furan-2-ylmethylene) benzohydrazide," *J. Mol. Struct.*, vol. 1219, pp. 128518, 2020.
- [18] S. Kansız, A. Tolan, H. İçbudak, and N. Dege, "Synthesis, crystallographic structure, theoretical calculations, spectral and thermal properties of trans-diaquabis (trans-4-aminoantipyrine) cobalt (II) acesulfamate," *J. Mol. Struct.*, vol. 1190, pp. 102-115, 2019.
- [19] N. K. Yağcı, S. Kansız, and E. Özcandan, "Synthesis, crystal structure, DFT studies, Hirshfeld surface analysis and drug delivery performance of bis (2-chloro-4, 6-diaminopyrimidine) copper (II)-dichloride," *J. Mol. Struct.*, vol. 1246, pp 131142, 2021.
- [20] S. Kansız, M. Azam, T. Basılı, S. Meral, F. A. Aktaş, S. Yeşilbağ, S., K. Min, A. A. Açar, and N. Dege, "Synthesis, structural studies, Hirshfeld surface analysis, and molecular docking studies of a thiophene-based Schiff base compound," *J. Mol. Struct.*, vol. 1265, pp. 133477, 2022.