



The Weak Intermolecular Interactions in 2,6-Bis(4-Isopropylbenzylidene) Cyclohexanone: Insights from Crystallographic Studies and Semi-Empirical Quantum Chemical Calculations

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ABSTRACT

In the molecular structure of 2,6-bis(4-isopropylbenzylidene) cyclohexanone, (I), the central cyclohexane ring adopts half-chair conformation quantified by ring puckering analysis and asymmetry parameters. The olefinic double bonds in the title compound have E-conformation. The conformational discrepancy between the experimental structure and theoretical one computed by AM1 semi-empirical method describes the role of short intramolecular C-H...O contacts and a weak C-H π interaction in the solid state of a molecule. The parametric molecular electrostatic potential (PMEP) calculated by semi-empirical method also shows the involvement of oxygen atom in the short intramolecular C-H... O contacts in crystal packing. The intramolecular charge transfer resulting from HOMO-LUMO transition reflects the chemical activity of a molecule.

Keywords: Cyclohexanone, semi-empirical method, parametric molecular electrostatic potential, Charge transfer interaction

1. INTRODUCTION

Bisbenzylidene cycloalkanone [BBCA], a versatile photo-active molecule bearing mesogenic unit has shown its potential for applications in biology, chemistry, materials science, medicine and technology, in general. BBCA in particular, when incorporated in polymeric architectures found useful applications in Photo responsive polymer, Conducting polymer, Chemotherapy, Information storage, Liquid crystalline polymer and Flame retardant polymer [1]. The cycloalkanone derivatives have wide spectrum of biological and pharmacological activities such as anti-carcinogen, immuno-modulation, anti-oxidant, anti-angiogenesis and anti-inflammation [2]. Bis(arylmethylidene) cycloalkanones are also reported to exhibit promising nonlinear optical properties [3]. Encouraged by these wide variety of applications, the title compound was synthesized and a single crystal X-ray diffraction analysis was carried out on the compound to investigate the geometry of the cyclohexanone moiety and also possible contributions like

intermolecular interactions towards the stabilization of the molecule together with theoretically computed structure are discussed herein. Figure 1 shows a schematic diagram of the molecule.

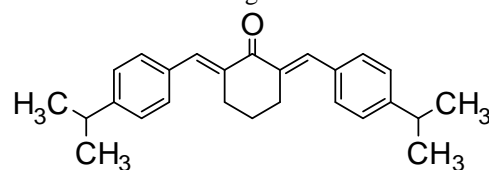


Figure1. Schematic diagram of the molecule (I).

2. EXPERIMENTAL

2.1. Synthesis

An aqueous solution of sodium hydroxide (10% w/v, 30 mL) was added to a solution of *p*-isopropyl benzaldehyde (0.02 mol) and cyclohexanone (0.01 mol) in ethanol (50 mL). The reaction mixture was stirred at 10-20 °C for 2 hr and left overnight in an ice chest to get a yellow colored solid. The product was filtered, washed with ice-cold water (100 mL) followed by ice-cold ethanol (20 mL), dried and

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recrystallized from DMF. The yield of product was 85 %, m.p.140-141 °C. The colourless block-like single crystals of the title compound were harvested by slow evaporation technique using methanol as solvent and the crystal structure has been determined by the X-ray diffraction method.

2.2. Crystal Structure Determination

Intensity data on BRUKER AXS KAPPA APEX2 CCD diffractometer are collected in ω and ϕ scan with θ ranging from 2.13 to 30.70° and 3648 unique reflections are recorded. The structure was solved by direct methods using SIR92 program [4] and refined by full-matrix least squares on F^2 using SHELXL-97 program [5]. All of the non-hydrogen atoms were refined anisotropically and all the H atoms were geometrically fixed and allowed to ride on the parent atom in the model with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$ for terminal methyl and $1.2U_{\text{eq}}(\text{C})$ for all other H-atoms. An absorption correction was performed using SADABS [6] and all calculations were performed using PLATON [7]. An ORTEP diagram of the molecule with the atom numbering scheme is as shown in Figure. 2. The crystal and experimental details are given in Table 1.

2.3. Semi-empirical Quantum Chemical Calculations

The geometry of a molecule is optimized by Austin Model 1 (AM1) semi-empirical method incorporated in MOPAC2009 program [8] with the experimental structure as a starting geometry. AM1 hamiltonian together with restricted Hartree-Fock closed shell wave function were used in the energy minimization process to obtain geometrically optimized structure through the convergence at r. m. s. gradient less than $0.01 \text{ kJ mol}^{-1} \text{ \AA}^{-1}$. Parametric molecular electrostatic potential (PMEP) was then calculated to predict the reactive sites for electrophilic and nucleophilic attack for the title molecule to confirm the role of interaction in the solid state of a molecule. The different forms of molecular energies and frontier molecular orbitals were also computed from AM1 semi-empirical method to describe the intramolecular charge transfer interaction. The HOMO-LUMO composition of frontier molecular orbitals to represent the cloud of charges around the atoms of molecules are depicted using a computational environment software Facio [9].

3. Results and discussion

3.1. 2,6-bis(-4-isopropylbenzylidene)cyclohexan-1-one

IR (KBr) vcm^{-1} 3060 (ArC-H), 2908 (AlpC-H str), 1668 (C=O str), 1596, 1492, 1447 (C=C str).. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 1.21 (d, 12H), 1.47 (m, 4H), 2.82 (t, 2H), 5.10 (q, 2H), 7.28 (dd, 4H), 7.64 (dd, 4H), 7.31 (s, 2H) $^{13}\text{C-NMR}$ (400 MHz, DMSO-d_6) δ 23.31, 25.16, 26.17, 33.27, 126.19, 128.38, 132.27, 132.49, 137.20, 147.68, 189.40.

3.2. X-ray structure analysis

3.2.1. Conformational Features

The molecular structure of title molecule, (I), has a bird-like conformation with the wings formed by isopropyl substituted benzenes rings on both the side of a central cyclohexane ring. A usual half-chair conformation adopted by a cyclohexane ring is quantified by Cremer-Pople ring puckering analysis [10]. The ring puckering parameters for cyclohexane ring are :

$q(2) = 0.368(2)$, $q(3) = 0.324(2)$ and $Q = 0.494(4) \text{ \AA}$ $\theta = 48.4(5)^\circ$ and $\phi = 122.3(6)^\circ$; the idealized values are $\theta = 50.8^\circ$ and $\phi = (60k + 30)^\circ$, where k is an integer.

The lowest displacement asymmetry parameter computed by PARST ΔC_s (C13) = 5.81623 also indicates the half-chair conformation of this ring. Both the olefinic double bonds of the title compound have the E-conformation in the structure. The angles at carbon C10 and C17 atoms which link phenyl rings with central cyclohexane ring may be increased due to non bonded steric strain between H atoms of cyclohexane and phenyl rings. This is characterized by bond angles at carbon C10 and C17 atoms, and torsional angles around C7-C10 and C12-C17 bonds. The phenyl rings as well as isopropyl moieties on both the side of cyclohexane have different orientations quantified by dihedral angles between mean planes through cyclohexane ring, phenyl rings and the plane of isopropyl groups given in Table 2. Though the structural refinement results obtained from SHELXL97 program show that terminal isopropyl atoms on both the side have large thermal parameters due to poorly grown single crystals of the compound, the final R-value for the structure obtained from the program indicates the completeness of the structure and hence the model is in acceptable form.

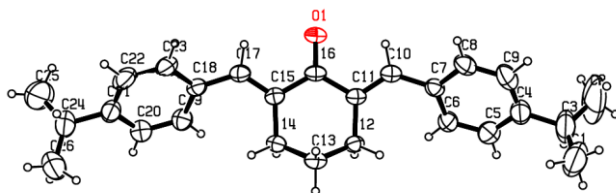


Figure 2. ORTEP diagram of the molecule at the 30% probability level.

Table 1. Summary of Crystal data, intensity data collection and refinement for cyclohexanone derivative.

Empirical Formula	C ₂₆ H ₃₀ O
Formula weight	358.50
Crystal system	Monoclinic
Space group	C2
Unit cell dimensions	a = 18.3628(9) Å b = 6.1581(3) Å c = 19.1547(5) Å β = 93.330(19)°
Z	4
V	2162.36(9) Å ³
T	293(2) K
D _x	1.8 Mg m ⁻³
μ	0.065 mm ⁻¹
Radiation(Mo Kα)	λ = 0.71073 Å
F(0 0 0)	776
θ range for data collection	2.7 to 30.7 °
Reflections used for refinement	3648
Number of parameters	248
Goodness of fit	1.089
Final R indices[I > 2σ(I)]	R1=0.0597 wR2 = 0.1587
R indices all data	R1=0.0812 wR2 = 0.1678
(Δ/σ) _{max}	0.001
(Δρ) _{max}	0.13 e Å ⁻³
(Δρ) _{min}	-0.12 e Å ⁻³

3.1.2. Packing Features

In the absence of potential hydrogen bonding interactions, the crystal is stabilized mainly by two short intramolecular C-H...O contacts and C-H π interaction. The benzene substituted carbon C10 and C17 atoms form pseudo five-membered rings on both the sides of oxygen atom through short intramolecular C-H...O interactions and have S(5) graph-set motif [11] in each case. The C13 atom which is at an apex from the plane of remaining five atoms of cyclohexane ring (deviation = 0.3553 Å) has a C-H π interaction (H...Cg = 2.87 Å, C...Cg = 3.780(6) Å, C-H...Cg = 156°; Cg = (C18-C23) benzene ring at 1-x, y, -z) with π-electron cloud of a symmetry related phenyl C18-C23 ring that links the molecules diagonally across ac-plane shown by a dashed line in Figure.3.

3.3. Geometry optimization

The optimized geometry of the molecule drawn using a graphical user interface Gabedit [12] is shown in Figure 4. The difference in crystallographic geometry around benzene substituted carbon C10 and C17 atoms on both the sides of cyclohexane ring from the energy minimized structure is due to the involvement of these atoms in the intramolecular C-H...O contacts with oxygen atom and the steric repulsion between respective H atoms of cyclohexane and benzene rings (Table 3). The difference in orientation of terminal propyl moieties at their respective benzene

rings in the experimental structure from theoretical one are due to their positional disorders characterized by large anisotropic thermal displacement parameters and short C-C bond lengths. Thus the discrepancy in the geometry between experimental and theoretical structure indicate the role of interactions in the crystal packing of a molecule.

3.4. Parametrization molecular electrostatic potential

The molecular electrostatic potential is a useful descriptor in understanding the sites for electrophilic attack, nucleophilic reactions and hydrogen bonding interactions which can be determined experimentally by diffraction or by computational methods [13,14]. The parametrization molecular electrostatic potential, also known as Wang-Ford electrostatic potential was calculated from the optimized geometry of the molecule to predict the reactive sites for an electrophilic attack and to confirm the involvement of atoms in the crystal packing interactions [15-17]. The structure has a possible sites for electrophilic attack over O1 and H13A atoms with the potentials of -70.4 and -13.5 kcal/mol. The significant values for these atoms confirm their role in the crystal packing interactions of a molecule.

3.5. Intramolecular charge transfer interaction

The different forms of energy such as heat of formation, transition energies, ionization potential etc. computed by semi-empirical quantum chemical calculations using MOPAC2009 are listed in Table 4.

The HOMO-LUMO composition of frontier molecular orbitals obtained from AM1 semi-empirical method is shown in Figure 5. The analysis of restricted Hartree-Fock wave function indicates that the transition from ground to first excited state is described by one electron transition from highest occupied molecular orbital (HOMO)

to lowest unoccupied molecular orbital (LUMO). The frontier molecular orbital HOMO is localized mainly around the carbon atoms of substituted benzene rings about C=O bond of cyclohexanone thereby forming wing-like cloud of charges. LUMO is localized with the large concentration around olefinic double bonds and C=O bonds of the title molecule. An electron transition from HOMO to LUMO through an absorption of energy equal to HOMO- LUMO energy gap (8.432 eV) reflects the chemical activity of a molecule thereby resulting intramolecular charge transfer between the atoms of molecule.

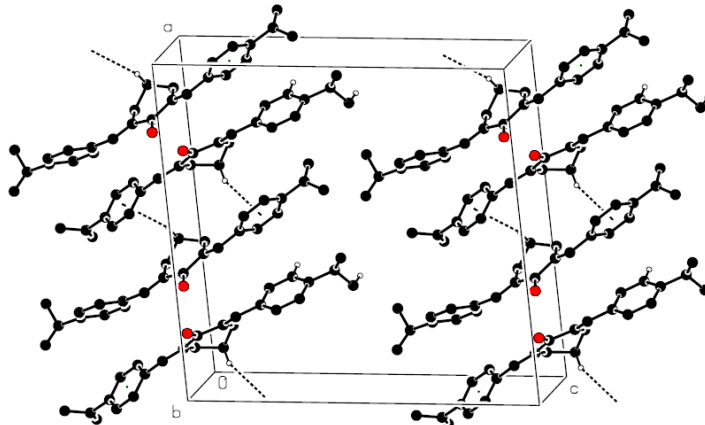


Figure 3. Crystal packing diagram of (I), showing C-H... π interactions.

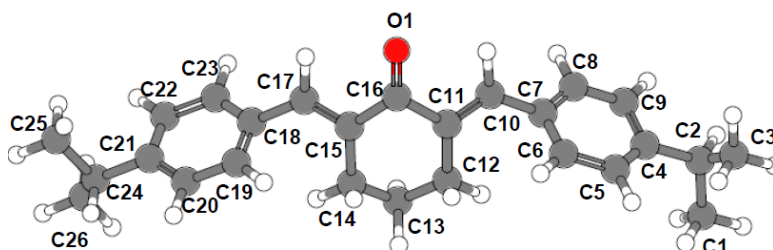
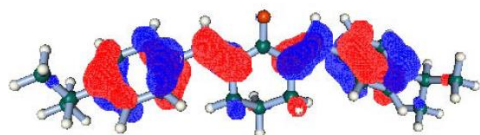
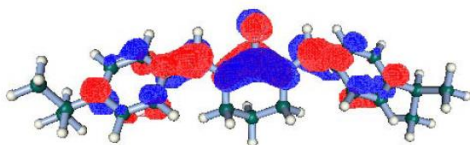


Figure 4. Geometrically optimized molecule of title compound with atom numbering scheme



(a) HOMO (-9.001 eV)



(b) LUMO (-0.569 eV)

Figure. 5 Frontier Molecular Orbitals

4. CONCLUSION

The insights from crystallographic studies and the geometry optimization from semi empirical quantum chemical calculations of the structure displays significant change in the orientation of isopropyl substituted benzene rings and the cyclohexanone moiety thereby resulting participation of such rings in the weak intra and intermolecular C-H...O interactions which may affect the crystal packing. The parametrization molecular electrostatic potential calculated from the optimized geometry of the molecule predicts the reactive sites in the title structure, for electrophilic attack over O1 and H13A atoms with the potentials of -70.4 and -13.5 kcal/mol. The significant values for these atoms confirm their role

Table 2. Comparison of molecular geometry.

Bond lengths (Å)		
	XRD	AM1
C7-C10	1.464(5)	1.454
C10-C11	1.333(5)	1.349
C15-C17	1.324(5)	1.349
C17-C18	1.488(5)	1.454
C16-O1	1.227(4)	1.244
C1-C3	1.468(13)	1.517
C2-C3	1.294(16)	1.517
C24-C25	1.429(10)	1.517
C24-C26	1.379(10)	1.517
Bond Angles (°)		
	XRD	AM1
C7-C10-C11	129.2(4)	127.02
C15-C17-C18	128.8(4)	126.976
Dihedral angles (°)		
	XRD	AM1
(C4-C9) - Cyclohexane	54.1(3)	55.83
(C18-C23) - Cyclohexane	52.8(3)	55.50
(C4-C9)-(C18-C23)	24.5(5)	35.59
C1/C2/C3- (C4-C9)	77.4(12)	89.86
C24/C25/C26- (C18-C23)	66.8(10)	89.94
Torsional angles (°)		
	XRD	AM1
C6-C7-C10-C11	36.4(9)	44.635
C15-C17-C18-C19	-38.9(9)	-44.406

Table 3. Comparison of short intramolecular C-H...O contacts.

D-H...A		D-H(Å)	H...A(Å)	D...A(Å)	D-H...A(°)
C1-H1A...O1	XRD	0.93	2.33	2.718(7)	105
	AM1	1.109	2.406	2.763	96.590
C19-H19...O3	XRD	0.93	2.35	2.739(7)	105
	AM1	1.109	2.407	2.763	96.557

Table 4. Molecular energies computed by AM1 semi-empirical method.

Heat of formation [KJ/mol]	-3.3089	Electronic Energy [eV]	-32239.933
Ionization potential [eV]	9.001	Core-Core repulsion [eV]	28177.660
HOMO-LUMO energies [eV]	-9.001, - 0.569	Total energy [eV]	-4062.273

in the crystal packing interactions of a molecule. The HOMO-LUMO energy gap of 8.432eV reflects the chemical activity of molecule thereby resulting charge transfer interaction. The role of intermolecular interactions on stability of the molecule is satisfactorily explained by crystallographic studies and this is very well supported by semi empirical calculations and PME potentials.

Supplementary Material

CCDC 871091 contains supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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5. REFERENCES

- [1]. M. Murali, A.B. Samir, (2010), Bisbenzylidene cycloalkanone: a versatile molecule as a polymer building block. *Journal of Material Chemistry*, 20, 2714 - 2737.
- [2]. W.J. Gilford, K.J. Shaw, J.L. Dallas, S. Koovakkat, W. Lee, A. Liang, D.R. Light, M.A. Mc Carrick, M. Whitlow, B. Ye, & M. M. Morrissey, (1999) Synthesis, characterization, and structure- activity relationships of amidine-substituted (bis)benzylidene-cycloketone olefin isomers as potent and selective factor Xa inhibitors, *Journal of Medicinal Chemistry*, 42, 5415-5425.
- [3]. R.C. Yu, A.V. Yakimansky, H. Kothe, I.G. Voigt-Martin, D. Schollmeyer, J. Jansen, H. Zandbergen, A.V. Tenkovtsev, (2000) Strategies for structure solution and refinement of small organic molecules from electron diffraction data and limitations of the simulation approach, *Acta Crystallographia Section A*, 56 (Pt 5), 436-50.
- [4]. A. Altomare, M.C. Burla, G. Camalli, G. Cascarano, C. Giacovazzo, A. Gualardi, G.J. Polidori, (1994), SIR 92 - a program for automatic solution of crystal structures by direct methods, *Journal of Applied Crystallography*, 27, 435-436.
- [5]. G.M. Sheldrick, (1997), SHELXL97, Program for crystal structures refinement, University of Göttingen, Germany.
- [6]. Bruker (2001) SADABS, Program for absorption correction, Bruker AXS Inc., Madison, Wisconsin, USA.
- [7]. A.L. Spek, (2009), Structure validation in chemical crystallography, *Acta Crystallographia Section D*, 65, 148-155.
- [8]. J.P. Stewart, MOPAC2009, Stewart Computational Chemistry, Version 8.351W.
- [9]. M. Suenaga Facio version 14.1.1 3D-graphics program for molecular modeling and visualization of quantum chemical calculations computational chemistry environment for MOPAC, GAMES and GAUSSIAN.
- [10]. D. Cremer, J.A. Pople, (1975), A general definition of ring puckering coordinates, *Journal of American Chemical Society*, 97, 1354-1358
- [11]. A. R. Allouche, (2010), Gabedit, A graphical user interface for computational chemistry, *Journal of Computational Chemistry*, Doi:10.1002/jcc.21600.
- [12]. J. Bernstein, R.E. Davis, L. Shimoni, N.L. Chang, (1995), Patterns in hydrogen bonding: functionality and graph set analysis in crystals, *Angewandte Chemie International Edition Engineering*, 34, 1555.
- [13]. E. Seroco, J. Tomasi, (1979), Electronic molecular structure, reactivity and intermolecular forces: an heuristic interpretation by means of electrostatic molecular potentials, *Advanced Quantum Chemistry*, 11, 115-193.
- [14]. F.J. Luque, J.M. Lopez, M. Orozco, (2000), Perspective on "Electrostatic interactions of a solute with a continuum. A direct utilization of ab initio molecular potentials for the prevision of solvent effects" *Theoretical Chemistry Accounts*, 103, 343-345.
- [15]. P. Politzer, P.R. Laurence, K. Jayasuriya, J. Makinney, (1985), Molecular electrostatic potentials: an effective tool for the elucidation of biochemical phenomena, *Environmental Health Perspectives*, 61, 191-202.
- [16]. B. Wang, G.P. Ford, (1994), Atomic charges derived from a fast and accurate method for electrostatic potentials based on modified AM1 calculations, *Journal of Computational Chemistry*, 15, 200-207.
- [17]. G.P. Ford, B. Wang, (1993), New approach to the rapid semiempirical calculation of molecular electrostatic potentials based on the am1 wave function: Comparison with ab initio hf/6-31g results, *Journal of Computational Chemistry*, 14, 1101-1111.

***Biographical Sketch**

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