Acidochromic Behavior of Dibenzylidene Cyclohexanone-Based Bischalcone: Experimental and Theoretical Study

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ABSTRACT: Synthesis and characterization of substituted 2,6-dibenzylidene cyclohexanone-based bischalcone derivatives and their optimized geometries were investigated by density functional theory. The synthesized compounds were identified through ultraviolet−visible, Fourier transform infrared, and 1H nuclear magnetic resonance spectroscopies and elemental analysis. Significant acidochromic behavior was observed for 2,6-bis(4-dimethylamino-benzylidene)-cyclohexanone 1e. This result is owing to the preferential protonation of the chromophoric N,N-dimethylamino group, that is, quaternary salt formation and deactivation of the resonance system. The result was consistent with computational studies where the protonation was favored by 211 kcal/mol in the gas phase. The compounds also showed solvatochromic behavior. The geometries of the synthesized compounds were optimized with B3LYP/6-311G+(d,p) and APFD/6-311+G(d,p) basis sets. The single point energy indicated that APFD/6-311+G(d,p) basis set gave the lowest energy of 445−655 kcal/mol for the studied bischalcone derivatives. Quantum chemical parameters were also calculated.

INTRODUCTION

Dibenzylidene-cyclohexanone is a cyclohexanone-based bischalcone that possesses two reactive keto-vinyl moieties (−CO−CH═CH−) and hence are categorized as bichromophoric molecules.1,2 Bischalcones possess a system of conjugated double bonds on both of the benzene rings and a completely delocalized electron system. Because of the presence of this chromophoric group, these compounds are very fascinating for researchers to develop new compounds.3,4 Similarly, one of the simple natural occurring chemical constituents, chalcones, found in lower kingdoms to higher plants, are considered to be precursors of flavonoids and isoflavonoids.5,6 Both natural and synthetic chalcones have attracted a great deal of interest among scientists and researchers for their important biological activities. In traditional medical treatment, chalcone-containing plants have been used so far.7−9 For pharmacological studies, chalcones have been isolated from different plants, and their clinical test for ailment of cancer, viral, and cardiovascular diseases has been done. Later, it was confirmed that these compounds display biological activities such as antiviral, antitumor, antioxidant, anticancer, anti-inflammatory, and antifungal and inhibit tyrosinase.10−13 On the other hand, the chromophoric group that is responsible for the change of color of compounds on interaction with acids, known as acidochromism, has a significant role in the sensor industry.14,15 These types of compounds have shown wide range of acidochromism behavior. The significant use of these compounds is as inhibitors of pulmonary carcinogens and ovarian cancer cell proliferation.6 Basically, the presence of α,β-unsaturation of the carbonyl compounds is liable for the biological activities of chalcones. The photophysical and optical properties of various substituted bischalcones have been studied.17,18 These compounds can also be used in several optical devices including fluorescent-based DNA assays, photoalignment layer of liquid crystal display, and metal ions.19 Therefore, it is a challenge to synthesize this lucrative-substituted bischalcone derivative in a solvent-free method with high yield, as well as its stability should be thoroughly checked. In this study, substituted dibenzylidene-cyclohexanone-based bischalcones were synthesized as shown in Scheme 1.
The structure of the compounds was identified by ultraviolet–visible (UV–vis), Fourier transform infrared (FTIR), and $^1$H nuclear magnetic resonance (NMR) spectroscopies and elemental analysis. Acidochromic behavior and solvatochromic behavior were examined with various solvents to explicate the interaction parameters. A computational study was carried out by the density functional theory (DFT) method. The geometries were optimized by both B3LYP/6-311G+(d,p) and APFD/6-311+G(d,p) basis sets. The quantum chemical parameters and frontier molecular orbitals were also calculated.

### RESULTS AND DISCUSSION

**Spectroscopic Properties.** The spectroscopic properties of the synthesized 2,6 dibenzylidenecyclohexanone derivatives 1a–1e were examined using UV–vis spectroscopy. The synthesized products were soluble in most organic solvents, and the absorption maxima in ethanol ranging from 330 to 452 nm are shown in Table 1.

| Substituents (X) | H | p-Cl | p-NO$_2$ | p-OCH$_3$ | p(N(CH$_3$)$_2$) |
|-----------------|---|------|----------|-----------|---------------|
| Wavelength, $\lambda_{max}$ (nm) | 330 | 333 | 340 | 359 | 452 |

The synthesized product 2,6-dibenzylidenecyclohexanone 1a showed absorption maxima at 330 nm, whereas 2,6-bis(4-dimethylamino-benzylidene)-cyclohexanone 1e showed high absorption maxima at 452 nm, as shown in Figure 1.

![Figure 1. UV–vis spectrum of compounds 1a–1e in ethanol.](image)

The bathochromic shift induced for compound 1e, compared with other synthesized products, is because the electron-donating N$_N$-dimethylamino substituents interact with electron-accepting moieties that might be stabilized by an internal charge transfer assisted by the lone pair of carbonyl oxygen. Compound 1a showed hypsochromic shifts compared to compound 1e for its basic chalcone framework. Because it has no substituent, no substituent effect was observed. Similarly, the compound 2,6-bis(4-methoxy-benzylidene)-cyclohexanone 1d showed a bathochromic shift (absorption maxima at 359 nm) which is lesser than that of compound 1e because of the presence of the electron-donating methoxy (−OCH$_3$) substituent. The presence of the electron-withdrawing substituent in 1b and 1c (containing halogen and nitro substituents) contributed very little effect to the absorption maxima at 333 and 340 nm, respectively. These findings may explain that the electronreactivity of the carbonyl oxygen of bischalcone is cancelled by the interaction of these electron-withdrawing groups.

**Acidochromic Properties.** Acidochromic behavior of the investigated compound 2,6-bis(4-dimethylamino-benzylidene)-cyclohexanone 1e was explored at different hydrogen concentrations using hydrochloric acid (HCl), as shown in Figure 2.

![Figure 2. UV–vis spectrum of compound 1e in ethanol with 0.02–0.11 M hydrochloric acid.](image)

The result revealed that on increasing the concentration of hydrochloric acid, hypochromic shifts ($n \rightarrow \pi^*$) occur, and with time, the absorption maxima at 452 nm gradually decreases, while a new absorption band at 322 nm gradually appears and becomes sharper. This change is due to the characteristics protonation of the chromophoric N$_N$-dimethylamino group and the formation of quaternary salt, as shown in Scheme 2. This quaternary system deactivates the $\pi$-electron delocalization, resulting in the absorption maxima shift to 322 nm.

**Scheme 2. Quaternary Salt Formation of 2,6-Bis(4-dimethylamino-benzylidene)-cyclohexanone**

![Scheme 2](image)

On the other hand, for the synthesized 2,6-bis(4-methoxy-benzylidene)-cyclohexanone 1d, there is no shift in wavelength when treated with protic acid, though the absorption maxima decreased a little, which is shown in Figure 3. This result is contradictory to the findings of Bedekar et al., where they have shown that in the presence of protic acid, a bathochromic shift was observed with a clear color change from yellow to red.

**Solvatochromic Properties.** The solute–solvent interactions usually play a vital role for a given solute. The UV–vis absorption maxima is shifted for different solvents of the studied compounds. This solvatochromic behavior is fascinat-
ing to explore the properties of the ground state of a molecule. The experimental absorption maxima is shown in Figure 1, and the values are summarized with the computational results in Table 2. The findings indicate that the bathochromic shift was observed for all substituted 2,6-dibenzylidene-cyclohexanones with increasing polarity of the solvent, with the exception of 1b and 1c.

These results showed the decrease the energy of the excited state with the increase in the polarity of the solvent, which is in the order of dichloromethane < ethyl acetate < ethanol. This behavior revealed that the molecules in the ground state as well as the excited state were dissimilar in different polarities. The examined compounds with nonpolarized ground state were highly polarized in protic solvents, causing the high energy polar structure of the excited state to be stabilized. Consequently, the excited state was lowered, and at the same time, the ground state was scarcely affected. The computationally calculated absorption maxima showed the general approach of the substituent effect that reflects the experimental results with the studied solvents. Most remarkably, the calculated solvatochromic behavioral trend is reliable and replicates the experimental results, though the magnitude of the absorption maxima among the solvents is small.

## COMPUTATIONAL RESULTS

**Single Point Energies.** Single point energies of the optimized structures 1a–1e were calculated at the B3LYP/6-311+G(d,p) and APFD/6-311+G(d,p) level of theories. All examined compounds showed that APFD/6-311+G(d,p) level of theories gave the lowest energy, and the value was lower than 445–655 kcal/mol. Single point energies for compounds 1a–1e are given in Table S7 (Supporting Information).

**Geometric Parameter Analysis.** Several geometric parameters, for example, bond lengths, bond angles, and dihedral angles were measured computationally at the APFD/6-311+G(d,p) level of theories. Among the studied compounds, one of the optimized structures of 2,6-bis(4-dimethylamino-benzylidene)-cyclohexanone is given in Figure 4.

The calculated values for the studied compounds are given in Table 3. The bond distance of O26–C3 is found significantly shorter for para-nitro-substituted bischalcones compared to others because of its strong electron-withdrawing capacity. Both the benzene rings are ordinary hexagonal shape, with C–C bond lengths (1.40 Å) somewhat in between the typical values for a single bond (1.54 Å) and a double (1.33 Å) bond.21 The two C–C bonds (connecting benzene ring) are in-plane but slightly distorted due to the fixed cyclohexane ring in both sides. In contrast to the protonated form of compound 1e, the dihedral angle of O26–C3–C4–C14 is −4.245°. It clearly indicates that the protonated form is significantly distorted from planarity and deactivates the conjugation of the π-electron. This finding was consistent with the experimental result, where a hypsochromic shift for compound 1e was observed in the presence of the acid.

**Global Reactivity Descriptors and Calculated Frontier Molecular Orbitals.** Frontier molecular orbital analysis is convenient in expecting the electronic transition involved in the conjugated system as well as its reactivity.23 The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) calculations were performed at the same level of theories. The energies of HOMO and LUMO for the studied compounds and the three-dimensional frontier molecular orbital schemes are shown in Figure 5.

It showed that the HOMO and LUMO are located on the whole molecule. Therefore, it exposed that conjugation is predominantly observed for the molecules. According to the quantum theory, the hard molecule has a high HOMO–LUMO gap, whereas a soft molecule has a small HOMO–LUMO gap. In the perception of chemical reactivity, the soft molecules having a small gap would be more reactive than the hard molecules. For the studied bischalcones, compound 1e having a small value of HOMO–LUMO gap indicates a soft molecule with high reactivity and hence promotes eventual charge transfer (CT) interactions within the molecules. Figure 6 shows the contour structure of 2,6-bis(4-dimethylamino-benzylidene)-cyclohexanone that revealed the delocalization of the π-electron.

The $E_{\text{HOMO}}$ energy corresponds to ionization energy (I) and the $E_{\text{LUMO}}$ energy is for electron affinity (A) according to Parr and Nitti.24,25 Quantum chemical parameters such as ionization potential (I), electron affinity (A), chemical hardness ($\eta$), electronic potential ($\mu$), electronegativity ($\chi$), chemical softness (S), and electrophilicity index ($\omega$) were

Table 2. Solvent Effect of Substituted 2,6 Dibenzylidene-cyclohexanone

| substituents (X) | dichloromethane (nm) | ethylacetate (nm) | ethanol (nm) |
|------------------|-----------------------|-------------------|--------------|
|                  | exp.  | calc.  | exp.  | calc.  | exp.  | calc.  |
| H                | 308   | 360    | 323.5 | 359    | 330   | 361    |
| $p$-Cl           | 333   | 366    | 328.5 | 367    | 333   | 368    |
| $p$-NO$_2$       | 340   | 375    | 336   | 352    | 340   | 357    |
| $p$-OCH$_3$      | 340.5 | 367    | 352   | 376    | 359   | 376    |
| $p$-N(CH$_3$)$_2$| 358.5 | 391    | 421.5 | 391    | 452   | 392    |

*Calculated at TD-SDF/DFT/B3LYP/6-311G+(d,p).
Quantum chemical parameters for compounds 1a–1e are $\gamma = -\mu = 4.42, 4.61, 5.41, 4.01, \text{and } 3.52 \text{ eV}$; $\eta = 1/S = 1.96, 1.90, 1.86, 1.82, \text{and } 1.64 \text{ eV}$; and $\omega = 1/\epsilon = 4.98, 5.58, 7.88, 4.42, \text{and } 3.54 \text{ eV}$, respectively. According to these parameters, the chemical reactivity varies with the substituent of bischalcones.

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**Table 3. Selected Bond Lengths, Bond Angles, and Dihedral Angles of Compounds 1a–1e Calculated at the APFD/6-311+G(d,p) Level of Theories**

| bond lengths (angstrom) | H  | p-Cl | p-NO$_2$ | p-OCH$_3$ | p-N(CH$_3$)$_2$ |
|------------------------|----|------|----------|-----------|----------------|
| O26–C3                 | 1.225 | 1.225 | 1.221    | 1.227     | 1.228          |
| C3–C2                  | 1.508 | 1.508 | 1.509    | 1.505     | 1.501          |
| C2–C13                 | 1.352 | 1.352 | 1.348    | 1.354     | 1.352          |
| C13–C27                | 1.454 | 1.463 | 1.462    | 1.460     | 1.454          |
| C27–C29                | 1.408 | 1.408 | 1.407    | 1.405     | 1.406          |
| C29–C32                | 1.390 | 1.389 | 1.384    | 1.391     | 1.381          |
| C32–C34                | 1.395 | 1.392 | 1.389    | 1.398     | 1.411          |
| C34–O47(N38)(Cl38)     | 1.756 | 1.472 | 1.472    | 1.351     | 1.383          |
| O47–(N38)C42(C48)      |      |      |          | 1.423     | 1.453          |
| C3–C4                  | 1.508 | 1.508 | 1.509    | 1.505     | 1.501          |
| C4–C14                 | 1.352 | 1.352 | 1.348    | 1.354     | 1.352          |
| C14–C16                | 1.454 | 1.463 | 1.462    | 1.460     | 1.454          |
| C16–C17                | 1.408 | 1.408 | 1.407    | 1.405     | 1.406          |
| C17–C19                | 1.390 | 1.389 | 1.384    | 1.391     | 1.381          |
| C19–C23                | 1.395 | 1.392 | 1.389    | 1.398     | 1.411          |
| C23–O46(N39)(Cl38)     | 1.756 | 1.472 | 1.472    | 1.361     | 1.383          |
| C46–O38                |      |      |          | 1.423     |                |

| bond angles (deg)      | H  | p-Cl | p-NO$_2$ | p-OCH$_3$ | p-N(CH$_3$)$_2$ |
|------------------------|----|------|----------|-----------|----------------|
| O26–C3–C4              | 120.65 | 120.66 | 120.61    | 120.68     | 120.69          |
| C3–C4–C14              | 115.75 | 115.66 | 115.59    | 115.75     | 115.87          |

| dihedral angles (deg)  | H  | p-Cl | p-NO$_2$ | p-OCH$_3$ | p-N(CH$_3$)$_2$ |
|------------------------|----|------|----------|-----------|----------------|
| O26–C3–C4–C14          | 179.3 | 9.999 | −2.573    | 9.646     | −1.904          |
| C3–C4–C14–C16          | −179.2 | −179.6 | −178.5    | −178.2    |                |

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**EXPERIMENTAL SECTION**

All starting materials and reagents were purchased and used without additional purification unless otherwise noted. UV–vis spectra of the samples were recorded on a UV-180 SHIMADZU spectrophotometer. FTIR spectra of the samples were measured on the IRTracer-100, SHIMADZU, Japan. $^1$H NMR spectra of the samples were measured with an AVANCE Bruker NMR spectrometer at 400 MHz using CDCl$_3$ as the solvent and trimethyl silane as an internal standard. The elemental analysis was performed using a CE-440 elemental analyzer, Exeter Analytical, Inc.

**General Procedure for the Synthesis of Compounds 1a–1e.** A mixture of 1.0 equiv of cyclohexanone, 2.0 equiv of substituted benzaldehyde, and 2.2 equiv of solid NaOH were ground in a mortar for about 30 min at room temperature. The progress of the reaction was monitored by thin-layer chromatography. After the reaction was completed, dilute hydrochloric acid (HCl) was poured carefully for neutralizing the mixture. The obtained solid products were filtered and dried on air. The crude product was purified by recrystallization.
2,6 Dibenzylidene-cyclohexanone (1a). Yellow powder, mp 106 °C, yield 94%. The IR (KBr) spectrum of the product (ν cm⁻¹) was measured. 1H NMR (400 MHz CDCl₃): δ 1.82 – 1.76 (m, 2H, CH₂), 2.93 (t, J = 14.4 Hz, 4H, 2 × CH₂), 3.74 (t, J = 14.4 Hz, 2H, Ar), 7.41 (t, J = 14.4 Hz, 4H, Ar), 7.47 (d, J = 7.4 Hz, 4H, Ar), 7.80 (s, 2H, allylic). Anal. Calcd for C₂₀H₁₆O₅ (364.35): C, 65.93; H, 7.83; N, 7.77; O, 4.44. Found: C, 65.72; H, 4.44; N, 7.59; O, 4.43. Computed structure and Cartesian coordinates of the optimized structure and the non-local correlation functional of LYP. 28 The correlation functional of LYP was used.

2,6-Bis(4-chloro-benzylidene)-cyclohexanone (1b). Yellowish green powder, mp 124 °C, yield 89%. The IR (KBr) spectrum of the product (ν cm⁻¹): 2964, 2927, 1667, 1585, 1576, 1465, 1265, 1160, 821, 800. 1H NMR (400 MHz CDCl₃): δ 1.88 – 1.82 (m, 2H, CH₂), 2.94 (t, J = 10.3 Hz, 4H, 2 × CH₂), 7.59 (d, J = 8.7 Hz, 4H, Ar), 7.81 (s, 2H, allylic), 8.24 (d, J = 8.7, 4H, Ar). Anal. Calcd for C₂₀H₁₆Cl₂O (343.25): C, 69.98; H, 4.70; Cl, 20.66; O, 4.76. Found: C, 69.62; H, 4.54; O, 4.51.

2,6-Bis(4-nitro-benzylidene)-cyclohexanone (1c). Light brown powder, mp 172 °C, yield 91%. The IR (KBr) spectrum of the product (ν cm⁻¹): 2923, 2850, 1669, 1599, 1517, 1491, 1345, 1300, 1268, 1160. 1H NMR (400 MHz CDCl₃): δ 1.84 – 1.77 (m, 2H, CH₂), 2.91 – 2.87 (m, 4H, 2 × CH₂), 7.38 – 7.25 (m, 8H, Ar), 7.73 (s, 2H, allylic). Anal. Calcd for C₂₀H₁₆N₂O₅ (360.49): C, 79.96; H, 7.83; N, 7.77; O, 4.44. Found: C, 79.52; H, 7.74; N, 7.54; O, 4.43.

2,6-Bis(4-methoxy-benzylidene)-cyclohexanone (1d). Pale yellow powder, mp 152 °C, yield 88%. The IR (KBr) spectrum of the product (ν cm⁻¹): 2938, 2827, 1657, 1595, 1199, 1184, 870, 837. 1H NMR (400 MHz CDCl₃): δ 1.84 – 1.78 (m, 2H, CH₂), 2.92 (t, J = 14.2, 4H, 2 × CH₂), 3.85 (s, 6H, 2 × CH₃O), 6.93 (d, J = 8.7 Hz, 4H, Ar), 7.45 (d, J = 8.7 Hz, 4H, Ar), 7.76 (s, 2H, allylic). Anal. Calcd for C₂₂H₂₂O₃ (334.41): C, 79.02; H, 6.63; O, 14.35. Found: C, 78.95; H, 6.53; O, 14.22.

2,6-Bis(4-dimethylamino-benzylidene)-cyclohexanone (1e). Yellow powder, mp 136 °C, yield 79%. The IR (KBr) spectrum of the product (ν cm⁻¹): 2926, 2853, 1645, 1609, 1361, 1302, 1157, 871, 818. 1H NMR (400 MHz CDCl₃): δ 1.83 – 1.79 (m, 2H, CH₂), 2.94 (t, J = 14.1, 4H, 2 × CH₂), 3.01 (s, 12H, 2 × N(CH₃)), 6.71 (d, J = 8.8 Hz, 4H, Ar), 7.45 (d, J = 8.8 Hz, 4H, Ar), 7.76 (s, 2H, allylic). Anal. Calcd for C₂₄H₂₈N₂O (360.49): C, 79.96; H, 7.83; N, 7.77; O, 4.44. Found: C, 79.82; H, 7.74; N, 7.54; O, 4.38.

Computational Details. DFT and time-dependent DFT were calculated using the B3LYP functional combined with the Becke’s three-parameter hybrid functional and the non-local correlation functional of LYP. 29–30 The structures were optimized by the B3LYP/6-311G+(d,p) and APFD/6-311G+(d,p) basis set. The harmonic vibrational frequencies were performed at the same level of theory to find out the local minima for the stationary points. All calculations were done using Gaussian 16, Revision C.01 series of programs.

CONCLUSIONS

Substituted 2,6-dibenzylidene cyclohexanone-based bischalcone derivatives were synthesized, and their structure was determined using UV–vis, FTIR, and NMR spectroscopies and elemental analysis. Significant acidochromic behavior was noticed for 2,6-bis(4-dimethylamino-benzylidene)-cyclohexanone. The absorption maxima shifted from 452 to 322 nm because of the characteristics protonation of the chromophoric N,N-dimethylamino group and the formation of quaternary salt, making the ring strongly deactivated. The result was consistent with computational studies. The synthesized compounds showed solvatochromic behavior. These results indicate that an intramolecular CT occurred because of electron donor–acceptor moieties of the synthesized compounds. A significant bathochromic shift was found for compounds 1a, 1d, and 1e in the increasing order of dichloromethane < ethylacetate < ethanol. These substituents showed positive solvatochromism for (n → π*) absorption in ethanol, whereas a negative solvatochromism was observed (π → π*) for the polar aprotic solvent. Compounds 1b and 1c deviated from this trend and explains that the electronegativity of the carbonyl oxygen of bischalcone is cancelled by the interaction of the electron-withdrawing groups. Computational results revealed that the substituents impart a vital role for its reactivity because of the planarity and effective conjugation.
