**AlCl₃-Catalyzed Cascade Reactions of 1,2,3-Trimethoxybenzene and Adipoyl Chloride: Spectroscopic Investigations and Density Functional Theory Studies**

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**ABSTRACT:** The reaction of 1,2,3-trimethoxybenzene with adipoyl chloride in the presence of AlCl₃ gave two isomeric cyclopentene derivatives, 1,6-bis(2,3,4-trimethoxyphenyl)hexane-1,6-dione, and two demethylation products of aryl methyl ethers. The cyclopentene derivatives including unconjugated or conjugated enones are products formed in a cascade reaction resulting from first the Friedel-Crafts acylation reaction and then aldol condensation. All compounds were optimized by density functional theory calculated using two functional levels, B3LYP and M06-2X, with the 6-311+G(d,p) basis set. The structural properties were established, natural bond orbital analysis of donor−acceptor interactions was carried out, and charges on the atoms and quantum chemical reactivity identifiers were determined to compare the strength of the intramolecular hydrogen bonds formed and their stabilities. To compare the experimental ¹H and ¹³C NMR chemical shifts with the calculated values, NMR chemical shift calculations were carried out using the gauge-invariant atomic orbital method.

1. **INTRODUCTION**

Friedel–Crafts acylation¹,² and aldol condensation³ reactions are two methods widely used to achieve fundamental organic reactions for C–C bond formation. By using these methods, many natural products and derivatives with bromophenol structures have been synthesized.⁴⁻⁹ There are very few studies in the literature in which these two reactions occur consecutively. Miyahara and Ito described a new cyclization method to form five- and six-membered rings (1 and 2) under mild reaction conditions via these two reactions (Figure 1). They reported that unconjugated enones were obtained instead of the more thermodynamically stable conjugated enones obtained by base-catalyzed aldol condensation.¹⁰ They also stated in the references section of the article that in a study by Călin and Frăsineanu, the main product in base-catalyzed aldol condensation of 1,6-bis(2,5-dimethylphenyl)hexane-1,6-dione is an unconjugated cyclocondensation product.¹⁰,¹¹

However, they also reported that they examined the ¹H NMR spectrum of the article and reported that the product was a mixture, and only a small amount of the unconjugated product was formed. Kakemi et al. stated that they synthesized bis(2-hydroxy-3,4-dimethoxyphenyl)alkane dione derivatives by the Friedel–Crafts reaction using 1,2,3-trimethoxybenzene and dicarboxylic chloride derivatives. In that reaction, they only obtained the demethylation product of both aryl methyl ethers in the ortho positions, and then they converted these OH groups to the methoxy groups with dimethyl sulfate.¹² On the other hand, unconjugated enones were formed by acid-catalyzed aldol condensation of 1,4-dibenzoylebutane, also called 1,6-diphenylhexane-1,6-dione.¹⁰,¹³,¹⁴

Very recently, by using these methods, we reported the synthesis of 1,6-diphenylhexane-1,6-dione derivatives (5), cyclopentenyl methanone derivatives 3a and 4a, and their...
hydroxylated derivatives 3b and 4b starting from 3,4-dimethoxybenzene and adipoyl chloride in the presence of AlCl₃ (Figure 1). In this reaction, in which the main product was conjugated cyclocondensation product 3a, substituted cyclopentene derivatives 3a and 4a were isolated in yields of 75 and 16%, respectively (Figure 1). Moreover, unsubstituted cyclopentene and cyclohexene derivatives (with similar structures to 3a and 4a) from cyclocondensation reactions of di(thiophen-2-yl)alkane diones in HCl/HOAc were synthesized.

In our previous work, we synthesized derivatives of compound 5 and investigated their biological activities. The derivatives of these phenolic compounds were observed to have antidiabetic potential in metabolic enzymes as well as important biological activities such as acetylcholinesterase and antioxidant.

In two of these studies, regioselective demethylation of aryl methyl ethers using BBr₃ or Br₂ was observed. Regioselective demethylation in aryl methyl ethers can be achieved using Lewis or protic acids such as AlCl₃, BBr₃, BCl₃, MgBr₂, BeCl₂, HI, and HBF₄. We reported regioselective demethylation in aryl methyl ethers, which occurs with HBr formed in an electrophilic aromatic substitution reaction in the presence of Br₂.

Herein, in continuation of these studies, we decided to investigate in detail the reaction of 1,2,3-trimethoxybenzene and adipoyl chloride in the presence of AlCl₃. Because ortho and para substituted aryl methyl ethers will be formed in this reaction, regioselective demethylation products can be formed by the cascade reaction in the presence of AlCl₃, a Lewis acid. Natural bond orbital (NBO) analysis and molecular electrostatic potential (MEP) analysis were performed, the structural parameters of all compounds were determined, and the gauge-invariant atomic orbital (GIAO) approach for calculating the NMR chemical shifts was applied using density functional theory (DFT) calculations including two functional levels, M06-2X and B3LYP, with the 6-31+G(d,p) basis set.

2. MATERIALS AND METHODS

2.1. Instrumentation and Chemicals. All reagents and solvents were used as purchased from their commercial provider without any purification. All column chromatography studies were performed on silica gel (60-mesh, Merck). Melting points were determined on a melting-point apparatus (Gallenkamp; WA11373) and are uncorrected. The ¹H and ¹³C NMR spectra were recorded on Varian and Bruker spectrometers at 400 (¹H) and 100 MHz (¹³C), and NMR shifts are presented as δ in ppm. The IR spectra were obtained from solutions in 0.1 mm cells with a PerkinElmer spectrophotometer. High-resolution mass spectrometry (HRMS) of all compounds was carried out using a quadrupole time-of-flight spectrometry device (1200/6210, Agilent).

2.2. Computational Details. DFT is an excellent computational method for obtaining vibrational frequencies, molecular interactions, and mechanical insights as well as thermodynamic and kinetic stability. This computational method is also used with hybrid functionals to calculate the structural, optical, and electronic properties of molecular systems and atoms. All computations were performed with the software package Gaussian 09W and carried out by DFT using B3LYP (Becke’s three parameter hybrid functional combined with the Lee–Yang–Parr correlation functional) and M06-2X hybrid functionals with the 6-311+G(d,p) basis set in the gas phase. The results were visualized using the software GaussView 5 and CYLview v1.0,561 BETA for data preparation and visualization of the results.

2.3. Synthesis. 2.3.1. Reaction of 1,2,3-Trimethoxybenzene (6) with Adipoyl Chloride (7) in the Presence of AlCl₃.

To a solution of 1,2,3-trimethoxybenzene (6) (5.0 g, 30 mmol) in CH₂Cl₂ (40 mL) were added adipoyl chloride (7) (2.723 g, 15 mmol) and AlCl₃ (4.37 g, 33 mmol) at rt. It was observed by thin-layer chromatography (TLC) that the reaction was completed at the same temperature after 3 h. Water (50 mL) and CH₂Cl₂ (50 mL) were added to the reaction mixture, consecutively. After the organic phase was separated, the aqueous phase was extracted with CH₂Cl₂ (2 × 50 mL). After the combined organic phases were dried over Na₂SO₄, the solvent was removed in the evaporator. Five stains were observed by TLC of the dark red mixture (9.30 g). The residual mixture was chromatographed on a silica gel column (90 g) with EtOAc/hexane (9:1). Cyclopentene derivatives 8 (1.12 g, 9%) and 9 (1.35 g, 11%) and diketones 10 (1.39 g, 10%), 11 (0.97 g, 8%), and 12 (4.02 g, 32%) were isolated.

2.3.1.1. (2,3,4-Trimethoxyphenyl)cyclopent-2-en-1-ylmethanone (8). Yellow oil, Rf (20% EtOAc/hexane) 0.24; ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.31 (d, A part of AB system, J = 8.7 Hz, 1H, aromatic), 6.89 (d, A part of AB system, J = 8.7 Hz, 1H, aromatic), 6.64 (d, B part of AB system, J = 8.7 Hz, 1H, aromatic), 6.53 (d, B part of AB system, J = 8.7 Hz, 1H, aromatic), 6.33 (bs, 1H, CH, olefinic), 5.04–4.97 (m, 1H, CH, aliphatic), 3.97 (s, 3H, OCH₃), 3.88 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.76 (s, 3H, OCH₃), 2.68–2.48 (m, 2H, CH₂), 2.47–2.34 (m, 1H, CH₂), 2.19–2.07 (m, 1H, CH₂), 13C NMR (100 MHz, CDCl₃) δ (ppm): 202.9 (CO), 156.8 (C), 153.5 (C), 152.6 (C), 151.6 (C), 142.3 (C), 141.9 (C), 139.4 (C), 131.8 (CH),
126.7 (C), 125.6 (CH), 123.8 (C), 123.6 (CH), 107.0 (CH), 106.9 (CH), 61.6 (OCH3), 60.82 (OCH3), 60.80 (OCH3), 60.3 (OCH3), 58.5 (OCH3), 56.0, 55.9, 32.2 (CH2), 29.5 (CH2). IR (CHCl3, cm−1): 3405, 2940, 2840, 1638, 1593, 1494, 1463, 1353, 1285, 1234, 1101, 1052, 1019, 982, 798, 751, 693. HRMS (ESI-TOF) m/z: [M]+ calcd for C28H28O3: 432.1784; found: 432.1779.

2.3.1.5. 1,6-Bis(2-hydroxy-3,4-dimethoxyphenyl)hexane-1,6-dione (12). Light yellow solid, Mp 172−174 °C (Lit.12 175 °C); Rf (20% EtOAc/hexane) 0.09; 1H NMR (400 MHz, CDCl3) δ (ppm): 12.62 (s, 2H, OH), 7.52 (d, A part of AB system, J = 9.1 Hz, 2H, aromatic). 6.48 (d, B part of AB system, J = 9.1 Hz, 2H, aromatic), 3.92 (s, 3H, OCH3), 3.85 (s, 6H, OCH3), 3.87 (s, 6H, OCH3), 1.86−1.80 (m, 4H, CH2) 13C NMR (100 MHz, CDCl3) δ (ppm): 205.2 (CO), 158.7 (C), 157.4 (C), 136.9 (C), 126.4 (CH), 115.1 (C), 103.2 (CH), 60.9 (OCH3), 56.3 (OCH3), 38.0 (CH2), 24.4 (CH2). IR (CH2Cl2, cm−1): 2952, 1637, 1504, 1444, 1421, 1278, 1127, 1074, 990, 870, 784.

2.3.2. Reaction of Diketone 12 with Bromine. After dissolving diketone 12 (0.1 g, 0.24 mmol) in CH2Cl2 (20 mL), Br2 (1 mL) was added dropwise over 5 min at room temperature. After the mixture was stirred at the same temperature for 50 min, the solvent was removed in the evaporator. The solid product formed was crystallized from CH2Cl2 to give tetrabromide 13 (165 mg, 94%).

2.3.2.1. 2.5-Dibromo-1,6-bis(2-hydroxy-3,4-dimethoxyphenyl)hexane-1,6-dione (13). Yellow solid, Mp 181−182 °C; Rf (10% EtOAc/hexane) 0.19; 1H NMR (400 MHz, CDCl3) δ (ppm): 12.08 (s, 2H, OH), 7.73 (s, 2H, aromatic), 5.13−5.05 (m, 2H, CHBr), 4.08 (s, 6H, OCH3), 3.92 (s, 6H, OCH3), 2.53−2.41 (m, 2H, CH2), 2.26−2.18 (m, 2H, CH2). 13C NMR (100 MHz, CDCl3) δ (ppm): 196.6 (CO), 159.0 (C), 156.8 (C), 142.0 (C), 127.9 (CH), 114.4 (C), 106.6 (C), 61.6 (OCH3), 61.4 (OCH3), 45.1 (CHBr), 31.3 (CH2). IR (CH2Cl2, cm−1): 2917, 1626, 1428,

Scheme 1. Reaction of 1,2,3-Trimethoxybenzene (6) with Adipoyl Chloride (7)
1377, 1306, 1268, 1186, 1129, 1055, 991, 958, 822, 801, 755, 736. HRMS (APCI-TOF) m/z: [M + H]⁺ calcd for C₂₂H₂₂Br₄O₈: 730.8126; found: 730.8124.

3. RESULTS AND DISCUSSION

3.1. Chemistry. Initially, by the method described in our previous report, the reaction of 1,2,3-trimethoxybenzene (6) with adipoyl chloride (7) gave 1,6-bis(2,3,4-trimethoxyphenyl)hexane-1,6-dione (10), its ortho demethylation derivatives 11 and 12, and cyclocondensation derivatives 8 and 9 (Scheme 1). NMR spectra of purely isolated isomeric products are found in the Supporting Information. These products, which are also formed by the cyclocondensation reaction, contain different cyclopentene units. Although compounds 8 and 9 are isomeric structures, compound 9 has an α,β-unsaturated carbonyl structure while compound 8 does not. One of these products also contains double bond hydrogen (at 6.33 ppm), while the other does not. Of these isomeric products, it was determined that the one containing the double bond hydrogen was 8 and the other was 9. Purification of such isomeric products by similar methods is also present in the literature.

It is an expected product to form 1,4-dibenzoylbutane derivatives as a result of Friedel−Crafts acylation of a benzene derivative containing methoxy groups with adipoyl chloride in the presence of AlCl₃. This reaction procedure is a standard organic chemistry procedure. Miyahara and Ito studied this acylation reaction of benzene with adipoyl chloride and observed the unconjugated enone 1 as well as 1,4-dibenzoylbutan. However, they did not observe the conjugated enone product. Kakemi et al. reported that bis(2-hydroxy-3,4-dimethoxyphenyl)alkane dione derivatives, which are the only demethylation products of methoxy groups in the ortho position, were formed by the Friedel−Crafts reaction with 1,2,3-trimethoxy benzene and dicarboxylic chloride derivatives having different chain lengths. They isolated only one
In the reaction of 1,2,3-trimethoxy benzene with adipoyl chloride in the presence of AlCl₃, the demethylation product was observed as well as various methoxy derivatives of benzene. However, in this study, in the reaction of 1,2,3-trimethoxy benzene with adipoyl chloride in the presence of AlCl₃, the products were isolated, with 1,4-dibenzoylbutane (10) and two demethylation products 11 and 12, as well as conjugated and unconjugated enone 8 containing cyclopentene units. In terms of the organic synthesis procedure, this study is an exemplary study that can shed light on the formation of both demethylation and cyclization products, especially in the syntheses of 1,4-dibenzoylalkane containing methoxy groups in the ortho position.

Cyclopentene derivatives 8 and 9 were observed in a cascade reaction, also known as a domino or tandem reaction. In the cascade reaction observed, first a Friedel–Crafts acylation reaction and then an aldol condensation reaction took place, which are widely used in organic synthesis. Although conjugated enone 9 is the main product in acid-catalyzed aldol condensation because it is thermodynamically more stable than unconjugated enone 8, they were obtained in very close yields of 11 and 9%, respectively. One methoxy group in the ortho position was demethylated during the formation of 11, while the methoxy groups in both ortho positions were demethylated during the formation of 12. To investigate the effect of bromine on the intramolecular hydrogen bonds formed in these demethylation products, 13 was synthesized from the reaction of 12 with excess bromine (Scheme 2). All spectra and data for synthesized diketones 8–13 are compatible with those of their proposed structures.

3.2. Theoretical Calculations. 3.2.1. Molecular Structure and Stability. Cyclopentenes 8 and 9 and diketones 10–13 were optimized at the 6-311+G(d,p) level by two functional levels, B3LYP and M06-2X, of the DFT method in the gas phase. The optimized geometries of compounds 8–13 using the B3LYP/6-311+G(d,p) basis set are given in Figure 2. To compare the stabilities of conjugated enone 9 and unconjugated enone 8, the structural parameters and total energies of their optimized structures were examined. The relative total energy for conjugated enone 9 at the B3LYP/6-311+G(d,p) level is 1.47 kcal/mol lower than that of unconjugated enone 8. However, the relative energy value for 8 optimized at the M06-2X/6-311+G(d,p) level is 0.98 kcal/mol lower than that of 9. In this case, the structural parameters of these compounds were investigated.

Some selected structural parameters of enones 8 and 9 and diketone 10–13 using the B3LYP/6-311+G(d,p) and M062X/6-311+G(d,p) basis set in the gas phase are given in the Supporting Information (Table S1). The bond length of double bond carbons C13–C18 calculated using B3LYP and M06-2X for 8 was 1.347 Å. The bond length of double bond carbons C11–C13 calculated using these two methods for 9 was 1.349 Å. The C18–C13–C21 bond angle formed between the double bond of the cyclopentene ring and the substituted phenyl group using B3LYP and M06-2X was 129.2° and 126.6° for 8, respectively. The C11–C13–C19 bond angle formed between the double bond of the cyclopentene ring and the substituted phenyl group using B3LYP and M06-2X was 126.9° and 125.6° for 9, respectively. For 9, because the double bond of cyclopentene forms a conjugated system with the carbonyl group and the phenyl group, they must be in the same plane. The bonds that should be in the planar structure were examined using dihedral angles. Comparing the structural parameters calculated by the B3LYP method and the M06-2X method for compounds 8–13, the bond angles and bond lengths were almost the same by the two methods.

The dihedral angles C2−C3−C9−O10 and C4−C3−C9−O10 using B3LYP and M06-2X for 8 and 9 are −114.9° and −113.0° and −32.0° and −15.1°, respectively. These values show that the carbonyl and phenyl groups for both compounds are not in the same plane because of weak conjugation. Similarly, the values of the dihedral angles C11–C13–C19–C21 and C11–C13–C19–C20 calculated by the B3LYP and M06-2X methods for 9 are 130.7° and 139.3° and −50.0° and −40.8°, respectively. According to these values, for 9, the double bond in the cyclopentene ring and in the phenyl group are not in the same plane because of weak conjugation. The planes of the dihedral angles C2–C3–C9–O10 and C4–C3–C9–O10 according to the two methods for 10 are inclined by −173.5° and −165.8° and 7.4° and −15.4° from the skeleton of the molecular plane (Table S1). However, the dihedral angles formed by the carbonyl group and the phenyl group in compounds 11–13 are coplanar because their values are very close to 0° or 180°. While the dihedral angles C2–C3–C9–O10 and C4–C3–C9–O10 between the phenyl and carbonyl groups determined by the B3LYP and M06-2X methods for 12 are 0.2° and 0.6° and 179.6° and −179.5°, respectively, these angles for 13 are −0.8° and −1.4° and 179.3° and 179.4°, respectively. In compound 13, the bromine atom in the molecule weakened the conjugation and intramolecular hydrogen bond. The NBO analyses support these results.

The intramolecular hydrogen bond parameters for 11–13 are listed in Table 1. The structures of 11–13 are stabilized by intramolecular O⋯H−O hydrogen bond interactions formed between the hydrogen of the OH groups and the oxygen atoms of the carbonyl group (Table 1).

3.2.2. NBO Analysis. NBO analysis, which is mostly used to investigate intramolecular interactions, hydrogen bonds, and charge transfers, is a useful theoretical method for measuring hyperconjugative interactions between atoms and molecules.52,53 A larger stabilization energy (E^2) value shows a more intense interaction between electron donors and electron acceptors, leading to more conjugation in the system. The energies of these interactions can be calculated by second-order perturbation theory using the following equation:

\[ E^2 = \sum_{ij} \frac{f_{ij}^2}{E_{ij}} \]
In Table 2, it can be clearly seen that the bromine atom in the compound 13 weakens the hydrogen bond by lowering the stabilization energy formed between the oxygen atom of the carbonyl group and the hydrogen atom of the OH group. All charges on atoms by NBO analysis using B3LYP/6-311+G(d,p) and M06-2X/6-311+G(d,p) basis sets for compounds 8–13 are given in the Supporting Information (Table S3).

### 3.2.3. NMR Spectral Analysis

The $^1$H and $^{13}$C chemical shift calculations of 10–13 were performed using the GIAO method$^{58,59}$ by B3LYP and M06-2X with the 6-311+G(d,p) basis set in the CDCl$_3$ with respect to tetrakis(dimethylamino)ethane (TMS). Experimental $^1$H and $^{13}$C NMR spectra of 10–13 are available in the Supporting Information (Table S4).

$$\Delta E = \Delta E_{ij} = q_i F_{ij}^{(2)} - e_j - e_i$$

where $q_i$ is the donor orbital occupancy, $e_j$ and $e_i$ are diagonal elements, and $F_{ij}^{(2)}$ is the off-diagonal NBO Fock matrix element.
given in Figures 3 and 4, respectively. In phenolic compounds containing a carbonyl group in the ortho position, strong intramolecular hydrogen bonds are formed between the oxygen atom of the carbonyl group and the hydrogen atom of the OH group. This OH proton forming the strong hydrogen bond resonates as a singlet in the $^1$H NMR spectrum in the range of about 12–13 ppm. When this hydrogen bond is stronger, it resonates in the downfield (toward 13 ppm), and when it is weaker, it resonates in the upfield (toward 12 ppm). On the other hand, phenolic OH protons generally resonate between 6 and 10 ppm. In compounds 11 and 12, the OH protons resonate in the lower field, while this proton in compound 13 resonates in the higher field. This shows that the hydrogen bond in compound 13 is weaker than in compounds 12 and 13. Surprisingly, stronger hydrogen bonds were expected because of the inductive effect of the bromine atoms at the alpha position of the carbonyl group in compound 12, while weaker hydrogen bonds were formed. Similarly, in the $^{13}$C NMR spectra of compounds 11 and 12, the carbon atom of the carbonyl group forming the hydrogen bond resonated in the lower field, while this carbon atom in the compound 13 resonated in the higher field. Computational studies have also been carried out to support these experimental data. Because the bromine atom in the molecule...
weakens the hydrogen bond, the calculated chemical shift values of the carbon atom in the carbonyl group and the hydrogen atoms in the hydroxyl group were compared with the experimental values (Table 3). Both atoms were observed in the most downfield region in the experimental and calculated $^1$H and $^{13}$C NMR spectra. As seen in Table 3, the experimental resonance signals of the $\text{−OH}$ protons for 11 (H35), 12 (H34, H36), and 13 (H30, H32) were the most downfield signals at $\delta$ 12.64, 12.62, and 12.08 ppm as a singlet in the $^1$H NMR spectra, while the theoretical chemical shift values for these hydrogen atoms were obtained at $\delta$ 12.95, 12.89, and 12.77 ppm at the B3LYP level and $\delta$ 12.84, 12.60, and 12.04 ppm at the M062X level. In the experimental $^{13}$C NMR spectra, chemical shift values for 10 (C9 or C23), 11 (C9, C23), 12 (C9 or C23), and 13 (C8 or C20) were observed in the most downfield signal at 201.06, 200.73–205.52, 205.17, and 196.60, respectively. The theoretical chemical shift values for these carbon atoms of carbonyl groups were obtained at $\delta$ 207.09, 206.56, 214.53, 213.92, and 206.45 ppm at the B3LYP level and $\delta$ 220.98, 219.00, 229.07, 228.00, and 219.53 ppm at the M062X level, respectively.

The maximum deviation from the experimental chemical shift for the $^{13}$C NMR chemical shift is 9.85 ppm for 13 (C8, C20) at the B3LYP level and 23.55 ppm for 11 (C23) at the
Table 3. Experimental and Calculated \(^1\)H and \(^{13}\)C Isotopic Chemical Shift Values (with Respect to TMS, All Values in ppm) of Hydroxyl Hydrogen and Carbonyl Carbon of 10–13

| compound | atom     | B3LYP   | M06-2X  | experimental |
|----------|----------|---------|---------|--------------|
| 10       | C9, C23  | 207.09  | 220.98  | 201.06       |
| 11       | C9       | 206.56  | 219.00  | 200.73       |
|          | C23      | 214.53  | 229.07  | 205.52       |
| 12       | H35      | 12.95   | 12.84   | 12.64        |
|          | H34, H36 | 12.89   | 12.60   | 12.62        |
| 13       | C8, C20  | 206.45  | 219.53  | 196.60       |
|          | H30, H32 | 12.77   | 12.04   | 12.08        |

M062X level. In the \(^1\)H NMR chemical shift, the maximum deviation from the experimental value is 0.69 ppm for 13 (H30, H32) at the B3LYP level and 0.2 ppm for 11 (H35) at the M062X level. In general, when compared with the experimental data, it was observed that the B3LYP level gave closer \(^{13}\)C NMR values, while the M062X level gave more consistent \(^1\)H NMR values. The calculated \(^1\)H NMR and \(^{13}\)C NMR chemical shift values of 8–13 (Table S2) and the experimental NMR spectra of all compounds are presented in the Supporting Information.

3.2.4. FMO Analysis. FMO analysis is widely used to predict the kinetic stability of molecules and the most reactive sites in conjugated systems. The stability and reactivity of a molecule are related to the difference in the highest occupied molecular orbital (HOMO)—lowest unoccupied molecular orbital (LUMO) energy gap (\(\Delta E = E_{\text{HOMO}} - E_{\text{LUMO}}\)). FMO analysis was performed for 8–13 using the B3LYP/6-311+G(d,p) and M062X/6-311+G(d,p) basis set in the gas phase (Figure 5).

![Figure 5. Frontier molecular orbitals of 8–13 using the B3LYP/6-311+G(d,p) basis set.](https://doi.org/10.1021/acsomega.2c04612)

The HOMO and LUMO energy values for 8–13 were calculated in eV (Figure 5). The frontier energy gaps (\(\Delta E\)) of 8–13 are 4.5614, 4.1274, 4.9454, 4.4891, 4.6633, and 3.8659 eV, respectively (Table 4). There is an important relationship between chemical stability and the energy gap between the HOMO and the LUMO. Chemical stability generally tends to increase with the large values of the energy gap (\(\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}}\)). Accordingly, we can presume that compound 10 (\(\Delta E = 4.9454\) eV) is the most stable compound, while compound 13 is the most reactive compound (\(\Delta E = 3.8659\) eV) (Table 4).

In the case of the HOMO, the charge density for 8 and 9 is mainly accumulated on the cyclopentene ring and its substituted phenyl ring. There is a very small contribution on the carbonyl group. However, in the case of the LUMO, the charge density for 9 spreads out from the phenyl group toward the other phenyl group, while the charge density for 8 spreads out from the cyclopentene ring toward the benzoyl group. In the case of the LUMO, the charge density for 11 spreads out on the benzoyl group with the phenol ring. In the HOMO, the density is only on the phenol ring. In symmetric compounds 10, 12, and 13, these charge densities spread out from the aromatic ring to the carbonyl group. The energy gap in compound 13, which is formed by adding four bromine atoms to compound 12, decreased by 0.5 eV. In this case, we can consider that the reactivity of compound 13 is greater than that of compound 12.

Global reactivity descriptors are important quantum chemical parameters used to predict the stability or reactivity of molecules. According to Koopman’s theorem,\(^{37}\) ionization energy (\(I = -\text{HOMO}\)) and electron affinity (\(A = -\text{LUMO}\)) are related to the HOMO and LUMO energies. In this paper, we also present values of reactivity descriptors such as global hardness (\(\eta\)), global softness (\(\sigma\)), electronegativity (\(\chi\)), chemical potential (\(\mu\)), and electrophilicity (\(\omega\)) calculated by the following equations (Table 4):\(^{54–56}\)

\[
\eta = (I - A)/2
\]
\[
\sigma = 1/\eta
\]
\[
\chi = (I + A)/2
\]
\[
\mu = -(I + A)/2
\]
\[
\omega = \mu^2 / 2\eta
\]

3.2.5. Molecular Electrostatic Potential. The MEP surfaces of 8–13 are illustrated in Figure 6. The MEP gives visual information about determining reactive sites for electrophilic and nucleophilic attacks and hydrogen bond interactions as well as total charge density formed in the molecule.\(^{37}\) Red depicts the electron-poor regions (negative side) in the molecule, while blue shows the electron-rich areas (positive side).

The electron-poor red regions in compounds 8–10 are mainly located around the carbonyl group. On the other hand, the electron-rich regions (blue) are on the benzene rings (for 8 and 10), cyclopentene (for 8 and 9), and CH\(_3\) groups (for 10) (Figure 6). In compounds 11 and 12, the electron-poor regions are located on the carbonyl groups and the methoxy groups adjacent to the hydroxyl groups, while in compound 13, the regions where the carbon atoms to which the bromine is attached are quite rich in electrons.

4. CONCLUSIONS

We synthesized two isomeric cyclopentene derivatives (8 and 9) and three 1,4-dibenzoylbutane derivatives (10–12) starting from 1,2,3-trimethoxybenzene with adipoyl chloride in the presence of AlCl\(_3\) in just one step. The formation of compounds 8 and 9 occurs by a cascade reaction, also known as a domino reaction or tandem reaction, resulting from the Friedel–Crafts reaction and then aldol condensation.
OH groups in the diketones 11 and 12 were formed by regioselective demethylation of the methoxy groups because they are at the ortho position of the carbonyl groups. These OH groups also form strong hydrogen bonds. Tetrabromide 13 was synthesized from the reaction of diketone 12 with excess bromine. All compounds were optimized by means of DFT calculations using two functional levels, B3LYP and M06-2X, with the 6-311+G(d,p) basis set. The same method was used to calculate the structural parameters and for NBO, FMO, and MEP analysis of all compounds, as well as for the GIAO approach for calculating the NMR chemical shifts. It was observed that the bromine atom in tetrabromide 13 weakened the conjugation and intramolecular hydrogen bonding in the molecule.

In terms of the organic synthesis procedure, this study is an exemplary study that can shed light on the formation of both demethylation and cyclization products, especially in the syntheses of 1,4-dibenzoylalkane containing methoxy groups in the ortho position.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04612.

Spectroscopic data (¹H and ¹³C NMR spectra) of the products; selected structural parameters, cartesian coordinates; and NBO charges for the optimized structures (PDF)

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**Table 4. Quantum Chemical Reactivity Identifiers (eV) of 8–13**

| parameters | 8    | 9    | 10   | 11   | 12   | 13   |
|------------|------|------|------|------|------|------|
| I          | 5.6526 | 5.6270 | 6.3547 | 6.2257 | 6.3218 | 6.5500 |
| A          | 1.0912 | 1.4996 | 1.4093 | 1.7366 | 1.8585 | 2.6841 |
| ∆E         | 4.5614 | 4.1274 | 4.9454 | 4.4891 | 4.4633 | 3.8659 |
| η          | 2.2807 | 2.0637 | 2.4727 | 2.2446 | 2.2317 | 1.9330 |
| σ          | 0.4385 | 0.4846 | 0.4044 | 0.4455 | 0.4481 | 0.5173 |
| χ          | 3.3719 | 3.5633 | 3.8820 | 3.9812 | 4.0902 | 4.6170 |
| μ          | −3.3719 | −3.5633 | −3.8820 | −3.9812 | −4.0902 | −4.6170 |
| ω          | 2.4926 | 3.0763 | 3.0473 | 3.5307 | 3.7482 | 5.5139 |
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