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Determination of the enol form of asymmetric 1,3-dicarbonyl compounds: 2D HMBC NMR data and DFT calculations

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Abstract: In this study, a series of asymmetric aryl 1,3-dicarbonyl compounds were synthesized and their enol forms were observed *via* experimental data and theoretical calculations. According to the ^1H - and ^{13}C -NMR results, all the investigated compounds were found as a single enol form in CDCl_3 solution. Moreover, their HMBC spectra were applied to identify the observed enol forms and correlations between certain protons and carbon atoms were considered. The dihedral angles of the asymmetric compounds that have aryl units on both sides were calculated by DFT to understand the reason for the observed enol forms. Small dihedral angles caused longer conjugation, resulting in more stable compounds and it was found that the observed enol forms were based on small dihedral angles, namely, resonance is the driving force. Furthermore, the compounds possessing both aryl and alkyl moieties prefer the enol form towards the aromatic ring side due to longer conjugation.

Keywords: enol tautomerism; dihedral angle; HMBC correlation.

INTRODUCTION

Tautomerism is a type of isomerism. It is a special area in organic chemistry, biochemistry, medicinal chemistry, pharmacology and molecular biology.¹ It explains many organic reactions and biochemical activities, such as important interactions with proteins, enzymes, and receptors, which make it essential to understand tautomerization.² Various tautomers have different molecular fingerprints, hydrophobicities, $\text{p}K_{\text{a}}$ values, 3D geometry and electrostatic properties.³ This can be seen in heterocyclic natural compounds and biomolecules. It is difficult to decide which tautomer plays a specific role in the biological activity, thermodynamically the most or least stable. Research of many special biological processes show that an effective intermediate is often the energetically less stable tautomer, which drives the mechanism and could be the reason of a specific product.⁴ For these reasons, quantification of the tautomer proportion is very imp-

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ortant. In addition, protein–ligand interaction studies show that exchange of a hydrogen atom may convert an acceptor into a donor and change the interactions of a protein–ligand complex. This is one of the most important reasons why tautomerism has gathered the attention of the molecular modelling community.²⁴ The tautomerism of 1,3-dicarbonyl compounds is one of the main subjects in physical organic chemistry. These compounds are found in UV-A sunscreens due to their strong UV absorption in the wavelength range 320–400 nm and photostability. One of the few UV-A sunscreens approved both in the USA and in Europe at the present time is 1-(4-*tert*-butylphenyl)-3-(4-methoxyphenyl)propane-1,3-dione, which is known as avobenzone and parsol.⁶

The existence of both keto and enol forms for 1,3-dicarbonyl compounds was proved by Claisen, Wislicenus and Knorr for different molecules. Claisen also found that the ratio of the keto–enol tautomers depends on various factors, such as temperature, nature of substituents and solvent.⁵ There are many examples of substituted 1,3-dicarbonyl compounds in early reports and in some of them, the effects of solvent, temperature and substituent on the keto–enol equilibrium are described.^{6–8} As is known, two possible enol forms for asymmetric 1,3-dicarbonyl compounds exist. However, the reasons for the observed enol form have rarely been described.^{9–11} Swarts and his group identified the observed enol form of some 1,3-dicarbonyl derivatives and discussed the reasons using cyclic voltammetry data, and electronic and resonance driving forces.^{9–11} To the best of our knowledge, the research group has not studied the characterization of different enol forms using 2D NMR spectra and explained the cause with dihedral angles. In the present study, the dominant tautomers of the synthesized 1,3-dicarbonyl compounds and reasons of observed enol forms were discussed in terms of 1D, 2D NMR data and DFT calculations.

EXPERIMENTAL

General methods

The NMR spectra were recorded on a 400 MHz spectrometer. Infrared (IR) spectra were recorded in the range 4000–600 cm^{-1} via an ATR diamond. The melting points were determined using a melting point apparatus and are uncorrected. The mass spectra were recorded by the LC–MS TOF electrospray ionization technique. Column chromatography was performed on silica gel (60-mesh), TLC was realised on 0.2 mm silica gel 60 F₂₅₄ analytical aluminium plates. Evaporation of solvents was performed at reduced pressure using a rotary vacuum evaporator.

Geometrical parameters of molecules were fully optimized at the hybrid density functional B3LYP (Becke-3-parameter-Lee-YangParr)^{16,17} level using the 6-311 G(d,p) basis set implemented in Gaussian 09,¹⁸ as a good compromise between accuracy and computational cost. In order to account for the polarization effects of the solvent, single point energy calculations using the polarisable continuum model¹⁹ (PCM) were performed at the PCM/B3LYP/6-311G(d,p) level with chloroform as the solvent since it was used in the experimental study. PCM is a common method to compute the polarization effect of the solvent implicitly as a dielectric continuum. Theoretical background of PCM and related solvation methodologies

was recently reviewed in detail by Tomasi *et al.*²⁰ Absolute values of NMR shielding were calculated using the gauge-independent atomic orbital method with the restricted closed shell formalism employing the 6-311 G(d,p) basis set over B3LYP/6-311G(d,p) optimized geometries.²¹

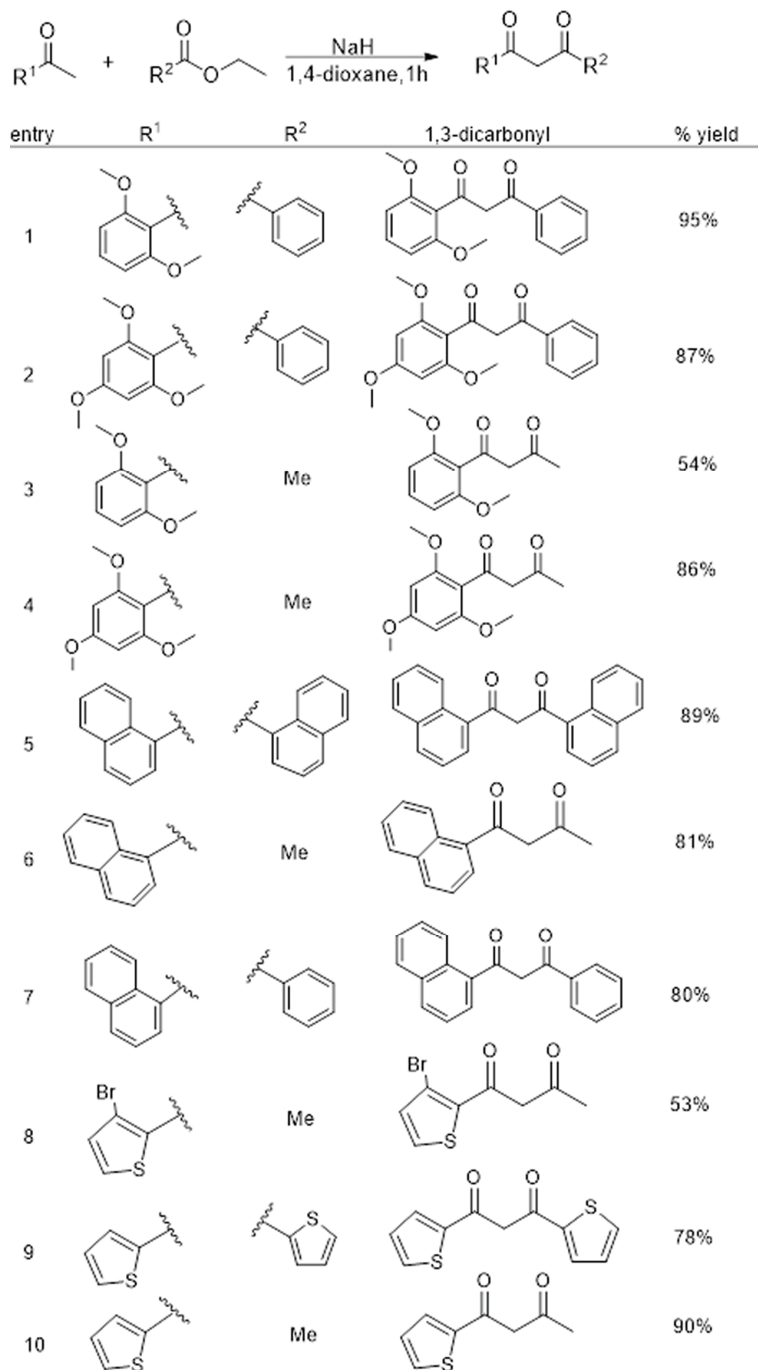
General procedure for the synthesis of compounds 1–10

A methyl ketone (1 eq.) was added to dry 1,4-dioxane and NaH (60 % oil suspension, 5 eq.) was added in portions to the mixture in an ice-bath. The resulting mixture was stirred at room temperature for 1 h. The required ester (5 eq.) was added to the mixture and refluxed for 1 h. After cooling, 10 % HCl solution was added to the reaction mixture and extracted with CH₂Cl₂ (3×20 mL). The crude product was dried over MgSO₄. Recrystallization or column chromatography gave the product, which was dried *in vacuo* (25 °C, 0.5 mbar), affording spectroscopically pure product.¹² More details of the syntheses of the individual products and their spectral data are given in the Supplementary material to this paper.

RESULTS AND DISCUSSION

Based on the previously reported methods, 1,3-dicarbonyl compounds were obtained by Claisen condensation using commercially available acetyl ketones and the appropriate esters. Pieces of sodium hydride (60 % oil suspension, 5 eq.) were added to a solution of acetyl ketone (1 eq.) in dry 1,4-dioxane cooled in an ice-bath and stirred at room temperature for 1 h. Then the required ester (5 eq.) was added to the reaction mixture and refluxed for 1 h (Scheme 1).

Compounds 1–10 were isolated by column chromatography and characterized by ¹H-, ¹³C-NMR, and FT-IR spectroscopies. In CDCl₃ solution, all molecules 1–10 were in the enol form, which was manifested by the signal of the R¹⁽²⁾C(=O)CH=C(OH)R²⁽¹⁾ (6–6.5 ppm) enol form in the NMR spectra. For example, in ¹H-NMR spectrum of the compound 6, the characteristic signal of the enol form was observed at 6.04 ppm. Moreover, presence of the hydroxyl group R¹⁽²⁾C(=O)CH=C(OH)R²⁽¹⁾, which may not always appear, proved the enol form with a single resonance at 16.12 ppm (Fig. 1). Compounds 1–10 showed the same characteristic signals in the NMR spectra (see the Supplementary material to this paper). The ¹H- and ¹³C-NMR spectra of compounds 1–10 were recorded in CDCl₃. Since the polarity of CDCl₃ is low when compared with D₂O, CD₃OD and DMSO-*d*₆, the keto–enol tautomerism shifts to the enol form for all the studied compounds. It is well known that the keto–enol tautomerization depends on polarity of solvent and this could be explained in terms of the solvation of the carbonyl groups by the molecules of a polar solvent, thus increasing the relative stability of the keto form.¹³ Moreover, the formation of an intramolecular hydrogen bond leads to the enol form having a pseudo-cyclic system in its structure, which is more favourable in non-polar solvents. The *cis*-enol forms of 1,3-dicarbonyl compounds are stabilized by a strong intramolecular hydrogen bond.⁷ The hydrogen bond formation leads to an enhancement of the resonance conjugation of the π-electrons, which causes a marked tendency for equalization of the bond order of the valence bonds in the resulting pseudo six-member chelated ring.⁸

Scheme 1. Synthesis of the substituted 1,3-dicarbonyl compounds **1–10**.

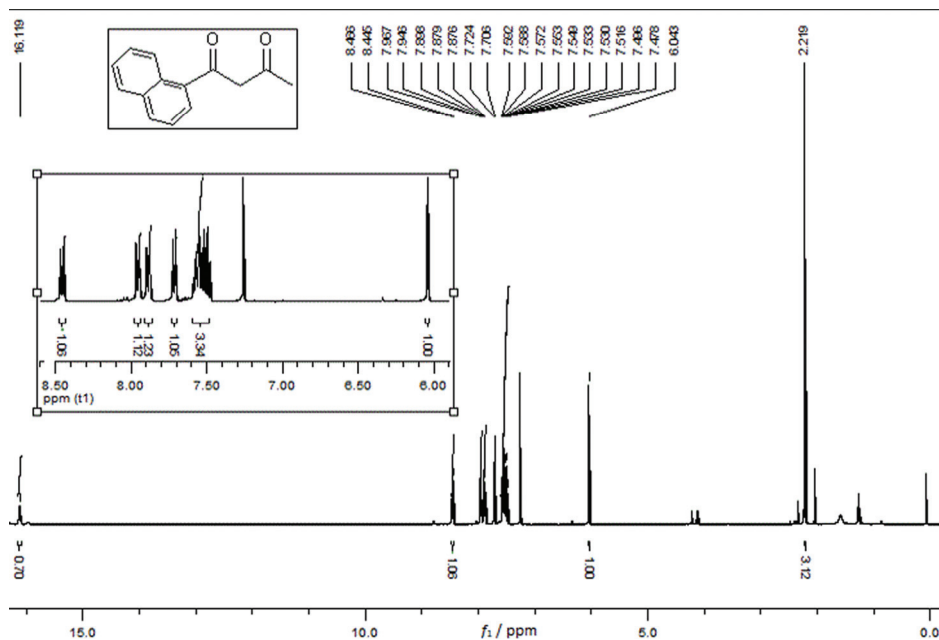


Fig. 1. ¹H-NMR spectrum of compound **6** (400 MHz, CDCl₃).

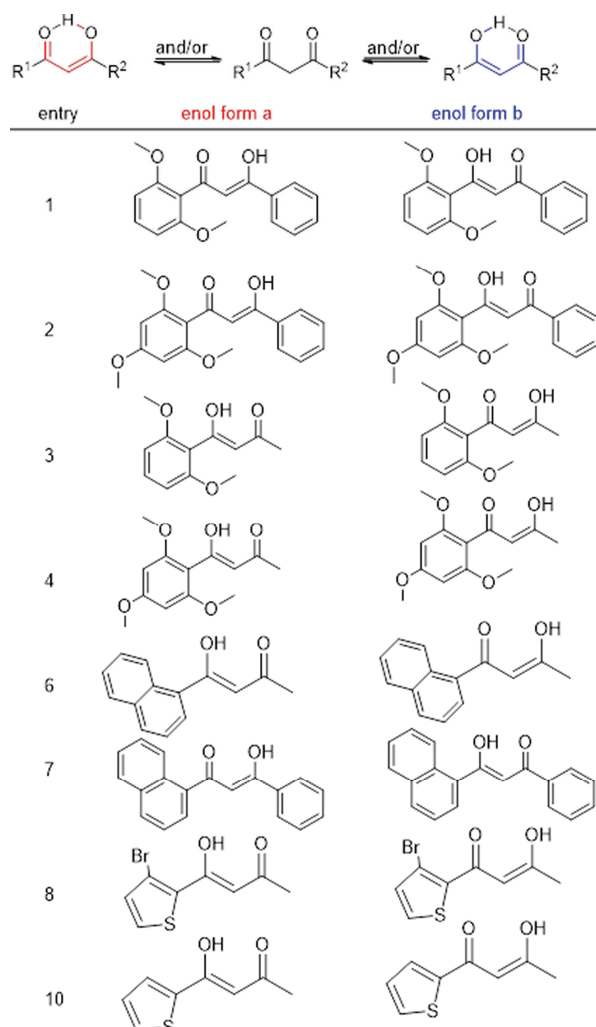
Determination of the enol forms by 1D NMR spectroscopy

Any factor that affects the electronic properties of the chelated ring changes the intramolecular hydrogen bond strength and the tautomerization equilibrium. If R¹ and R² substituents are electronically different, one of the enol forms might be more stable than the other. This fact has been established by theoretical and experimental studies, such as quantum-mechanical calculations, FTIR, Raman, microwave and NMR spectroscopies, and X-ray, electron and neutron diffraction measurements.¹⁴

The key point for enol tautomerization is to define the side of the substituents of the enol form when they are different (Scheme 2). This issue was the focus of this study.

The synthesized asymmetric 1,3-dicarbonyl compounds **1–4**, **6–8** and **10** possess two potential enol forms that are shown in Scheme 2.

Application of the 1D-NMR technique for characterization of compounds gives simple information that the molecule possesses keto or enol form. It has already been identified that all compounds are in the enol form. However, although all reactions were realised at room temperature, it was decided to control whether or not any keto or enol form could be identified by changing temperature while recording NMR data. The ¹H-NMR experiments were therefore recorded for compound **2** at 50, 25, 15, –10 and –20 °C (Fig. 2). The chemical shifts of compound **2** at room temperature are shown in Fig. 3.



Scheme 2. Asymmetric compounds **1–4**, **6–8** and **10** with two possible enol forms.

It can be seen in Fig. 2 that there was only one form belonging to the enol tautomer that was characterized with the $R^{1(2)}C(=O)CHC(OH)R^2$ proton resonating at 6.41 ppm. The 1H -NMR data recorded at different temperatures showed that no keto form or second enol were present. The only observed change was a broadening of the signals. This NMR scan allowed ensured that only one enol form was present, even when the temperature was changed.

However, 1H -NMR data is not sufficient to distinguish possible enol forms. It is known that 1,3-dicarbonyl compounds might have two enol forms when bearing two different substituents, enol forms *a* and *b* (Scheme 2). For this reason, 2D HMBC NMR data of the compounds were recorded.

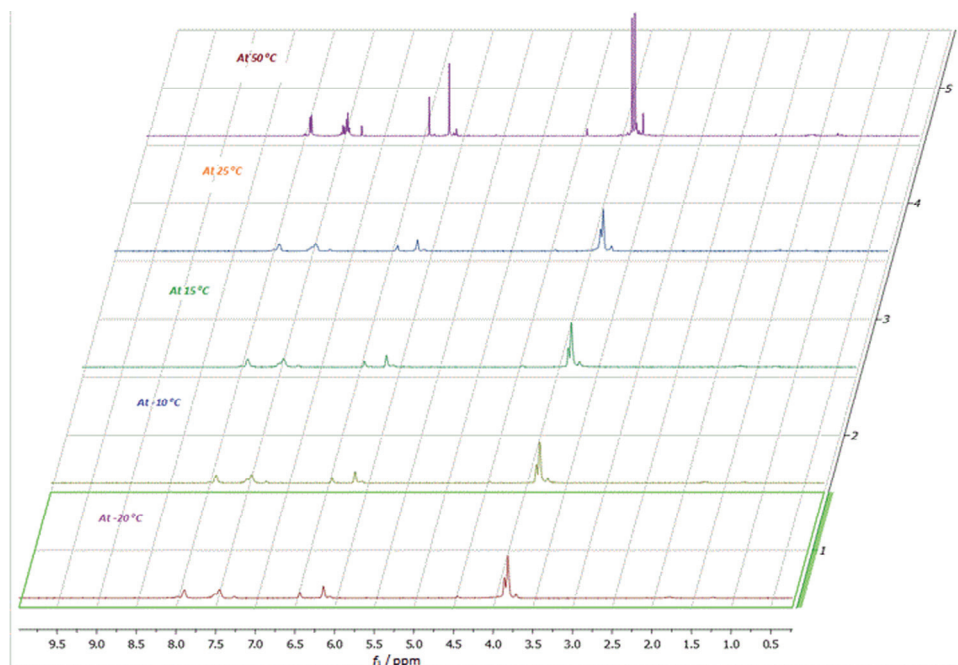


Fig. 2. $^1\text{H-NMR}$ scanning data for compound **2** (400 MHz, CDCl_3).

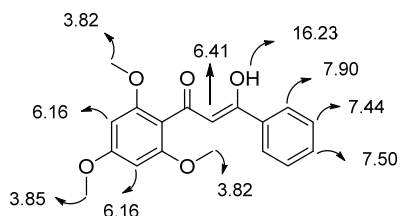


Fig. 3. $^1\text{H-NMR}$ data for compound **2** at 25 °C (400 MHz, CDCl_3).

Determination of tautomers using 2D HMBC NMR

2D HMBC NMR spectroscopy was applied to reveal observed enol form and for this reason, correlations between certain protons of R^1 or R^2 group and C_1 or C_2 carbon atoms were utilized (Fig. 4).

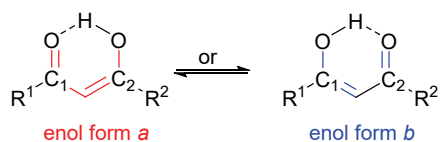


Fig. 4. Interconversion of enol forms to each other.

However, as shown in Table I, the carbon atoms of $\text{R}^1(2)\text{C}(=\text{O})\text{CH}=\text{C}(\text{OH})\text{R}^2(1)$ and $\text{R}^1(2)\text{C}(=\text{O})\text{CH}=\text{C}(\text{OH})\text{R}^2(1)$ have similar chemical shifts and the chemical shifts could not be distinguished from one

another. In this respect, the correlations between H and C atoms cannot be clarified. Starting from this point of view, theoretical ^{13}C -NMR data of both enol forms *a* and *b* were calculated to determine which chemical shift belongs to the carbonyl group. The calculated ^{13}C -NMR data for both enol forms for all compounds showed that the carbonyl carbons were responsible for the peaks with chemical shifts at the lowest field. With the available information, the correlation between the carbon atom of the carbonyl group and the hydrogen atom of the aryl group would reveal the groups connected to each other.

TABLE I. Theoretical and experimental chemical shifts, ppm, of two possible enol forms of compounds **1–4**, **6–8** and **10**

Entry	Theoretical C=O	Experimental C=O	Theoretical C–OH	Experimental C–OH
1a	201.5	189.4	179.0	181.5
1b	194.0		185.2	
2a	199.2	188.7	177.8	181.4
2b	193.8		184.1	
3a	202.9	189.5	182.4	186.9
3b	201.8		186.8	
4a	204.6	189.5	181.6	186.0
4b	198.9		184.8	
6a	206.3	192.3	186.8	188.4
6b	201.7		189.2	
7a	202.0	190.7	181.7	184.5
7b	195.1		189.2	
8a	205.6	190.9	174.6	178.8
8b	186.0		188.3	
10a	205.3	187.3	173.5	181.7
10b	186.7		188.4	

Identification of enol forms by 2D HMBC NMR correlation

Compound **6**, which includes a naphthalene ring and an acetyl unit, has two possible enol forms, *i.e.*, **6a** and **6b**. According to the HMBC spectrum, carbon atom of C=O group and carbon atom of C(OH) group resonate at 192.3 and 188.4 ppm, respectively (Fig. 5). These signals are compatible with theoretical NMR data. Carbonyl carbon has a correlation with methyl protons, which resonate at 2.22 ppm ($\text{C}_1\text{--H}_9$). This means that the methyl group is connected to the carbonyl group. On the other hand, a correlation between carbon atom of C(OH) and the β proton of the naphthalene ring resonating at 7.73 ppm ($\text{C}_2\text{--H}_{18}$) was also observed. With the information at hand, it could be stated that the observed enol form of compound **6** is **6a**, shown in Scheme 2.

A similar situation was observed when the correlations of compound **7** were analysed. The carbon atoms of the C=O and C(OH) groups of compound **7** resonate at 190.7 and 184.8 ppm, respectively (Fig. 6). The carbon atom of carbonyl group correlates with a proton of the naphthalene ring resonating at 7.62 ppm

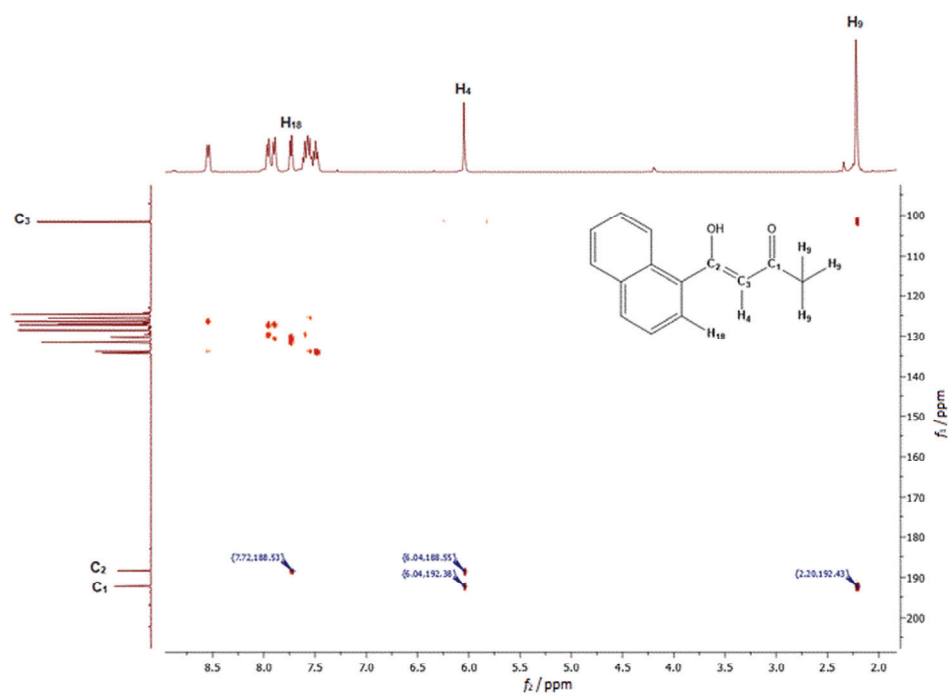


Fig. 5. HMBC spectrum of compound 6.

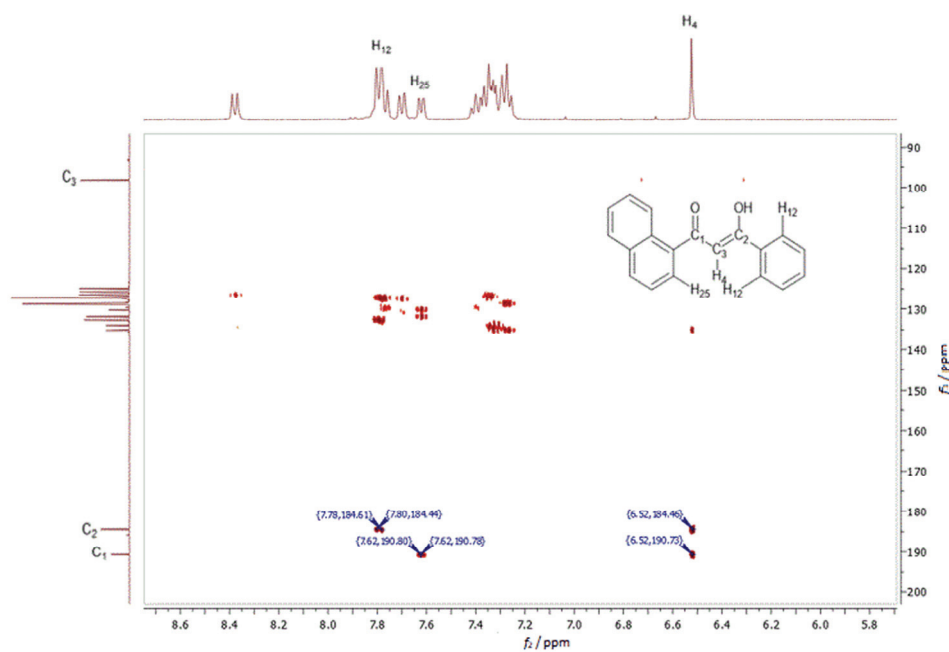


Fig. 6. HMBC spectrum of compound 7.

and the carbon atom of the C(OH) group correlate with two protons of phenyl ring resonating at 7.80 ppm (C₂-H₁₂). According to the obtained results, the carbonyl group is connected to the naphthalene ring and C(OH) group is connected to the phenyl ring, resulting in compound **7a** (Scheme 2).

After identification of all correlations (for all spectra, see Supplementary material), it was concluded that the enol form *a* was the observed enol form for all compounds.

Dihedral angle studies using the DFT

Observed enol form and the reasons for its formation have rarely been reported and none of the studies were based on 2D NMR data and DFT calculations. Swarts *et al.* described that two driving forces, electronic and resonance driving forces, may determine the preferred enol isomer of 1,3-diketones. The former implies that the group electronegativity, χ_R , of the substituents R and R' on the 1,3-dicarbonyl (R'C(=O)CH₂C(=O)R) will determine which of enol isomers will be favoured. However, the electronic driving force is not applicable in determining which of enol isomers will be observed when either R or R' is an aromatic group, such as ferrocenyl or phenyl. On the other hand, the resonance driving force was suggested to determine the observed enol form by using bond distances arising from crystallographic determinations.⁹⁻¹¹

Due to difficulties in X-ray analysis and the lack of a general theoretical method, a theoretical method to predict was sought to predict which enol form could be the most abundant. It is well known that the dihedral angle affects conjugation, resonance and aromaticity.^{15,16} Based on the resonance driving force, it was decided to compare the contributions of the tautomers to conjugation *via* the dihedral angles (twist angle) and therefore, the dihedral angles were calculated for both possible enol forms. The obtained hybrid compounds were subjected to conformational analysis at the B3LYP/6-311G(d,p) level to obtain the most stable geometry of the optimized structures. The connection between aromatic and alkyl moieties was free rotation, resulting in an infinite number of conformations. Therefore, the C₂-C₃ bond was rotated around itself by 5 degrees in each step to observe the energy change through rotation.

Maximum conjugation makes a molecule more stable.^{22,23} In this study, it was assumed that a plane could be found that correlated with the observed enol form, which was called the enol plane. If the dihedral angle of the enol plane of dicarbonyl compounds is 0 or 180°, the molecule will reach maximum planarity resulting in the largest conjugation (θ of C₁-C₂-C₃-C₄ in Table II – the enol forms *a* and *b*). The dihedral angle was calculated between the C₁=C₂ double bond of the enol form and C₃=C₄ double bond of the aromatic ring, which makes an enol plane and minimum dihedral angle of any enol conformer, could determine the observed enol form, which was confirmed by 2D-NMR. It should also

be noted that the conjugation would be extended from the enol plane and deviation from the dihedral angle for enol plane would be undesired. For this reason, the dihedral angles of the enol plane were calculated for both enol forms *a* and *b* of the aryl–aryl substituted dicarbonyl compounds **1**, **2** and **7** after dihedral scanning in which the conformers in the lowest energy were determined (see the Supplementary material). The results of the calculations are summarized in Table II. From this idea, the predicted and determined enol form *a* should possess a smaller dihedral angle than the enol form *b* (Fig. 7). The alkyl–aryl and symmetrical aryl–aryl compounds were not subjected to dihedral scans as they have only the possibility of one enol form.

TABLE II. Dihedral angles of the enol plane ($^{\circ}$) of the most stable conformer of the two possible enol forms for compounds **1**, **2** and **7**

Compound	Enol form <i>a</i>	Enol form <i>b</i>
1	14.68	65.61
2	14.55	55.49
7	15.49	45.49

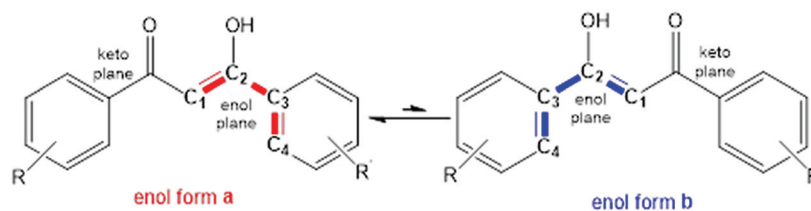


Fig. 7. Possible enol planes of compounds **1**, **2** and **7**.

A dihedral scanning study was performed on compound **1** and the most and the least stable conformers of the two possible enol forms were determined (Fig. S-41 of the Supplementary material). According to this study, the dihedral angle of enol plane for **1a** was found to be 14.68° (Fig. 8a and b). This conformer is the most stable conformer of the enol form **1a**, which was determined by 2D NMR data. As the dihedral angle increases, the energy of the molecule also increases (Fig. 8c). The angle of the same plane for the most stable conformer of the enol form **1b** was found as 65.61° , because the repulsion between the two –OMe groups and the –OH group make steric hindrance (Fig. 8d and e). The molecule moves away from the planarity to reduce this effect and a higher dihedral angle appears (Fig. 8f).

Furthermore, the most and least stable conformers of the enol forms of compound **2** were calculated (Fig. S-42 of the Supplementary material). When the dihedral angles of the most stable conformer of the enol form of **2a** are examined, it can easily be seen that dihedral angle for enol plane is 14.55° (Fig. 9a and b). The energy of the conformer rises with increasing dihedral angle (Fig. 9c).

Steric hindrance causes the molecule to move away from planarity in the most stable conformer of the unobserved enol form **2b** (Fig. 9d) and conjugation in the molecule is therefore diminished ($\theta = 55.49^\circ$, Fig. 9e and f).

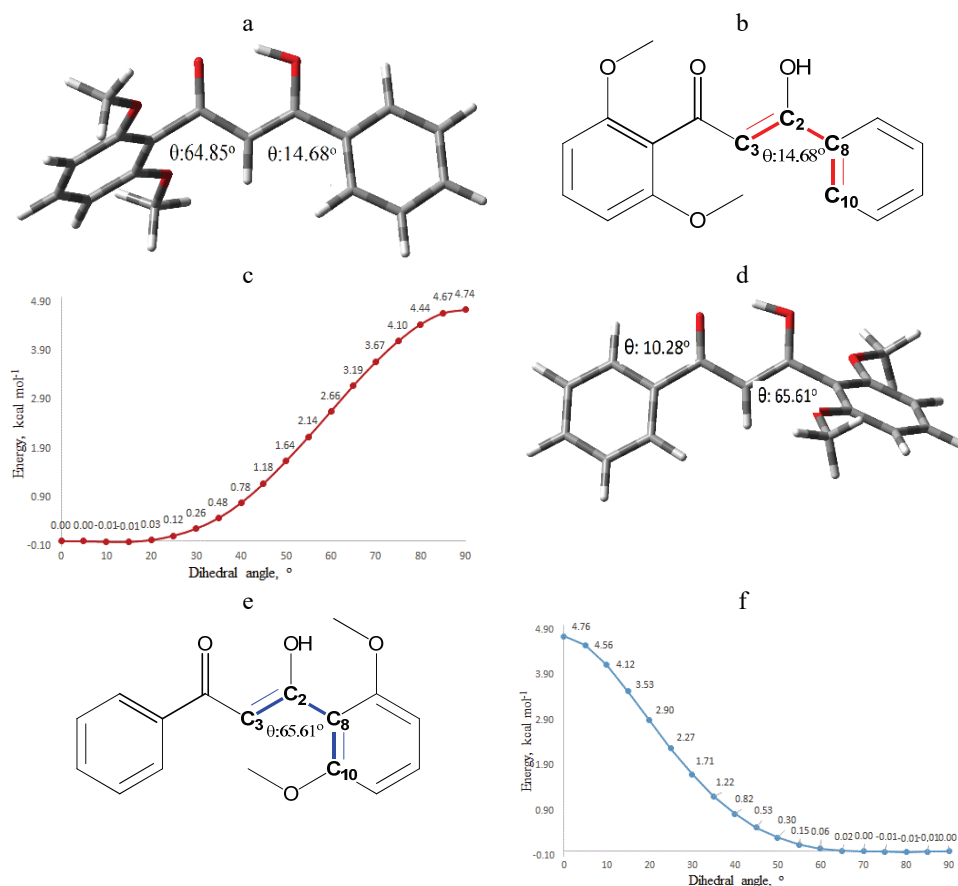


Fig. 8. a) 3D model of **1a** with dihedral angles; b) 2D model of **1a** with the dihedral angle of the enol plane; c) graphical image of the energy as a function of the dihedral angle for the most stable conformer of compound **1a**;^{*} d) 3D model of compound **1b** with dihedral angles; e) 2D model of **1b** with the dihedral angle of the enol plane; f) graphical image of the energy in dependence on the dihedral angle for the most stable conformer of compound **1b**.^{*}

In the last aryl-aryl substituted dicarbonyl compound **7** (Fig. S-43), dihedral angle of enol plane is 15.49° in the most stable conformer of the enol form **7a** (Fig. 10a and b). The energy of the conformer increases when the dihedral angle is increased (Fig. 10c). Of course, the dihedral angle is smaller in this most stable conformer compared with the most stable conformer of the enol form **7b**. How-

^{*} 1 kcal = 4184 J

ever, the deviation from planarity in the most stable conformer of the enol form **7b** is greater than expected ($\theta = 45.49^\circ$, Fig. 10d and e). The reason for this is the repulsion between the proton of the $-\text{C}=\text{CH}-$ group and the β -proton of the bulky naphthalene ring (Fig. 10f).

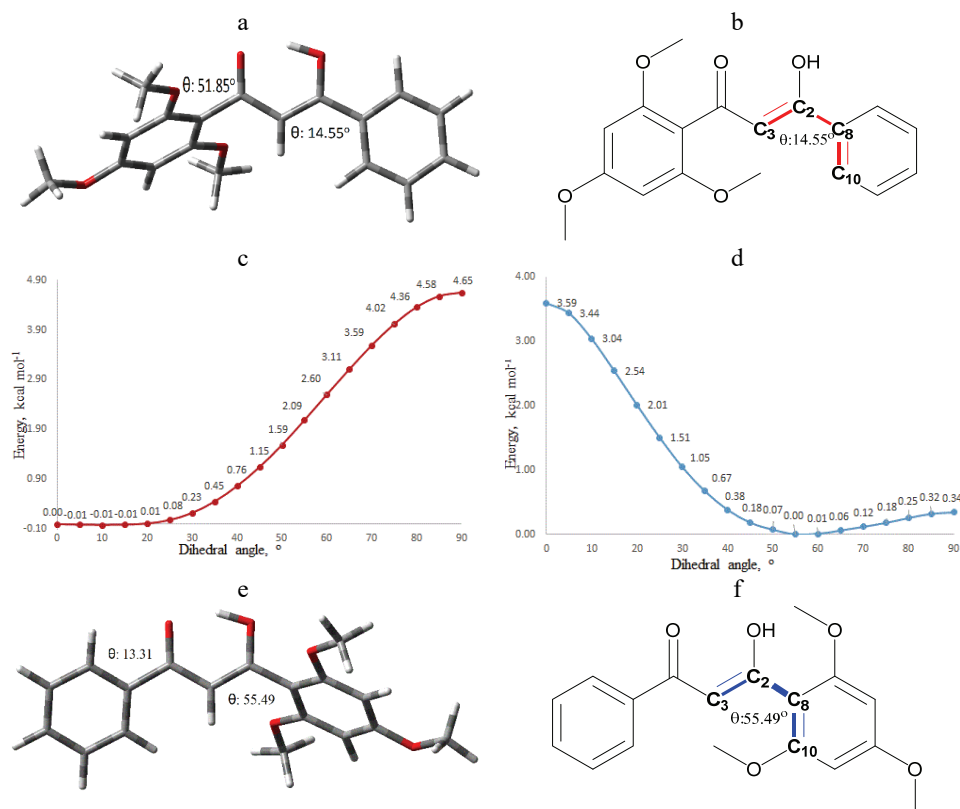


Fig. 9. a) 3D model of **2a** with dihedral angles; b) 2D model of **2a** with the dihedral angle of the enol plane; c) graphical image of energy as a function of dihedral angle for the most stable conformer of compound **2a**; d) graphical image of energy as a function of dihedral angle for the most stable conformer of compound **2b**; e) 3D model of **2b** with dihedral angles; f) 2D model of **2b** with the dihedral angle of the enol plane.

It can be seen in Table II that dihedral angles for more stable conformer of all of enol forms **a** are smaller than the dihedral angles for the more stable conformer of all enol forms **b**. According to this information, the enol form with the smallest dihedral angle will be more favourable because of less twisting, resulting in effective overlapping of the π -bonds. Hence, it could be stated that enol form **a** is the observed form. If all the dihedral angles of both enol forms of compound **1**, **2** and **7** were analysed, it could be seen that all the observed enol forms that were characterized by 2D NMR have the smallest dihedral angle of enol plane.

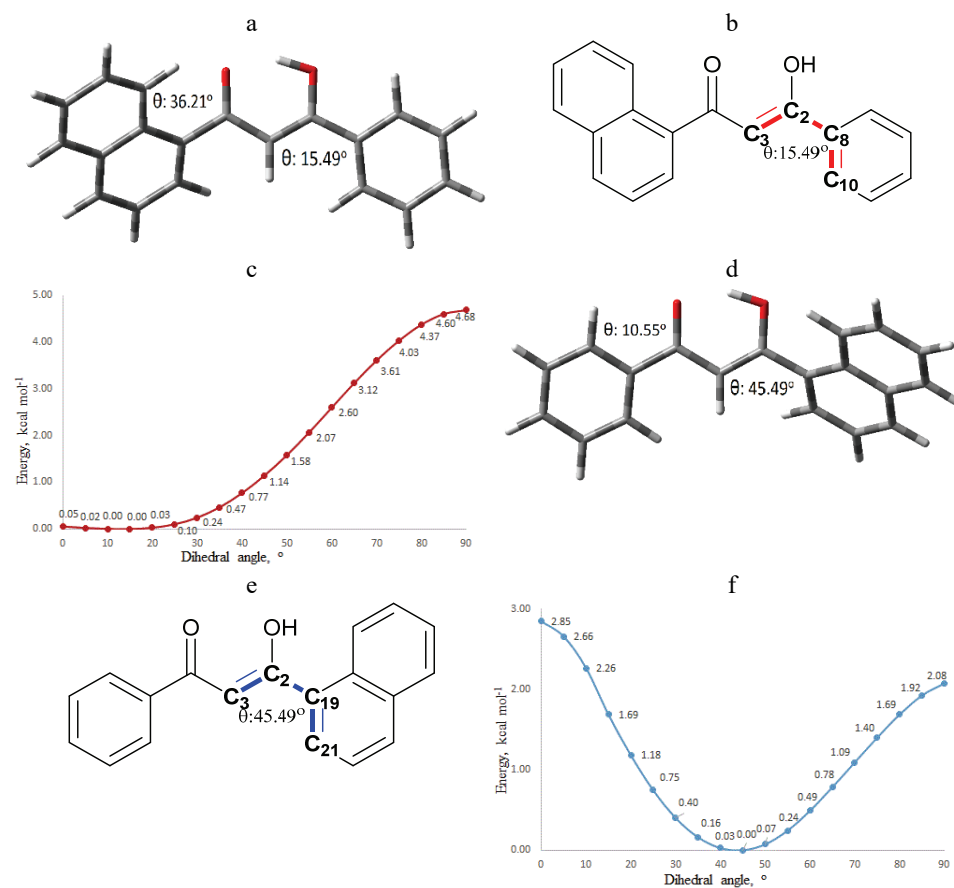


Fig. 10. a) 3D model of **7a** with dihedral angles; b) 2D model of **7a** with the dihedral angle of the enol plane; c) graphical image of energy as a function of dihedral angle for the most stable conformer of compound **7a**; d) 3D model of **7b** with dihedral angles; e) 2D model of **7b** with dihedral angle of the enol plane; f) graphical image of energy as a function of dihedral angle for most stable conformer of compound **7b**.

Besides aryl–aryl 1,3-dicarbonyl compounds, it was observed that the enol form occurred towards the aromatic ring when the 1,3-dicarbonyl compounds involve aryl and alkyl units, *i.e.*, compounds **3**, **4**, **6**, **8** and **10**. Longer conjugation occurs, as expected, towards the aromatic ring *via* the formation of a C(OH) bond.

CONCLUSIONS

It was shown that the keto–enol equilibrium can be effectively identified from 1D-NMR spectra but this method is insufficient to understand which of the enol form is observed. For this reason, it was shown that HMBC spectra could be utilized to identify the observed enol forms. The performed study also mentioned

that there is a plane between the enol carbons and an adjacent aromatic ring, which was called the enol plane. This enol plane was calculated and used to identify theoretically the observed enol form. The concept of an enol plane was applied to three different 1,3-dicarbonyl compounds and same results were obtained. To identify the enol plane, a dihedral scan was performed and the most stable conformers of the tautomers were found. It was assumed that this theory could be used to find the most abundant tautomer of 1,3-dicarbonyl compounds. The single enol form of some 1,3-dicarbonyl compounds that have aryl-aryl (symmetric and asymmetric) and aryl-alkyl groups were characterized *via* 2D-NMR, revealing a new approach for the explanation of observed enol form *via* dihedral angles determined in DFT calculations.

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ИЗВОД

ОДРЕЂИВАЊЕ ЕНОЛНИХ ОБЛИКА АСИМЕТРИЧНИХ 1,3-ДИКАРБОНИЛНИХ
ЈЕДИЊЕЊА: 2D НМВС NMR ПОДАЦИ И DFT ПРОРАЧУНИ

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У овом раду описана је синтеза серије асиметричних 1,3-дикарбонилних једињења, и испитивани су њихови енолни облици експерименталним методама и теоријским прорачунама. На основу ¹H- и ¹³C-NMR спектра, утврђено је да се сва испитивана једињења налазе у једном енолном облику у CDCl₃ раствору. Такође, на основу НМВС спектра и уочених корелација између одређених протонских у угљеникових језгара идентификовани су енолни облици. Израчунати су диедарски углови код асиметричних једињења која садрже ароматичне делове на обе стране, применом DFT методе, са циљем да се објасне фактори који одређују уочени енолни облик. Мали диедарски углови омогућавају дуже коњугације и настајање стабилнијег облика. Уочено је да се енолни облици формирају са мањим диедарским угловима, односно да је резонанциони фактор доминантан у формирању енолног облика. Осим тога, једињења која садрже арил- и алкил-групе доминантно формирају енолни облик усмерен према ароматичном прстену како би била образована дужа коњугација.

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