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A study of the tautomerism of β-dicarbonyl compounds with special emphasis on curcuminoids

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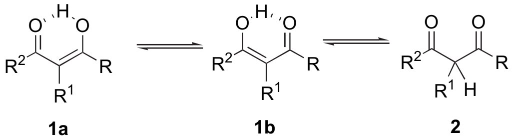
ABSTRACT

Six β-diketones related to curcumin and curcumin itself have been studied by ^{13}C NMR spectroscopy in chloroform in order to determine the equilibrium constant between the two keto/enol tautomers. In order to do this GIAO/B3LYP/6-31G** calculations of absolute shieldings (σ, ppm) were carried out. To establish relationships between σ and experimental chemical shifts (δ, ppm), three simple β-diketones (acetylacetone, dibenzoylmethane and benzoylacetone) have been studied. The preference for different groups to be conjugated with the C=O has been determined.

1. Introduction

The tautomerism of β-dicarbonyl compounds has been and still is one the main subjects in physical organic chemistry (Scheme 1). The keto/enol equilibrium between **2** and **1** has been studied from old and nothing really new has been published on this topic in recent years.[1] This is not so for the enol/enol equilibrium between **1a** and **1b**, where much more research is still needed.



Scheme 1. The prototropic tautomers of β-dicarbonyl compounds.

2. Results and discussion

All the β-diketones discussed in this work (Scheme 2) are reported in Section 4.

2.1. The tautomerism of β-diketones: simple models

We have studied compounds **3**–**9** as well as acetylacetone (**10**), dibenzoylmethane (**11**) and benzoylacetone (**12**). The determination of tautomer **c** by ^{1}H NMR in solution is obvious but irrelevant for the purposes of the present paper; that of determining the **a**/**b** ratio is difficult and should be done by interpolation.[1] We have decided to use the ^{13}C signals of both C–O atoms.

First we have calculated at the GIAO/6-31G** level a series of simple compounds (TMS, CH_4, $H_2C{=}CH_2$, $HC{\equiv}CH$, benzene, $H_2C{=}O$) and compared the absolute shieldings (σ, ppm) with the experimental δ values in parts per million.[2] Taking into account an empirical solvent effect of −5.2 ppm, this allows to establish an empirical relationship relating both values: $\delta\ ^{13}C = 199.51 - 1.055\sigma\ ^{13}C$. Then, we have calculated the absolute shieldings σ of **10**, **11**, **12a** and **12b** (only the C–O carbons are reported, Scheme 3 top) and transformed them into δ (Scheme 3, bottom).

Many authors have attempted to estimate the δ values of Scheme 3 but never using the data from GIAO calculations. Some of them used model compounds, such methyl vinyl ketone, and corrected them by the effect of the hydrogen bond, others used a constant $\Delta\delta$ value of 24 ppm (besides ^{13}C NMR, ^{17}O chemical shifts have also been used).[3–10] Note that the $\Delta\delta$ values of Scheme 3 change considerably for the different β-diketones.

With the δ values of Scheme 3 we have calculated the chemical shifts and tautomeric equilibrium constants, K, of the three β-diketones (Table 1).

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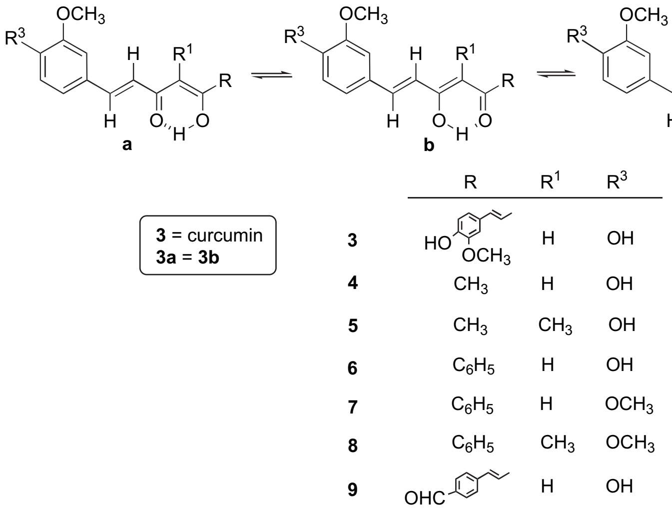
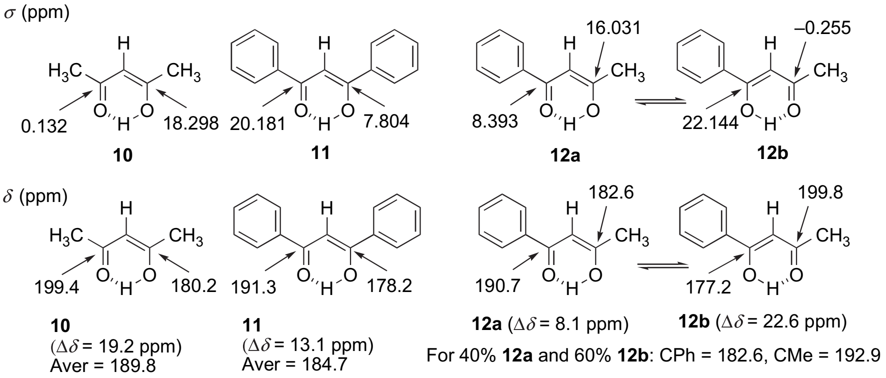


Scheme 2. β-Diketones.



Scheme 3. ^{13}C chemical shifts of the C–O signals of simple β-diketones.

Table 1
Chemical shifts, δ, and tautomeric equilibrium constants, *K*

Comp.	Phase	C(=O)Me	C(OH)Me	C(=O)Ph	C(OH)Ph	*K*
10	Acetone calcd	189.8	189.8	—	—	1
	Exp.[a]	191.1	191.1	—	—	
11	Acetone calcd	—	—	184.7	184.7	1
	Exp.[b]	—	—	185.3	185.3	
12	Acetone calcd	192.9	192.9	182.6	182.6	1.50 (40% **12a**, 60% **12b**)
	Exp.	193.7	193.7	183.3	183.3	
10	Solid calcd	196.9	182.7	—	—	7.33 (87/13)
	Exp.[c]	196.7	182.5	—	—	
11	Solid calcd	—	—	187.4	182.2	2.33 (70/30)
	Exp.[b]	—	—	188.2	182.9	
12	Solid calcd	193.8	193.8	181.9	181.9	1.86 (35% **12a**, 65% **12b**)
	Exp.[a]	192.3	192.3	180.1	180.1	

[a] This work.
[b] From Refs. 7,14.
[c] From Ref. 15.

All the papers agree with the result that tautomer **12b** is predominant, but the estimated values differ considerably from one author to the other. For instance, in solution and using almost the same experimental chemical shifts (193.6 and 183.4 ppm), but very different estimated values (211.5, 158.3, 214.4 and 166.8 instead of 190.8, 176.8, 199.6 and 183.0, Scheme 3), Geraldes, Barros, Maycock and Silva[5] found *K*(CMe)=1.29 and *K*(CPh)=1.12 instead of 1.50 (Table 1).

One of the difficulties that the study of enol/enol tautomerism of β-dicarbonyl compounds presents compared to other cases of tautomerism is the fact that the equilibrium is fast in the NMR time scale even in the solid state, thus preventing the use of ^{13}C as well as ^{17}O CPMAS chemical shifts. The dynamic disorder of crystals of

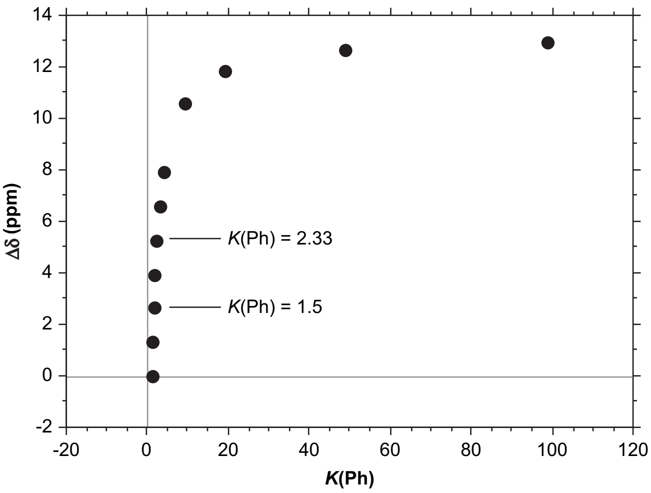
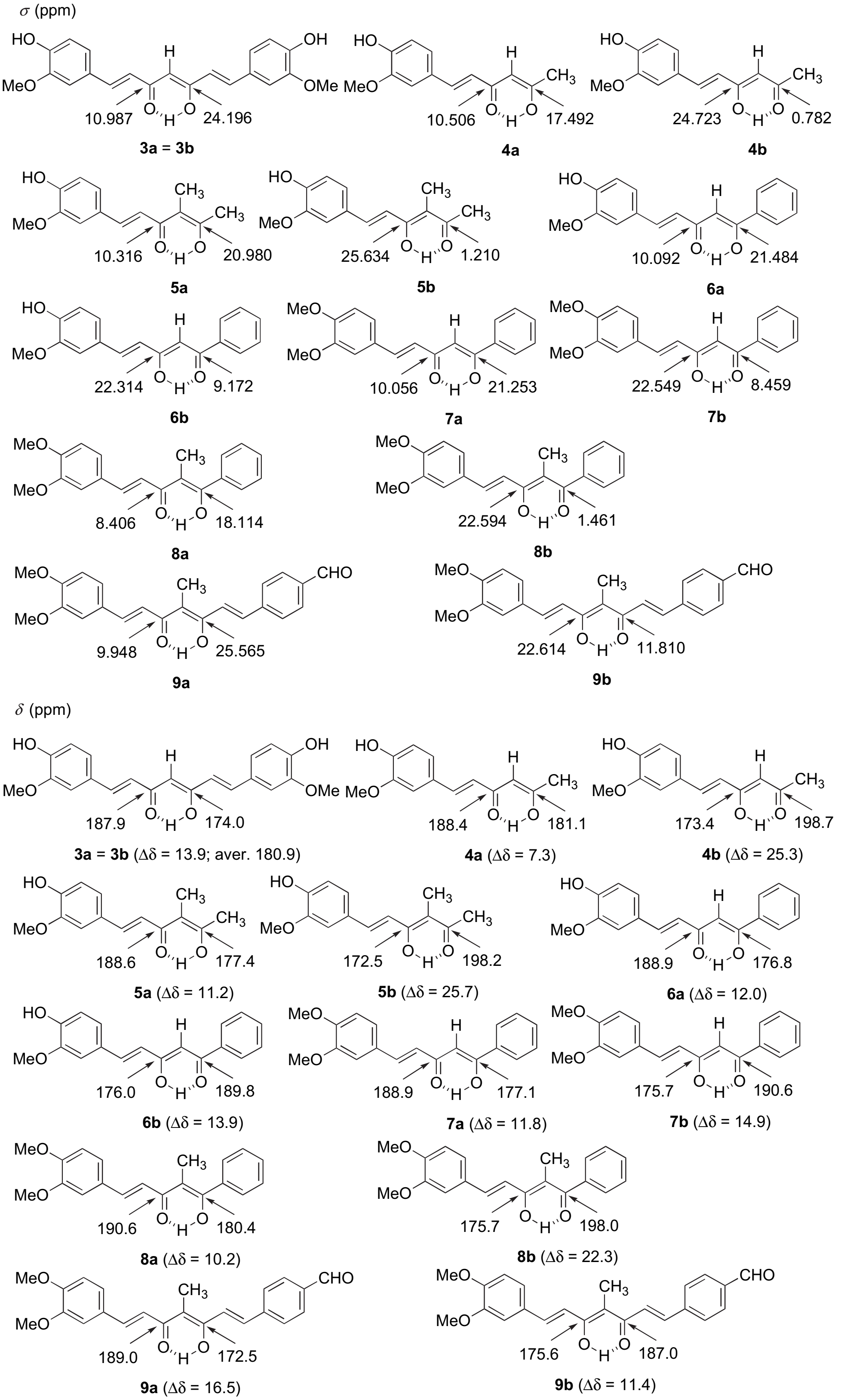


Figure 1. Variation of Δδ=13.2 ppm with the equilibrium constant *K*(Ph).



Scheme 4. Calculated ^{13}C chemical shifts of curcumin and curcuminoids.

β-diketones has been established by both X-ray and neutron diffraction crystallography at low temperatures.[11–14] For symmetric β-diketones, such as **10** (which is a liquid at room temperature) and **11** one averaged signal should not be expected because the asymmetry of the crystal environment 'desymmetrized' the rapid averaging due to prototropy.

Dibenzoylmethane (1,3-diphenylpropane-1,3-dione **11**) shows in the solid state two C–O signals at 188.2 and 182.9 ppm ($\Delta\delta$=5.3 ppm).[7] The authors assuming a $\Delta\delta$ gap of 24 ppm (197.3 and 173.3 ppm) obtain a K(Ph)=1.5 (60/40). With the values of Scheme 3 ($\Delta\delta$=13.1 ppm), we obtain K(Ph)=2.33 (70/30). We have represented the evolution of $\Delta\delta$ as a function of K(Ph) in Figure 1.

Acetylacetone (**10**) can be studied in the solid state as the solvate of a solid compound (a mixture of 5,5-diphenylhydantoin and 9-ethyladenine).[15] In the host–guest compound, two C–O signals were observed at 196.7 ppm (C=O) and 182.5 ppm (C-OH). Interpolation using the values of Scheme 3 (Table 1) affords K(Me)=7.33 (88/12). That is, there is still proton transfer between a tautomer present at about 90% and the other present at about 10%.

If we consider now the case of benzoylacetone (**12**), in the solid state tautomer **12b** still is predominant. The agreement between experimental and calculated chemical shifts is less good, probably because the chemical shifts of the model compounds are different in the solid state.

2.2. The tautomerism of β-diketones: curcumin and curcuminoids

We have reported in Scheme 4 the calculated σ values (top) and the corresponding calculated chemical shifts (bottom), including the differences between both CO carbon atoms.

The equation relating the experimental values in $CDCl_3$ with the best fit ones (corresponding to different equilibrium constants) is exp. ppm=1.008 best fit ppm, n=14, r^2=1.000 (Table 2).

Table 2
Chemical shifts, δ in ppm, and tautomeric equilibrium constants, K

Comp.	Phase	R	R^1	R^3	δ C(O)R	δ C(O)styryl	K
3	Solution	CH=CH–Ar	H	OH			
	$CDCl_3$[a]				183.3	183.3	1
	DMSO-d_6[b]				183.2	183.2	1
	DMSO-d_6[c]				183.3	183.3	1
	$CDCl_3$/DMSO-d_6[d]			0.1 ppm between DMSO-d_6 and $CDCl_3$			
	DMSO-d_6				183.2	183.2	1
	Best fit (50/50)				181.0	181.0	1
4	Solution	CH_3	H	OH			
	$CDCl_3$				196.9	178.0	
	Best fit (20/80)				195.2	176.4	0.25
5	Solution	CH_3	CH_3	OH			
	$CDCl_3$				197.4	174.0	
	Best fit (10/90)				196.1	174.1	0.11
6	Solution	C_6H_5	H	OH			
	$CDCl_3$				188.4	180.5	
	Best fit (20/80)				187.2	178.6	0.25
7	Solution	C_6H_5	H	OCH_3			
	$CDCl_3$				188.4	180.3	
	Best fit (35/65)				190.0	176.2	0.54
8	Solution	C_6H_5	CH_3	OCH_3			
	$CDCl_3$				190.9	182.1	
	Best fit (45/55)				190.1	182.4	0.82
9	$CDCl_3$	CH=CH–C_6H_4–CHO	H	OH			
	Exp.				179.7	186.1	
	Best fit (10/90)				176.9	185.6	0.11

[a] From Ref. 16.
[b] From Ref. 17.
[c] From Ref. 18.
[d] From Ref. 19.

2.3. Theoretical calculations of the tautomerism of non-symmetric β-diketones

See Table 3 and Figure 2.

Table 3
Differences in energy (kJ mol^{-1}, positive values indicate that the most stable is b), tautomeric equilibrium constants, percentages and K by interpolation

β-diketone	ΔE	$K_{298.15}$	$\%_{298.15}$	K Interpolation
4	1.36	0.58	37% **4a**–63% **4b**	0.25
5	2.06	0.43	30% **5a**–70% **5b**	0.11
6	2.38	0.38	28% **6a**–72% **6b**	0.25
7	2.09	0.43	35% **7a**–65% **7b**	0.54
8	0.25	0.90	48% **8a**–52% **8b**	0.82
9	−0.17	1.07	52% **9a**–48% **9b**	0.11

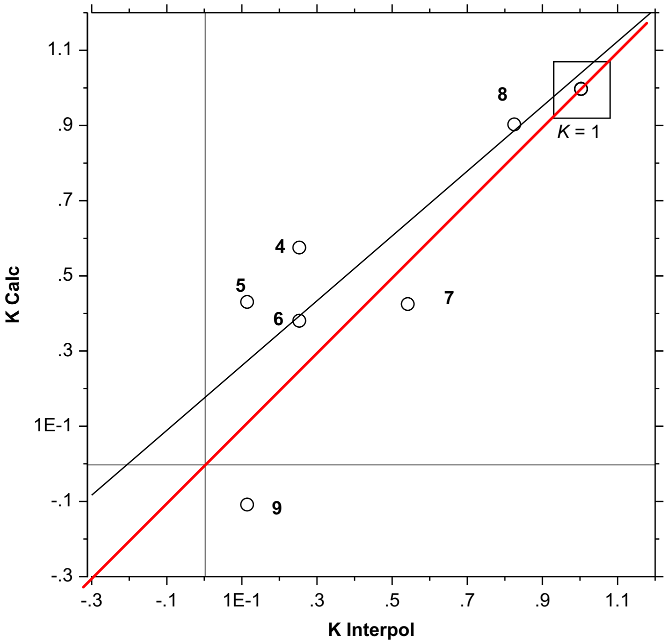


Figure 2. Plot of tautomeric equilibrium constants of Table 3. The red line is the slope=1, intercept=0 best line. The fitted line is: K Calcd=0.14+0.86 K Interpolation, r^2=0.81.

3. Conclusions

Theoretically calculated and experimentally determined equilibrium constants are related in a loose way, good enough to discuss both together in what concerns the preferences for a group to be linked to the C=O or linked to the COH. Considering identical the 3-methoxy-4-hydroxy and 3,4-dimethoxy groups, the phenyl group is the one that shows the strongest preference for the **a** tautomer, followed by $-CH=CH-C_6H_4-CHO$ and then $-CH=CH-C_6H_3(OR)_2$, which is reasonable in terms of electronic effects. The methyl group shows the same preference but the effect is almost negligible. The contribution terms to K are: 1.6 (C_6H_5)>1.0 ($-CH=CH-C_6H_4CHO$)>0.9 ($-CH=CH-C_6H_3(OR)_2$)>0.5 (CH_3).

4. Experimental part

4.1. Synthesis

Curcumin [(1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (**3**)] is commercially available and the general procedure for the preparation of the remaining diketones **4–9** has

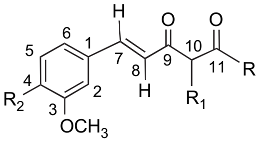


Figure 3. NMR atom numbering of diketone derivatives.

been described elsewhere.[20] Only the NMR data are given and the atom numbering used in the assignments is reported in Figure 3.

NMR experiments. The NMR spectra were recorded on a Bruker DRX 400 (9.4 T, 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C) spectrometer with a 5-mm inverse detection H-X probe equipped with a *z*-gradient coil at 300 K. Chemical shifts (δ in ppm) are given from internal solvent, for ^{1}H, CDCl$_3$ (7.26), DMSO-d_6 (2.49) and for ^{13}C, CDCl$_3$ (77.0), DMSO-d_6 (39.5). 2D (^{1}H–^{1}H) gs-COSY and inverse proton detected heteronuclear shift correlation spectra (^{1}H–^{13}C) gs-HMQC, and (^{1}H–^{13}C) gs-HMBC were acquired and processed using standard Bruker NMR software and in non-phase-sensitive mode.[21]

4.1.1. (E)-6-(4-Hydroxy-3-methoxyphenyl)hex-5-ene-2,4-dione (4)

^{1}H NMR (CDCl$_3$) δ: 2.16 (s, 3H, CH$_3$-11), 3.94 (s, 3H, OCH$_3$), 5.63 (s, 1H, CH=COH), 5.83 (s, 1H, OH-4), 6.32 (d, 1H, J=15.8 Hz, H-8), 6.92 (d, 1H, J=8.3 Hz, H-5), 7.02 (d, 1H, J_4=1.9 Hz, H-2), 7.09 (dd, 1H, J_3=8.3 Hz, J_4=1.9 Hz, H-6), 7.53 (d, 1H, J=15.8 Hz, H-7), 15.46 (s, 1H, OH). ^{13}C NMR (CDCl$_3$): δ=26.8 (11-CH$_3$), 55.9 (3-OCH$_3$), 100.7 (C-10), 109.5 (C-2), 114.8 (C-5), 120.3 (C-8), 122.6 (C-6), 127.7 (C-1), 140.1 (C-7), 146.8 (C-3), 147.7 (C-4), 178.0 (C-9), 196.9 (C-11).

4.1.2. (E)-6-(4-Hydroxy-3-methoxyphenyl)-3-methylhex-5-ene-2,4-dione (5)

^{1}H NMR (CDCl$_3$): δ=2.01 (s, 3H, CH$_3$-10), 2.24 (s, 3H, CH$_3$-11), 3.94 (s, 3H, OCH$_3$-3), 5.88 (s, 1H, OH-4), 6.78 (d, 1H, J_{trans}=15.5 Hz, H-8), 6.92 (d, 1H, J_3=8.2 Hz, H-5), 7.02 (d, 1H, J_4=1.5 Hz, H-2), 7.13 (dd, 1H, J_3=8.2 Hz, J_4=1.5 Hz, H-6), 7.58 (d, 1H, J_{trans}=15.5 Hz, H-7), 16.45 (s, 1H, OH). ^{13}C NMR (CDCl$_3$): δ=12.6 (10-CH$_3$), 26.2 (11-CH$_3$), 56.0 (3-OCH$_3$), 105.1 (C-10), 109.9 (C-2), 114.8 (C-5), 117.2 (C-8), 122.2 (C-6), 128.3 (C-1), 140.1 (C-7), 146.8 (C-3), 147.5 (C-4), 174.0 (C-9), 197.4 (C-11).

4.1.3. (E)-5-(4-Hydroxy-3-methoxyphenyl)-1-phenylpent-4-ene-1,3-dione (6)

^{1}H NMR (CDCl$_3$): δ=3.95 (s, 3H, OCH$_3$-3), 5.86 (s, 1H, OH-4), 6.33 (s, 1H, CH=COH), 6.52 (d, 1H, J_{trans}=15.8 Hz, H-8), 6.94 (d, 1H, J_3=8.3 Hz, H-5), 7.07 (d, 1H, J_4=1.9 Hz, H-2), 7.14 (dd, 1H, J_3=8.2 Hz, J_4=1.9 Hz, H-6), 7.47 (m, 2H, H-*m*), 7.53 (m, 1H, H-*p*), 7.63 (d, 1H, J_{trans}=15.8 Hz, H-7), 7.95 (m, 2H, H-*o*), 16.26 (s, 1H, OH). ^{13}C NMR (CDCl$_3$): δ=56.0 (3-OCH$_3$), 97.2 (C-10), 109.6 (C-2), 114.9 (C-5), 121.1 (C-8), 122.9 (C-6), 127.3 (C-*o*), 127.7 (C-1), 128.6 (C-*m*), 132.4 (C-*p*), 136.3 (C-*ipso*), 140.4 (C-7), 146.9 (C-3), 147.8 (C-4), 180.5 (C-9), 188.4 (C-11).

4.1.4. (E)-5-(3,4-Dimethoxyphenyl)-1-phenylpent-4-ene-1,3-dione (7)

^{1}H NMR (CDCl$_3$): δ=3.91 (s, 3H, OCH$_3$-4), 3.93 (s, 3H, OCH$_3$-3), 6.33 (s, 1H, CH=COH), 6.53 (d, 1H, J_{trans}=15.8 Hz, H-8), 6.88 (d, 1H, J_3=8.2 Hz, H-5), 7.09 (d, 1H, J_4=1.8 Hz, H-2), 7.15 (dd, 1H, J_3=8.2 Hz, J_4=1.8 Hz, H-6), 7.46 (m, 2H, H-*m*), 7.53 (t, 1H, J_3=7.3 Hz, H-*p*), 7.64 (d, 1H, J_{trans}=15.8 Hz, H-7), 7.95 (m, 2H, H-*o*), 16.27 (s, 1H, OH). ^{13}C NMR (CDCl$_3$): δ=55.87 (3-OCH$_3$), 55.94 (4-OCH$_3$), 97.2 (C-10), 109.8 (C-2), 111.2 (C-5), 121.3 (C-8), 122.5 (C-6), 127.2 (C-*o*), 128.1 (C-1), 128.6 (C-*m*), 132.4 (C-*p*), 136.3 (C-*ipso*), 140.1 (C-7), 149.3 (C-3), 151.0 (C-4), 180.3 (C-9), 188.4 (C-11).

4.1.5. (E)-5-(3,4-Dimethoxyphenyl)-2-methyl-1-phenylpent-4-ene-1,3-dione (8)

^{1}H NMR (CDCl$_3$): δ=1.54 (s, 3H, CH$_3$-10), 3.89 (s, 6H, OCH$_3$-3 and OCH$_3$-4), 6.69 (d, 1H, J_{trans}=15.8 Hz, H-8), 6.83 (d, 1H, J_3=8.3 Hz, H-5), 7.01 (dd, 1H, J_4=1.4 Hz, H-2), 7.10 (dd, 1H, J_3=8.3 Hz, J_4=1.4 Hz, H-6), 7.45 (m, 2H, H-*m*), 7.55 (t, 1H, J_3=7.6 Hz, H-*p*), 7.60 (d, 1H, J_{trans}=15.8 Hz, H-7), 8.00 (m, 2H, H-*o*). ^{13}C NMR (CDCl$_3$): δ=13.8 (CH$_3$), 55.4 (3-OCH$_3$), 55.9 (4-OCH$_3$), 107.4 (C-10), 110.0 (C-2), 111.0 (C-5), 120.7 (C-8), 123.6 (C-6), 127.1 (C-1), 128.7 (C-*o*), 128.7 (C-*m*), 133.4 (C-*p*), 136.3 (C-*ipso*), 144.6 (C-7), 149.2 (C-3), 151.7 (C-4), 182.1 (C-9), 190.9 (C-11).

4.1.6. 4-[(1E,6E)-7-(4-Hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dienyl]benzaldehyde (9)

^{1}H NMR (DMSO-d_6): δ=3.84 (s, 3H, 3-OCH$_3$), 6.18 (s, 1H, H-10), 6.82 (d, 1H, J_{trans}=16.0 Hz, H-8), 6.83 (d, 1H, J_3=8.1 Hz, H-5), 7.09 (d, 1H, J_{trans}=15.9 Hz, H-9), 7.18 (dd, 1H, J_3=8.1 Hz, J_4=1.7 Hz, H-6), 7.35 (d, 1H, J_4=1.3 Hz, H-2), 7.62 (d, 1H, J_{trans}=16.0 Hz, H-7), 7.93 (m, 2H, H-*o*), 7.96 (m, 2H, H-*m*), 9.71 (s, 1H, 4′-OH), 10.03 (s, 1H, CHO), 16.14 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ=55.7 (3-OCH$_3$), 102.0 (C-10), 111.4 (C-2), 115.7 (C-5), 121.1 (C-8), 123.6 (C-6), 126.1 (C-1), 127.2 (C-12), 128.7 (C-*o*), 130.0 (C-*m*), 136.6 (C-*p*), 137.7 (C-13′), 140.5 (C-*ipso*), 142.2 (C-7), 148.0 (C-3), 149.7 (C-4), 179.7 (C-11), 186.1 (C-9), 192.5 (CHO).

4.2. Computations

The relative stabilities have been determined using DFT calculations at the B3LYP/6-31G** level. Harmonic frequency calculations verified the minimum nature of the stationary points (all real frequencies) and were used to provide an estimation of the zero point energies (ZPE), which were not scaled.[22–26] The minimum geometries were used to calculate the absolute shieldings (σ, ppm) within the GIAO approximation.[27]

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