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Nuclear magnetic resonance and molecular modeling study of exocyclic carbon–carbon double bond polarization in benzylidene barbiturates

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HIGHLIGHTS

- Synthesis, NMR analysis and molecular modeling of benzylidene barbiturates.
- ^{13}C chemical shift difference correlates well with Hammett σ_p and σ_m.
- Solvent interaction and conformation influence calculated NBO atomic charges.
- ^{13}C chemical shift differences correlates well with NBO charge differences.
- Benzylidene barbiturates polarization defines their reactivity.

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ABSTRACT

Benzylidene barbiturates are important materials for the synthesis of heterocyclic compounds with potential for the development of new drugs. The reactivity of benzylidene barbiturates is mainly controlled by their exocyclic carbon–carbon double bond. In this work, the exocyclic double bond polarization was estimated experimentally by NMR and correlated with the Hammett σ values of the aromatic ring substituents and the molecular modeling calculated atomic charge difference. It is demonstrated that carbon chemical shift differences and NBO charge differences can be used to predict their reactivity.

1. Introduction

Bond polarization, an important feature for many reactions and molecular properties [1–8], occurs when the two linked atoms have different electronegativity, a process that leads to differences in atomic charge and electronic density. The bond polarization is observed in terms of the bond dipole moment $\vec{\mu}$, expressed as $\vec{\mu} = \Delta\mathbf{ed}\vec{\mathbf{v}}$, where $\Delta\mathbf{e}$ is the atomic charge difference, $\mathbf{d}$ is the distance between the two atoms and $\vec{\mathbf{v}}$ is the unitary vector parallel with the bond axis.

The polarization of carbon–carbon double bonds is a very important defining molecular reactivity factor, being directly involved on the type of mechanism, like reduction, cycloaddition and Michael addition reactions. The carbon–carbon double bond polarization depends on the electronic characteristics of the double bond substituents, which have a stronger influence on the π-bond. This information has been studied by molecular modeling and experimental processes, being confirmed by the bond lengths, bond dipole moment are and rotational barriers [1–6].

One of the important methods for polarization prediction is the nuclear magnetic resonance, being based on coupling constants, parameters which are certainly related with the bond length and its electronic density. The double bond length is certainly related to its polarization, as well as its rotation capacity, as it was shown for 2-(tetrahydropyrimidin-2(1*H*)-ylidene)-N^1,N^3-diphenylmalonamide [2]. Similar results were also found in polymers [7]. Interestingly, one factor that is not usually applied to describe bond polarization is the chemical shift difference between the two atoms directly involver on the bond.

One example of molecules with polarized carbon–carbon double bond is the benzylidene barbiturates (Fig. 1), of simple preparation [9–18], and used as important intermediates for the synthesis of new heterocyclic compounds [10,11,19–25]. The exocyclic carbon–carbon double bond polarization of benzylidene barbiturates is promoted by its conjugation with the two carbonyl groups from the barbituric acid ring and with the benzene aromatic ring, which effect certainly can be altered by the electronic properties and the position of the R_2 groups.

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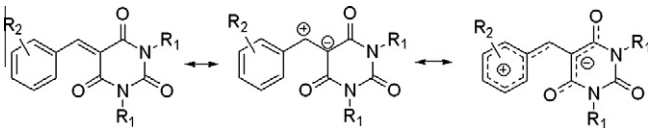


Fig. 1. Benzylidene barbiturates and their polarization.

The main reactivity of benzylidene barbiturates occurs at the C7–C5 double bond conjugated with two carbonyl groups of the barbituric acid ring, which mainly leads to Michael or cycloaddition reactions, as shown in Fig. 2 [10,11,19–25].

The electrophilicity parameters of the benzylidene barbiturates have been shown to be correlated with their reactivity as Michael acceptors and were used to predict other reactions [21]. Recently, the electrophilicity effect of the aromatic ring substituents on *N*,*N*-dimethylbenzylidene barbiturates was correlated with ^{1}H and ^{13}C NMR chemical shift differences of the *N*-methyl protons and between the C4 and C6 carbonyl signals of the barbituric ring, which also displayed correlation with the calculated substituents electrophilic constants σ_{ω} [26].

In our previous works with benzylidene barbiturates we observed that their reactivity is related to the polarization of their C7–C5 double bond [10,18,19,23,25], and considered that this polarization depends on the electronic properties and position of the aromatic ring substitutents. Because carbon–carbon double bond polarization must be related to the involved atoms charge difference, in this work we investigated and proved the possibility of using the experimental difference of ^{13}C NMR C7–C5 chemical shift ($\Delta\delta_{C7-C5}$), the calculated NBO (Natural Bond Orbital) atomic charges (Δe_{C7-C5}) and the Hammett substitution constants (σ_p and σ_m) to describe the polarization of benzylidene barbiturates.

2. Results and discussion

Benzylidene barbiturates of this work were prepared by condensation of benzaldehydes (1–24) with barbituric acid (25) in 95% ethanol and reflux for 30 min (Fig. 3 and Table 1) [10]. When these reactions were carried out under reflux with salicylaldehyde (**8**), 5-hydroxysalicyladehyde (**18**) and 5-chlorosalicylaldehyde (**20**), the obtained products were the respective 5-(2,4-dioxo-2,3,4,5-tetrahydro-1H-chromeno[2,3-d]pyrimidin-5-yl)pyrimidine-2,4,6(1H,3H,5H)-triones **33a**, **43a** and **45a** [18]. In order to prepare their respective benzylidene barbiturates **33**, **43** and **45**, the reaction was carried out at 25 °C, leading to the orange cationic intermediates **33b**, **43b** and **45b**, which were converted to the respective benzylidene barbiturates by dissolution in polar solvents like EtOH, MeOH and DMSO (Fig. 4) [18]. Due to the strong electron withdrawing effect of the nitro group, the 5-nitrosalicylaldehyde (**21**) was able to react with barbituric acid under reflux to afford the respective benzylidene barbiturate (**46**) without the formation of the respective orange cationic intermediate. All products (**26**–**49**) were purified by recrystallization in ethanol, leading to yields from 50% to 99%.

Since most of these benzylidene barbiturates were previously reported [9–18], in this work their structures were completely characterized by ^{1}H and ^{13}C NMR spectroscopy. The ^{13}C NMR spectra were used to obtain the C7–C5 difference in chemical shift ($\Delta\delta_{C7-C5}$) (Table 1), a parameter that we considered directly correlated with the exocyclic double bond polarization of the benzylidene barbiturates. In order to confirm these assignments, all compounds were submitted to APT and GATED decoupled ^{13}C NMR spectroscopy (GATED), which display the multiplicity and the short and long range couplings for each carbon atom. In all GATED spectra, the signal of C5 appears as single doublet with $^{2}J_{CH}$ from 3.0 to 4.5 Hz, while C7 is displayed as doublet of broad

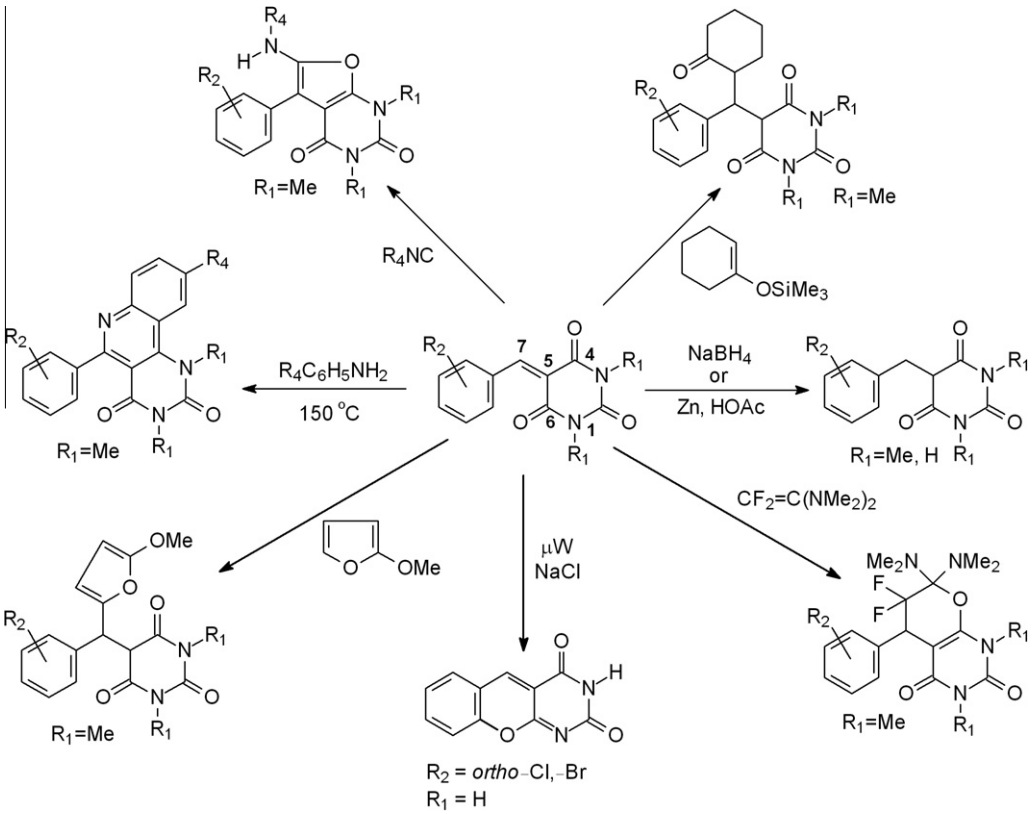


Fig. 2. Michael-type reactions with benzylidene barbiturates.

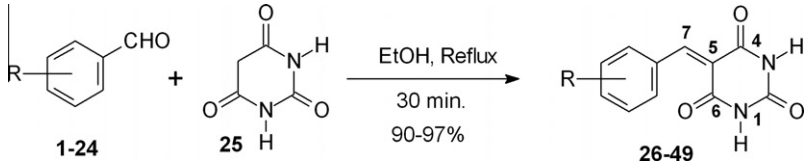
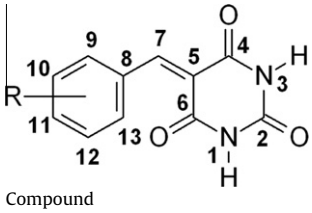


Fig. 3. Synthesis of benzylidene barbiturates (the R groups are identified in Table 1).

Table 1
Type and position of R groups, Hammett sigma values, chemical shifts (ppm) of C5, C7 and their chemical shift difference $\Delta\delta_{C7-C5}$ for all the prepared benzylidene barbiturates.



Compound	R	σ_p or σ_m	δ_{C5}	δ_{C7}	$\Delta\delta_{C7-C5}$
26	11-OH	−0.37	114.1	155.5	41.4
27	11-OMe	−0.27	115.5	154.9	39.4
28	11-Me	−0.17	117.7	155.3	37.6
29	H	0.00	119.0	154.8	35.8
30	11-Cl	0.2	119.7	152.9	33.2
31	11-Br	0.23	119.8	153.0	33.2
32	11-NO_2	0.78	122.3	151.3	29.0
33	9-OH	–	117.2	150.4	33.2
34	9-OMe	–	118.5	150.0	31.5
35	9-OEt	–	111.8	150.0	38.2
36	9-Br	–	121.5	152.0	30.5
37	9-Cl	–	121.8	149.8	28.0
38	9-NO_2	–	120.5	152.4	31.9
39	9-F	–	121.4	145.8	24.4
40	10-OMe	0.12	119.2	154.7	35.5
41	10-Br	0.39	120.5	152.5	32.0
42	10-NO_2	0.71	121.9	148.7	26.8
43	9,12-diOH	–	116.5	148.7	32.2
44	9,10-diOMe	–	116.4	150.2	33.8
45	9-OH-12-Cl	–	118.7	148.3	23.6
46	9-OH-12-NO_2	–	120.0	147.2	27.2
47	9-Cl-12-NO_2	–	123.8	146.9	23.1
48	9-Br-11,12-OCH_2O–	–	119.3	151.0	31.7
49	9-OEt-10,12-diNO_2	–	123.8	144.4	20.6

multiplets (dbm), doublet of triplets (dt), double doublet of doublets (ddd) or doublet of doublets (dd), depending on the presence of substituents at the *ortho* position. In all benzylidene barbiturates the initial doublet of C7 corresponds to $^1J_{CH}$ from 150 to 160 Hz.

The correlation of the chemical shift difference C7–C5 with the σ_p and σ_m constants is shown in Fig. 5, displaying a r^2 value of 0.9632. The r^2 values, which refer to the fraction of variance explained by the used model, indicates the quality of correlation of the tested data. When r^2 closer to 1.0, especially when superior to 0.9 the correlation is of good quality. However, for more complex cases, r^2 values above 0.7 are also good results. As expected, for the *para*- and *meta*-substituted benzylidene barbiturates (**16**–**21** and **40**–**41**), the C7–C5 double bond polarization is controlled by the R groups' properties, confirming that the chemical shift difference is a predictive polarization parameter. As expected, this result confirms that polarization of the C7–C5 double bond is controlled by the R groups electronic properties.

The other parameter that is related to bond polarization is the atomic charge difference. The charges of C5 and C7 were calculated in vacuum by molecular modeling using the B3LYP method and the 6-311++G** basis set using the Spartan 04 program [27], which afforded the electrostatic, Mulliken and natural charges (NBO) for each carbon. In Table 2 only the NBO charges are shown because these are the only atomic charge difference values that correlate well with chemical shifts.

The initial correlation of the chemical shift difference ($\Delta\delta_{C7-C5}$) with the NBO atomic charge difference (Δe_{C7-C5}) was carried out with the *p*-substituted benzylidene barbiturates, leading to $r^2 = 0.8833$ ($0.0038x + 0.1172$). Interestingly, the elimination of *p*-hydroxybenzylidene barbiturate (**26**) from the graphic lead to $r^2 = 0.9427$, indicating that the calculated Δe_{C7-C5} of compound **26** was affecting the correlation with $\Delta\delta_{C7-C5}$ because **26** was the only hydroxylated *para*-substituted benzylidene barbiturate. The OH group contributes to formation of hydrogen bonds as H-donor and H-acceptor, but in this case, because all NMR spectra were determined in DMSO-d_6 solution, we considered the participation of the OH group only as H-donor. Because the NBO charges were calculated in vacuum, it was clear that the interaction of compound **26** with the solvent would change the NBO atomic charges of C7 and C5. Accordingly, the atomic charges of **26** were re-calculated with formation of H-bond with DMSO (**26-DMSO**), leading to $\Delta\delta_{C7-C5}$–Δe_{C7-C5} correlation with $r^2 = 0.9632$ ($y = 0.0047x + 0.0889$). The reason for this type of calculation was based on the effect of the hydrogen bonding of the OH group with

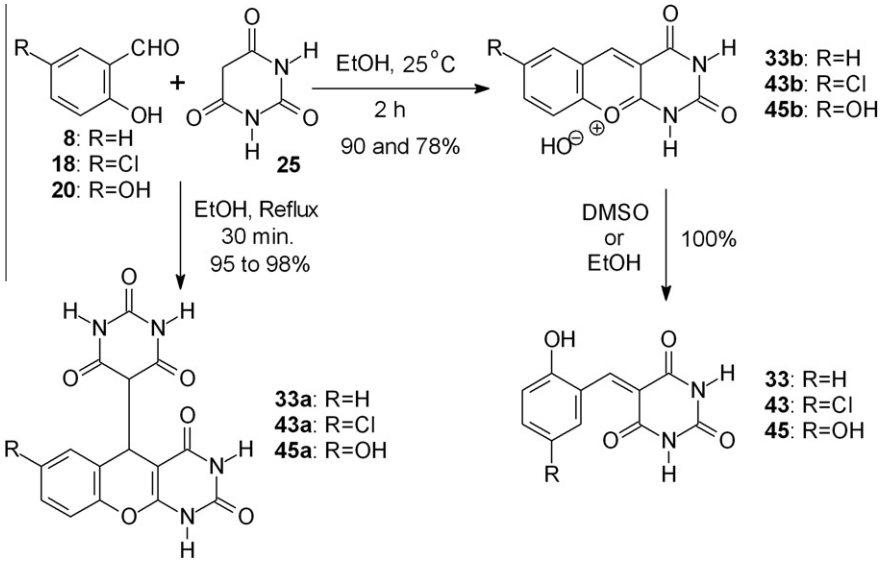


Fig. 4. Preparation of *ortho*-hydroxybenzylidene barbiturates.

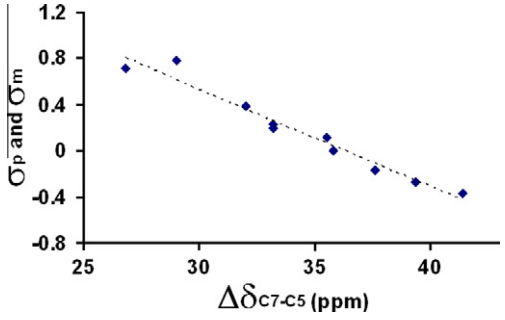


Fig. 5. Linear correlation of the C7–C5 chemical shift difference ($\Delta\delta_{C7-C5}$) with the Hammett substitution constants of R in *para*- and *meta*-substituted benzylidene barbiturates (σ_p and σ_m) (**26**–**32** and **40**–**42**).

DMSO on the electronic properties of the hydroxyl group, a process that is confirmed on the data of Table 2, line 3, showing a 0.016 e difference between the Δe_{C7-C5} of both conditions. It is clear that the *p*-OH group is involved on intermolecular interactions, mainly by the formation of a hydrogen bond between the OH group of **26** and the oxygen of DMSO, which is only an H-acceptor, as shown in Fig. 6. This process affects the electronic properties of the OH group and effects the C7–C5 double bond polarization. This result confirms that electronic properties of R groups can be affected by solvents, indicating that solvent–molecule interactions, depending on their nature, can be included in the molecular modeling calculations. The other R groups were not involved in important solvent interaction, for example, the atomic charge calculation including electrostatic interaction of DMSO the nitro group of **32** did not lead to important improvement of r^2.

In order to correlate the calculated atomic charge differences with $\Delta\delta_{C7-C5}$ the second analysis was conducted with the *p*- and *m*-substituted benzylidene barbiturates (compounds **26**–**32** and **40**–**42**), using only the NBO results, which confirmed a good correlation with chemical shift differences, as shown in Fig. 8 ($r^2 = 0.9244$, $y = 0.004x + 0.1158$).

As expected from Figs. 5 and 7, there is a good correlation between the natural charge difference (Δe_{C7-C5}) and $\sigma_p + \sigma_m$ ($r^2 = 0.9558$, $y = -20.359x + 5.2944$), as shown in Fig. 8. These results indicate that for *m*- and *p*-benzylidene barbiturates any one of the three parameters σ_p, Δe_{C7-C5} and $\Delta\delta_{C7-C5}$ can be used to estimate and compare their polarization. As mentioned before, the calculated Mulliken and electrostatic charges do not correlate well with the chemical shift differences, displaying r^2 values lower than 0.5 (graphics not shown).

The Hammett constants can be applied to substitution groups located at the *para* and *meta* position of aromatic rings, and could not be used with benzylidene barbiturates with R groups at the *ortho* position, like **33**–**39** and **43**–**49**, simply because the *ortho*

Table 2
Calculated NBO atomic charges of C_5, C_7 and the charge differences for all the benzylidene barbiturates.

Compound	N_{C5}	N_{C7}	Δe_{C7-C5}	Compound	N_{C5}	N_{C7}	Δe_{C7-C5}
26	−0.276	−0.009	0.267	**38**	−0.259	0.007	0.266
26 + DMSO	−0.290	−0.007	0.283	**39**	−0.254	−0.022	0.232
27	−0.278	−0.009	0.269	**40**	−0.263	−0.004	0.259
28	−0.270	−0.007	0.263	**41**	−0.255	−0.011	0.244
29	−0.264	−0.007	0.257	**42**	−0.247	−0.017	0.230
30	−0.261	−0.012	0.249	**43-syn**	−0.266	−0.021	0.245
31	−0.260	−0.012	0.248	**43-anti**	−0.267	−0.017	0.250
32	−0.240	−0.021	0.219	**44**	−0.266	−0.013	0.253
33-syn	−0.263	−0.027	0.236	**45**	−0.257	−0.022	0.235
33-anti	−0.265	−0.017	0.248	**46**	−0.245	−0.029	0.216
34	−0.268	−0.015	0.253	**47**	−0.237	−0.020	0.217
35	−0.270	−0.014	0.256	**48**	−0.263	−0.027	0.236
36	−0.251	−0.023	0.228	**49**	−0.239	−0.033	0.206
37	−0.253	−0.010	0.243				

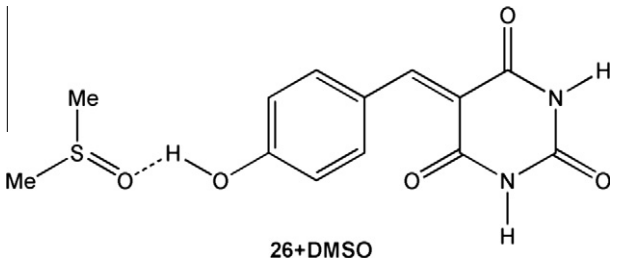


Fig. 6. Hydrogen bonding of the OH group of **26** with DMSO.

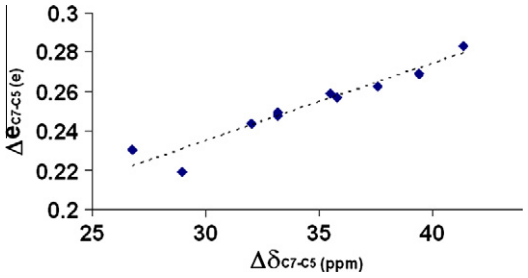


Fig. 7. Correlation of the natural charge difference C7–C5 (electrons) (Δe_{C7-C5}) with the chemical shift difference C5–C7 ($\Delta\delta_{C7-C5}$) for the *para*-substituted, compounds **26**–**32**, and the *meta*-substituted compounds, **40**–**42**.

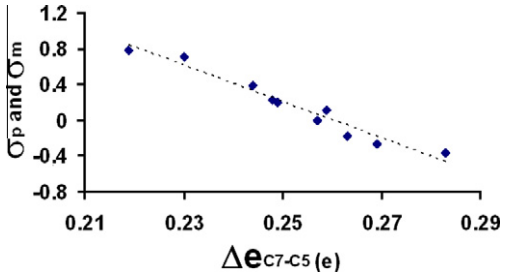


Fig. 8. Correlation of the natural charge difference C7–C5 (electrons) with the R Hammett substitution constants of the *meta*- and *para*-benzylidene barbiturates ($\sigma_p + \sigma_p$) for compounds **26**–**32** and **40**–**43**.

position of substituents, which include steric effects, are not appropriate for the Hammett approach [28]. Therefore, to expand the description of the C7–C5 bond polarization it was tested the correlation of the calculated natural charges and the chemical shift differences with all the studied benzylidene barbiturates. Even using the different conformations of all the benzylidene barbiturates, there is a clear correlation between the charge difference (Δe_{C7-C5}) and the chemical shift difference ($\Delta\delta_{C7-C5}$). Among the studied benzylidene barbiturates there are compounds with OH groups at the *ortho* position, which different conformations (syn and anti, Fig. 9) atomic charges were studied by molecular modeling. Fig. 9 shows the conformations syn and anti for compounds **33** and **43**. On the syn conformation the O–H bond is oriented towards the barbituric acid ring, a condition that leads to strong repulsion of OH with H7, while the anti conformations have the O–H bond at the opposite position, with a lower repulsion with H10.

Interestingly, this conformational variation leads to Δe_{C7-C5} differences of 0.012 and 0.005 for compounds **33** and **43**, respectively, and in all cases, the best correlations between Δe_{C7-C5} and $\Delta\delta_{C7-C5}$ or $\sigma_p + \sigma_m$ are better with the **33-anti** and **43-anti**, which display $r^2 = 0.7664$ ($y = 0.0031 + 0.1474$) (Fig. 10).

The analysis of Fig. 10 results indicate that the major differences with the average correlation occur for the *ortho*-substituted compounds, suggesting that these differences are due to their conformational difference as compared with the *m*- and *p*-benzylidene barbiturates. For example, in the case of compound **38** the *ortho* position of the nitro group clearly leads to a non-planar conformation (Fig. 11a) with a dihedral angle H7–C7–C8–C9 of 63°, different from the planar conformation of the isomer with the nitro group at the *para* position (**32**), which is completely planar (Fig. 11b) (dihedral angle 0°). These conformational differences, confirmed by the molecular modeling, explain the out of line behavior of compounds like **38**, because the loss of planarity decreases the conjugation of the aromatic ring with the C5–C7 double bond. A similar case was only observed with the *o*-chlorinated benzylidene barbiturate (**36**), which possesses a H7–C7–C8–C9 dihedral angle of 32°, much greater than that of the *o*-brominated analogue (**35**), in which possess a 0° dihedral angle. Despite Br is much bulkier than Cl, molecular modeling shows that the *o*-brominated compound is perfectly plane, because the C–Br bond distance (1.920 Å) is 9% longer than the C–Cl bond distance (1.788 Å). All the other *o*-substituted benzylidene barbiturates (**33**–**36**) display H7–C7–C8–C9 dihedral angles from 1° to 0° due to conjugation with the C7–C5 double bond and the barbituric ring.

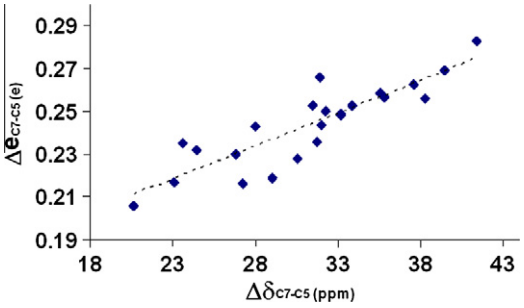


Fig. 10. Correlation of the natural charge difference C7–C5 (Δe_{C7-C5}) versus $\Delta\delta_{C7-C5}$ for all the benzylidene barbiturates (**33**–**49**).

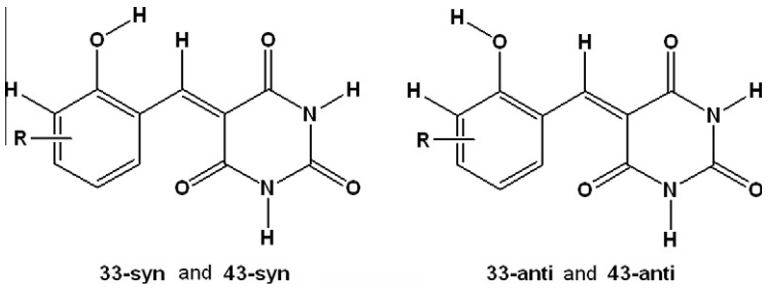


Fig. 9. Different conformations of the benzylidene barbiturates **33** and **43**.

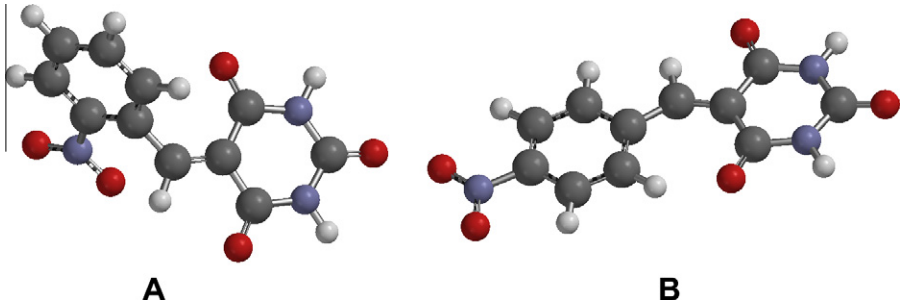


Fig. 11. Conformations for compounds **32** and **38** calculated by molecular modeling.

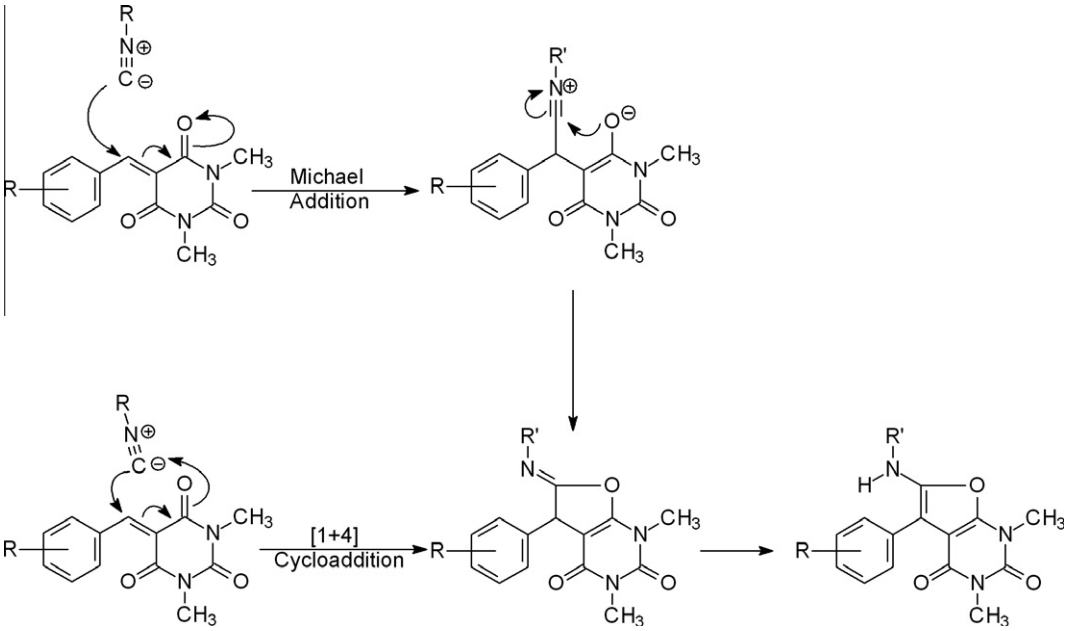


Fig. 12. Mechanistic scheme of the reaction of isocyanides with *N,N′*-dimethylbenzylidene barbiturates.

These results confirm that it is possible to estimate the C7–C5 bond polarization with $\Delta\delta_{C7-C5}$ for any benzylidene barbiturate because there is a reasonable correlation between Δe_{C5-C7} and $\Delta\delta_{C5-C7}$ for all the tested compounds (r^2 0.7664). This information is important since the polarization of the benzylidene barbiturates controls their reactivity. For example, it has been shown that *N,N′*-dimethylated benzylidene barbiturates can react with isocyanides by Michael-type addition reactions, as well as by [1 + 4] cycloaddition processes [19,24], as shown in Fig. 12.

If the C5–C7 double bond polarization of benzylidene barbiturate is high, the Michael-type addition reaction is favored. On the other hand, if the bond polarization is lower, the [2 + 4] cycloaddition should be expected.

3. Experimental

3.1. NMR analysis

The ^{1}H and ^{13}C NMH spectra were obtained in a Varian UNITY-300 spectrometer, using DMSO-d_6 as solvent. The DMSO-d_5 residual protons (δ 2.49) and the deuterated carbon signal (δ 39.5) were used as relative chemical shift references. All samples were prepared in 5 mm NMR tubes with 20 mg of the respective benzylidene barbiturate dissolved in 0.6 mL of DMSO-d_6. All spectra were recorded as 20.0 ± 0.1 °C. For the ^{1}H NMR spectra, there were used 16 transients, a 30° pulse and a delay (d_1) of 0.5 s. The ^{13}C NMR spectra were obtained with 2048 transients using a 45° pulse and a delay time (d_1) of 5.0 s. All samples were also analyzed using the GATED ^{13}C NMR (d_1 of 20.0 s and 8192 transients) in order to confirm the carbons multiplicity and HETCOR to confirm the H–C correlation.

3.2. General synthetic procedure

In a 200 mL round bottom flask, 1.54 g (12 mmol) of barbituric acid (**25**) were dissolved in 50 mL of hot distilled water. To this solution it was added a solution of the aldehyde (**1**–**24**) (12 mmol) in 10 mL of 95% ethanol. The mixture was kept under reflux and agitation for 30 min with the formation of a precipitate. The solid was separated by filtration and recrystallized in methanol to obtain the pure form of the respective benzylidene barbiturate, in yields from 90% to 99%. The data for the synthesis of the benzylidene barbiturates **26**–**49** is shown in Table 3, and the specific synthetic procedure data for the four new compounds is described below.

3.2.1. Synthesis of 5-(2,5-dihydroxybenzylidene)pyrimidine-2.4.6(1H.3H.5H)-trione ***(43)***

There were used 1.66 g of 2,5-dihydroxybenzaldehyde (**18**) and stirring at 20–22 °C, leading to 1.79 g of compound 4**3** as a gray solid. M.p. 390 °C (decomposition); 60% yield. Using a 30 °C reaction temperature, it was obtained the cationic intermediate **43b** as a violet solid in 50% yield, which was completely converted to

Table 3
Experimental data of benzylidene barbiturates synthesis.

Reagent No.	Amount (g)	Product No.	Amount (g)	Yield (%)	MP (°C)
1	1.46	**26**	2.65	95	234 (dec.)
2	1.63	**27**	2.77	95	265–268
3	1.44	**28**	2.54	92	281–283
4	1.27	**29**	2.60	99	274–276
5	1.68	**30**	2.95	98	287–289
6	2.22	**31**	3.34	94	252–254
7	1.81	**32**	3.10	99	282–284
8	3.55	**33a**	4.63	90	283 (dec.)
9	1.63	**34**	2.71	92	266–268
10	1.80	**35**	2.90	93	260–262
11	2.22	**36**	3.20	90	265–267
12	1.68	**37**	2.90	97	242–243
13	1.81	**38**	2.91	93	290–292
14	1.47	**39**	2.81	96	270–272
15	1.63	**40**	2.77	94	262–264
16	2.22	**41**	3.20	90	278–279
17	1.81	**42**	3.00	95	270–273
18	1.38	**43a**	2.12	98	390 (dec.)
19	1.61	**44**	2.58	88	206–207
20	0.39	**45**	0.44	84	281–282
21	2.00	**46**	3.16	95	258–260
22	2.23	**47**	3.37	95	390–393
23	2.74	**48**	3.90	96	260 (dec.)
24	2.70	**49**	4.08	90	232–233

compound **43** by solution in polar solvents (EtOH or MeOH); ^{1}H NMR (DMSO-d_6) δ 11.27 (1H,s), 11.13 (1H,s), 9.98 (1H,s), 8.61 (1H,s), 7.72 (1H,s), 6.87 (1H,d), 6.78 (1H,d); ^{13}C NMR (DMSO-d_6) δ 163.9 (s), 161.8 (s), 152.7 (s), 150.4 (s), 150.3 (s), 148.7 (d), 123.3 (d), 120.0 (d), 117.7 (d), 116.5 (s), 116.1 (s). Elemental analysis: calcd. for $C_{11}H_8N_2O_5$: C 53.23, H 3.25, N 11.29; found: C 53.63, H 3.45, N 10.97.

*3.2.2. Synthesis of 5-(2-hydroxy-5-nitrobenzylidene)pyrimidine-2.4.6(1H.3H.5H)-trione **(46)***

There were used 2.00 g (12 mmol) of 2-hydroxy-5-nitrobenzaldehyde (**21**), leading to 3.16 g of compound **46** as a yellow solid. M.p. 258–260 °C; 95% yield; ^{1}H NMR (DMSO-d_6) δ 12.2 (1H,s), 11.44 (1H,s), 11.31 (1H,s), 9.08 (1H,d), 8.44 (1H,s), 8.25 (1H,dd), 7.11 (1H,d); ^{13}C NMR (DMSO-d_6) δ 163.7 (s), 163.0 (s), 161.6 (s), 150.1 (s), 147.2 (d), 138.7 (s), 128.8 (d), 128.6 (d), 125.3 (s), 120.0 (s), 116.0 (d). Elemental analysis: calcd. for $C_{11}H_7N_3O_6$: C 47.66, H 2.55, N 15.16; found: C 46.81, H 2.72, N 14.86.

*3.2.3. Synthesis of 5-(2-chloro-5-nitrobenzylidene)pyrimidine-2.4.6(1H.3H.5H)-trione **(47)***

There were used 2.23 g (12 mmol) of 2-chloro-5-nitrobenzaldehyde (**22**), leading to 3.37 g of compound **47** as a crème solid. M.p. 390–393 °C; 95% yield; ^{1}H NMR (DMSO-d_6) δ 11.57 (1H,s), 11.38 (1H,s), 8.57 (1H,s), 8.26 (1H,d), 8.19 (1H,s), 7.83 (1H,d); ^{13}C NMR (DMSO-d_6) δ 162.3 (s), 161.2 (s), 150.3 (s), 146.9 (d), 145.6 (s), 139.5 (s), 134.4 (s), 130.5 (d), 126.6 (d), 125.8 (d), 123.8 (s). Elemental analysis: calcd. for $C_{11}H_6N_3O_5Cl$: C 44.69, H 2.04, N 14.21; found: C 45.23, H 2.21, N 14.44.

*3.2.4. Synthesis of 5-(2-ethoxy-3,5-dinitrobenzylidene)pyrimidine-2.4.6(1H.3H.5H)-trione **(49)***

There were used 2.70 g of 2-ethoxy-3,5-dinitrobenzaldehyde (**24**), leading to 4.08 g of product **49** as a white solid. M.p. 232–233 °C; 90% yield; ^{1}H NMR (DMSO-d_6) δ 11.60 (1H,s), 11.44 (1H,s), 8.90 (2H,s), 8.36 (1H,s), 4.15 (2H,q), 1.28 (3H,t); ^{13}C NMR (DMSO-d_6) δ 162.0 (s), 161.0 (s), 155.5 (s), 150.0 (s), 144.4 (d), 142.8 (s), 141.0 (s), 131.0 (s), 130.0 (d), 123.8 (s), 121.5 (d). Elemental analysis: calcd. for $C_{13}H_9N_4O_8$: C 44.71, H 2.60, N 16.04; found: C 43.89, H 2.67, N 15.89.

3.2.5. Molecular modeling

All the benzylidene barbiturates had their structures minimized using the B3LYP system, with the 6-311++G** basis set with the Spartan 04 program [27]. The calculations were prepared to provide the electrostatic, Mulliken and NBO (natural charge) atomic charges of all the atoms, as well as the simulated ^{13}C NMR spectra of each molecule.

The interaction of compound **26** with the solvent (DMSO) was established before the calculation, and the different conformations of the *ortho*-substituted benzylidene barbiturates were also previously prepared to the energy minimization process, and these conformations were maintained to the final results.

4. Conclusion

The ^{13}C NMR chemical shift difference between the two carbon atoms of the exocyclic double bond of benzylidene barbiturates ($\Delta\delta_{C7-C5}$) is an experimental parameter directly correlated with the bond polarization. This information is confirmed by the correlation between the chemical shift differences with the *para* and *meta* Hammett sigma values of the aromatic ring substituents (σ_p and σ_m) (r^2 0.96), as well as the $\Delta\delta_{C7-C5}$ correlation with the NBO charge difference between the two carbon atoms (Δe_{C7-C5}), which is also very appropriate for the *para*- and *meta*-substituted compounds (r^2 0.92). The correlation of Mulliken and electrostatic charge differences with $\Delta\delta_{C7-C5}$ or σ_p and σ_m indicate that they are not efficient to estimate bond polarization. It was also shown that substitution groups with stronger electron donating capacity lead to greater bond polarization, a condition that promotes Michael-type addition reactions, while electron withdrawing groups lead to lower polarization and must facilitate [1 + 4] and [2 + 4] cycloadditions.

It was shown that conformational changes and intermolecular interaction process modify the atomic charge differences on the C7–C5 carbon–carbon double bond, this being a process that must be monitored in order to establish better correlations between atomic charge differences and the tested parameters (σ_p and σ_m), as well as ($\Delta\delta_{C7-C5}$).

The benzylidene barbiturates with substituents at the *ortho* position display a less planar conformation when compared with the *meta*- and *para*-substituted compounds. Because *meta*- and *para*-substituted benzylidene barbiturates display planar structures, there exists a better conjugation between the aromatic ring and the exocyclic double bond of the barbituric acid ring. Therefore, it is also clear that *ortho*-substitution leads to lower double bond polarization, a condition that should be better for [1 + 4] cycloaddition reactions.

Despite the differences in conformations and planarity, the correlation of $\Delta\delta_{C7-C5}$ with Δe_{C7-C5} to estimate the exocyclic double bond polarization for the diverse type of tested compounds gives reasonable results (r^2 = 0.7664), indicating that both, chemical shift differences ($\Delta\delta_{C5-C7}$) and calculated charge differences (Δe_{C7-C5}), are appropriate to estimate the relative polarization of all types of benzylidene barbiturates.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molstruc.2012.09.021.

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