The Effects of Substituents and Solvents on the Conformation of Benzophenones

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Abstract

Motivation. Natural and synthetic benzophenones are compounds of great scientific and applied interest due to the varied biological and physicochemical properties that they posses. As part of a program aimed at investigating new physicochemical properties of substituted benzophenones, we carry out a study on the influence of the substituents and solvents upon the molecular conformations of these compounds. In the future, we expect to propose relationships between the molecular structural parameters with diverse experimental properties of the compounds that are currently being determined in our laboratory.

Method. Basis sets at the HF/6-31G(d) and B3LYP/6-31G(d) levels of theory were used for calculations. Onsager's and Tomasi's methods were used to analyze the solvent effects on the nine benzophenones studied.

Results. A conformational equilibrium was proposed between the two conformers of benzophenones with the greatest thermodynamic stability. The total energies, torsional angles, dipole moments, structural and reactivity molecular parameters, and conformational equilibrium constants were calculated in vacuum, ethanol, methanol and water. The calculated magnitudes were correlated with Hammett's substituent constants and parameters of solvating solvents.

Conclusions. The benzophenones investigated possess non-planar structures. Very good linear relationships between the molecular dihedral angles and Hammett's *p*-substituent constants were obtained. The electron-donating substituents increase the planarity of the substituted benzoyl group that involves phenyl ring A of the molecules, as well as the folding of phenyl ring B. The conformational equilibrium constants of *o*-hydroxy-benzophenones ranged approximately between 10^{-7}-10^{-6}. On the other hand, it was concluded that greater HBD capability of a solvent increases the polarization of the compounds and consequently, increases their DMs. It was further concluded that the electron-donating groups increase the strength of the IHB and that in the solvents used the *o*-hydroxy-benzophenones possess an important IHB of the moderate class.

Availability.

Keywords. Substituted benzophenones, effects of substituents and solvents, conformational equilibrium, hydrogen bonding, ab initio and DFT methods.

Abbreviations and notations

BPs, benzophenones	DM, dipole moment
DFT, density functional method	σ_P, Hammett's substituent constants
Conf$_1$ and Conf$_2$, conformers of benzophenones	*D,* dihedral angle
PEC, potential energy curve	*A*, bond angle
IHB, intramolecular hydrogen bond	HBD, hydrogen-bond donor capability

1 INTRODUCTION

Benzophenones (BPs) are obtained naturally from shafts, flowers and fruits of plants [1], and by synthesis methods [2]. These compounds are object of continuous investigations due to the varied biological and physicochemical properties that they posses. Thus, they are used for their bacteriostatic [3], tuberculostatic [4] and antimicrobial [5] activity. On the other hand, some polyhydroxylated BPs act as antithrombic agents and as inhibitors of the aggregation of platelets [6]. One of the most important properties of BPs is their capability to absorb UV radiation. These compounds absorb a wide range of UVA and UVB radiation (200-350nm). For this reason, they are widely used in commercial sunscreen formulations [7], which avoid the photosensitization, phototoxicity or allergic reactions of patients under different medical treatments [8].

It is known that the structural characteristics of a compound are fundamental in the determination of their biological and physicochemical properties. This fact has constituted the focus of a number of investigations, which explain some stereochemical properties of BPs [9]. Nevertheless, it should be noticed that several structural characteristics of substituted BPs of great medical and scientific importance have not been completely defined yet.

As part of a program aimed at investigating new physicochemical properties of BPs, the UV solvatochromic shifts [10], the metal complexing capability [11] and acid-base constants [12] of *o*-hydroxy-BPs were recently studied. Now, we carry out a study on the influence of the substituents and solvents upon the molecular conformations of substituted BPs, by means of ab initio and density functional (DFT) methods. In the future, we wish to propose relationships between the obtained molecular structural parameters and several experimental properties of the compounds that are currently being determined in our laboratory.

2 MATERIALS AND METHODS

2.1 Calculations

The structures and chemical numbering system of the BPs studied are shown in Figure 1. Figure 2 shows the practical numbering system adopted for carrying out the calculations, which were performed with known procedures [13]. For the determination of the potential energy surface minima of BPs in vacuum and water at HF/6-31G(d), energetic magnitudes of molecular structures were calculated as a function of dihedral angles (ω, ϕ) using increments of 10º in the 0-180º interval, and sometimes in the 0-360º interval. It was proposed that dihedral angle ω (or angle ϕ) is

formed by the plane containing the substituted or unsubstituted ring A (or ring B) and the plane containing the rest of the molecule. The two planes intersect along the single bond C_1-CO (or single bond OC-$C_{1'}$). The potential energy surface minima obtained by the scan of BPs were optimized with the Gaussian 98 [14] program packages, using basis sets at the HF/6-31G(d) and B3LYP/6-31G(d) levels of theory and the default convergence criteria.

Onsager's [15] and Tomasi's [16] methods were used to analyze the solvent effect on the rotamers of BPs. On the other hand, the equilibrium constant between molecules that have intramolecular hydrogen bondings (IHBs) and those that lack this type of bonds were calculated to analyze the strength of the IHB of o-hydroxy-benzophenones (compounds **6** to **9**), which involves the hydrogen of the OH group at position 2 and the carbonyl oxygen.

3 RESULTS AND DISCUSSION

According to Wilson et al. [17], the number of conformers of a compound can be calculated with Eq. (1),

$$\text{Number of conformers} = (360/\text{angle increment})^{\text{No. rotatable bonds}} \qquad (1)$$

In the analyzed BPs, by rotating the planes that involve the phenyl rings A and B with respect to the plane containing the rest of the molecule around the single bonds C1-CO and OC-C1' (Figure 1), respectively, the existence of two principal conformers ($Conf_1$ and $Conf_2$) with highest thermodynamic stability was detected. To analyze more easily the stereochemical characteristics of the investigated BPs, it is convenient to separate them into two groups.

3.1 Group 1.

This group is formed by the *p*-substituted BPs, this is to say, by compounds **1** to **5**. $Conf_1$ and $Conf_2$ of each BP of this group have the same thermodynamic stability. As an example, Figure 3 shows the potential energy curves (PECs) computed at HF/6-31G(d) for BP **1**. It can be observed that the PECs exhibit three minima, characterized by the dihedral angles $(0 + \omega_1)$, $(180 + \omega_1)$, $(360 + \omega_1)$, which have practically the same energy. The energy difference of the minima at the torsional angles $(0 + \omega_1)$ and $(180 + \omega_1)$ is smaller than 1 kcal mol^{-1}. Obviously, when these symmetrical structures are optimized at the HF/6-31G(d) or B3LYP/6-31G(d) levels, they show identical energies. Consequently, in this group we will refer mainly to $Conf_1$. Table 1 reports the calculated dihedral angles at the B3LYP/6-31G(d) level in vacuum and water (Onsager's method) for $Conf_1$ of

BPs, and Hammett's substituent constants (σ_P) [18,19].

The torsional angles ω_1 calculated at B3LYP/6-31G(d) for Conf$_1$ of **2-5** were plotted against σ_P as shown in Figure 4. It is observed that the effect of the substituents on the structure of the compounds is more marked in aqueous medium than in vacuum. The linear equations of Figure 4 show that the coefficients of σ_P are positive, which means that the electron-donating groups favor the decrease of dihedral angle ω_1. This fact implies that a higher coplanarity of the carbonyl group with the aromatic ring A increases the π-electronic delocalization of the substituted benzoyl group. Obviously, the simple bond nature of the C=O group and the electronic density of the carbonyl oxygen atom increase.

In general, it can be concluded that the introduction of electron-withdrawing or electron-donating substituents in compound **1** increases the molecular planarity of Conf$_1$. Also, that the variations of θ_1 indicate that the planes containing the aromatic rings A and B are inclined by approximately 49.7-51.1º (vacuum) and 49.7-51.2º (water) with respect to one another. These results are coherent with the value given ($\theta_1 \cong 54.4$º) by Cox et al. [20] for 2(CH$_3$-NH),5(Cl)-BP.

3.2 Group 2.

This group includes all the *o*-hydroxy-benzophenones, i.e., compounds **6** to **9**. The BPs of this group, besides having symmetrical conformers exhibit non-symmetrical conformers with different energies. The conformers of BPs **6** to **9** obtained by the rotation of ring B (Figure 1 and Figure 2, dihedral angle $\phi \equiv DO_1C_2C_9C_{10}$) are symmetrical but the rotamers that result from the complete rotation of ring A (Figure 1 and Figure 2, dihedral angle $\omega \equiv DO_1C_2C_3C_4$), which implies the rupture of a significant IHB [21], are not symmetrical. Figure 5 shows the PEC calculated for compound **6**. It can be observed that the PEC exhibits four energy minima at the torsional angles $(0 + \omega_1)$, $(180 + \omega_2)$, $(360 - \omega_3)$, $(360 + \omega_1)$, but only the non-symmetrical conformers have different energies. As an example, Figure 6 shows the two non-symmetrical conformers with the highest thermodynamic stability optimized at B3LYP/6-31G(d) for BP **6**, in water at 25ºC. On the other hand, the total free energy in solution (G^o_{sol}), the dipole moment (DM) and the interaction distances (dO$_1$-oHO) between the carbonyl oxygen atom and hydrogen atom of *o*-hydroxyl group of the conformers of group 2, calculated at B3LYP/6-31G(d) with Tomasi's method in water, methanol and ethanol, are summarized in Tables 2-4, respectively.

From Tables 2-4 it can be observed that the thermodynamic stability of Conf$_1$ is higher than that of Conf$_2$, in the three solvents used. It must be noted that the important IHB [21] characteristic

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of BPs **6** to **9** intensely affects the geometry of their molecules. From Table 1 it can be observed that in vacuum and water, the values of dihedral angles ω_1 and θ_1 of $Conf_1$ of BPs group 2 are lower than those exhibited by $Conf_1$ of group 1. On the other hand, the variations of torsional angle ϕ_1 are exactly opposite those of ω_1 and θ_1. These facts indicate that the electron-donating groups increase the planarity of the substituted aromatic ring A and the folding of ring B. Nevertheless, the values of θ_1 ($\cong 46°$) for the BPs of group 2 reveal that these compounds possess a higher coplanarity between their rings A and B with respect to BPs **1** to **5** ($\theta_1 \cong 51°$).

On the other hand, it was proposed that $Conf_1$ and $Conf_2$ of BPs **6** to **9** are related by the conformational equilibrium,

$$Conf_1 \text{ (with IHB)} \quad \rightleftharpoons \quad Conf_2 \text{ (without IHB)} \tag{2}$$

which is characterized by the equilibrium constant K_C. Eq. (2) describes an equilibrium between intramolecularly hydrogen bonded molecules and molecules lacking the internal hydrogen bond. The values of K_C calculated at B3LYP/6-31G(d) are also given in Tables 2-4. It is clear that when $Conf_1$ and $Conf_2$ of a BP have the same energy, the corresponding K_C is equal to one. This means that in this case there is 50% of each conformer. This is the behavior observed for the BPs of group 1. However, for the BPs of group 2 the calculated K_C in water, methanol and ethanol ranged between 9.44×10^{-7}-3.79×10^{-6}, 1.06-3.87×10^{-6} and 1.01-3.80×10^{-6}, respectively. Since $K_C \ll 1$, these BPs are almost completely under the $Conf_1$ form; for example, for the $Conf_1$ (**6**) $\rightleftharpoons$ $Conf_2$ (**6**) equilibrium in water at 298 K, $K_C = 3.79 \times 10^{-6}$. In this way, the theoretical calculations predict 99.99962% of $Conf_1$ (**6**) and 0.00038% of $Conf_2$ (**6**) in the equilibrium. Lamola et al. [22], in a study of the environmental effects on the excited states of *o*-hydroxy aromatic carbonyl compounds, suggested that the molecules of 2-hydroxy-benzophenones in ethanol solutions exhibit two different structural forms, with and without IHBs. Recently, based on UV spectroscopic determinations and semiempirical MO calculations, Blanco et al. [10] formulated similar proposals for *o*-hydroxy-benzophenones dissolved in primary alcohols.

From Tables 2-4 it can be observed that the K_C constants do not change significantly with the solvent. For the conformers of **6** the following total energies (TE) were obtained in vacuum and water,

In vacuum:

TE $Conf_1$ (**6**) = -409049 kcal mol^{-1}

TE $Conf_2$ (**6**) = -409041 kcal mol^{-1}

In water:

TE Conf_1 (**6**) = -409050 kcal mol^{-1}

TE Conf_2 (**6**) = -409042 kcal mol^{-1}

These data reveal that the thermodynamic stability of the conformers in aqueous medium increases by 1 kcal mol^{-1} with respect to those in vacuum, an increase that is obviously insignificant. Similar thermodynamic properties were observed in all the BPs of group 2. Consequently, it is concluded that the solvents used practically do not affect the K_C constants of the BPs in this group and, also, that Conf_1 constitute their predominant form.

The DM of the compounds proved to be highly dependent on the solvents. Figure 7 shows the changes of DM_1 of BPs group 2 with the solvation parameter *Acity* [23] of the solvents used. The parameter *Acity* is very useful for measuring the hydrogen bond donating ability (HBD capability) of a solvent, this is to say, the capability of the solvent to provide a proton. The values of *Acity* determined for ethanol, methanol and water are 0.66, 0.75 and 1.00 [24], respectively. From Figure 7, it is observed that the linear equations obtained have very good correlation coefficients ($r > 0.98$). These equations indicate that the greater HBD capability of a solvent increases the polarization of the BPs and consequently, increases their DM.

The *p*-substituents exert a strong influence on the K_C constants. Figure 8 shows the change of K_C with Hammett's σ_P constants. The slopes of lineal equations included in Figure 8 indicate that the effect of *p*-substituents increases with the medium permittivity. Moreover, the $d\text{O}_1$-*o*HO interaction distances of *o*-hydroxy-benzophenones were related with the σ_P constants by means of the following equation,

$$d\text{O}_1\text{-}o\text{HO} = 0.0379\ \sigma_P + 1.6672 \qquad (r=0.9412) \tag{3}$$

The above equation suggests that the electron donating groups, by decreasing the $d\text{O}_1$-*o*HO distance, increase the corresponding H-Bond angle A-$\text{O}_1\text{H}_{25}\text{O}_{15}$ (Figure 6a) and, consequently, the strength of the IHB. Eq. (3) also permits to infer that the acid dissociation constant (K_a) of BP **6** should be greater than the K_a of BP **8**. This prediction agrees with the experimental values pK_a (**6**)= 9.44 and pK_a (**8**)= 9.54 [12]. On the other hand, considering that in BPs group 2 the $d\text{O}_1$-*o*HO distances vary in the 1.652-1.666 Å range, the A-$\text{O}_1\text{H}_{25}\text{O}_{15}$ angles vary in the 144.4-148.9º range and the involved energies vary between -7.4 and -8.2 kcal mol^{-1}, it is concluded that in the solvents used these compounds possess an important IHB of the moderate class [25].

4 CONCLUSIONS

The BPs investigated possesses non-planar structures and each of them has two principal conformers in equilibrium. The symmetrical conformers of mono-substituted BPs have a more flexible structure than the conformational structures of *o*-hydroxy-BPs. For the compounds of group 1 the K_C constants are equal to one, while those of group 2 ranged between approximately 10^{-7}-10^{-6}. Also, it was determined that the planes containing the aromatic rings A and B of the two principal conformers of groups 1 and 2 are inclined by approximately 51º and 46º with respect to one another, respectively. Very good linear relationships between the molecular dihedral angles and Hammett's *p*-substituent constants were obtained. Firstly, it was concluded that the electron-donating substituents increase the planarity of the substituted benzoyl group that involves the phenyl ring A of the molecules as well as the folding of phenyl ring B. These effects are higher in the BPs of group 2, due to their important IHB. On the other hand, the DM_1 of BPs group 2 were related with the solvation parameter *Acity* of the solvents used. The equations obtained indicate that the greater HBD capability of a solvent increases the polarization of these BPs and consequently, increases their DM. Also it was determined that the *p*-substituents exert a strong influence on the K_C constants and it was demonstrated that their effect increases with the medium permittivity. Moreover, the interaction distances between the carbonyl oxygen atom and hydrogen atom of *o*-hydroxyl group of BPs of group 2 were related with Hammett's constants. It was concluded that the electron donating groups, by decreasing these interaction distances, increase the corresponding H-bond angle and, therefore, the strength of the IHB. It was also concluded that in the solvents used the BPs of group 2 posses an important IHB of the moderate class.

5 REFERENCES

[1] G. E. Henry, H. Jacobs, C. M. S. Carrington, S. McLean and W. F. Reynolds, *Tetrahedron*, **1999**, *55*, 1581-1596.

[2] F. Karrer, H. Meier and A. Pascual, *J. Fluorine Chem*. **2000**, *103*, 81-84.

[3] F. Fujikawa, K. Nakajima, A. Tokuova, Y. Hitosa, S. Nakazawa, T. Omatsu and T. Sumiyama, *J. Pharm. Soc. Japan*. **1953**, *73*, 740-743.

[4] B. L. Freedlander, *Am. Rev. Tuberc*. **1944**, *49*, 543-548.

[5] H. Kato, A. Takashashi, H. Tamuya, M. Kono and M. Shimo, *Shokuhin Eiseigku Zasshi*. **1966**, *7*, 60-66, Japan.

[6] J. Elks and C. R. Ganellin, *Dictionary of Drugs*, pp. 413, 569, 628, 1238. London, Chapman & Hall, 1990.

[7] P. Collins and J. Ferguson, *British J. Dermat*. **1994**, *131*, 124-129.

[8] A. M. Kadry, C. S. Okereke, M. S. Abdel-Rahman, M. A. Friedman and R. A. Davis, *J. App. Toxicol*. **1995**, *15*, 97-102.

[9] T. M. Kolev and B. A. Stamboliyska, *Spectrochim. Acta Part A-Mol. Biomol. Spectrosc*. **2000**, *56*, 119-126.

[10] S. E. Blanco, J. J. Silber and F. H. Ferretti, *J. Molec. Struct. (Theochem)*. **2002**, *582*, 91-105.

[11] G. T. Castro, S. E. Blanco, S. L. Arce and F. H. Ferretti, *Spectrochimica Acta Part A: Mol. & Biomol. Spectroscopy*. **2003**, *59*, 2685-2696.

[12] G. T. Castro, O. S. Giordano and S. E. Blanco, *J. Molec. Struct. (Theochem)*. **2003**, *626*, 167-178.

[13] K. S. Lau, A. Mantas, G. A. Chass, F. H. Ferretti, M. R. Estrada, G. Zamarbide and I. G. Csizmadia, *Can. J. Chem*. **2002**, *80*, 845-855.

[14] Gaussian 98, Revision A.9, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1998.

[15] M. W. Wong, K. B. Wiberg and M. J. Frisch, *J. Am. Chem. Soc*. **1992**, *114*, 1645.

[16] S. Miertus, E. Scrocco and J. Tomasi, *Chem. Phys*. **1982**, *65*, 239.

[17] Wilson and Gisvold's, *Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 10th ed, Edit. J. N. Delgado and W. A. Remers, Lippincott-Raven Publishers, N.Y., 1998, pp. 3-42.

[18] F. Ruff and I. G. Csizmadia, Organic Reactions. Equilibria, Kinetics and Mechanism, Elsevier, London, 1994, pp. 161-168.

[19] N. Isaacs, *Physical Organic Chemistry*, 2nd ed., Longman, England, 1996, pp. 151-152.

[20] P. J. Cox, A. T. Anisuzzaman, G. G. Skellern, R. H. PryceJones, A. J. Florence and N. Shankland, *Acta Cryst. Sec. C-Crystal. Struct. Comm*. **1997**, *53*, 476-477.

[21] A. C. Bhasikuttan, A. K. Singh, D. K. Palit, A. V. Sapre and J. P. Mittal, *J. Phys. Chem*. A, **1998**, *102*, 3470-3480.

[22] A. A. Lamola and L. J. Sharp, *J. Phys. Chem*. **1966**, *73*, 2634-2638.

[23] C. G. Swain, M. S. Swain, A. L. Powell and S. Alunni, *J. Am. Chem. Soc*. **1983**, *105*, 502.

[24] Y. Marcus, *Chem. Soc. Rev*. **1993**, *22*, 409-416.

[25] G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, Oxford University Press, Oxford, 1997, pp. 11-12.

TABLE 1. Calculated dihedral angles for conformer 1 of benzophenones in vacuum and water (Onsager's model) at 298 K, and Hammett's substituent constants (ω_1, ϕ_1 = torsional angles (º) $DO_1C_2C_3C_4$ and $DO_1C_2C_9C_{10}$, respectively; θ_1 = inclination angle ($DC_7C_4C_{10}C_{13}$) formed by the planes containing the aromatic rings A and B with each other; σ_p= Hammett's *p*-substituent constants).

	Optimization B3LYP/6-31G(d).			
Compound	Conformer 1 (vacuum)			σ_p
	ω_1	ϕ_1	θ_1	
1	26.2	26.2	51.1	0.00
2	25.2	26.4	50.6	0.24
3	24.3	27.2	50.5	0.07
4	22.1	28.4	49.7	-0.38
5	22.4	28.3	49.8	-0.28
6	12.3	36.3	46.4	0.00
7	11.7	36.3	46.0	-0.14
8	10.6	37.2	45.7	-0.28
9	10.7	37.2	45.9	-0.38
Compound	Conformer 1 (water). Onsager's method.			σ_p
	ω_1	ϕ_1	θ_1	
1	26.2	26.2	51.2	0.00
2	25.9	25.8	50.6	0.24
3	24.9	26.7	50.5	0.07
4	22.1	28.4	49.7	-0.38
5	22.4	29.1	50.0	-0.28
6	12.5	36.1	46.0	0.00
7	11.8	36.5	45.8	-0.14
8	10.6	37.7	45.8	-0.28
9	10.8	37.4	45.9	-0.38

TABLE 2. Calculated molecular magnitudes for the species involved in the conformational equilibrium of *o*-hydroxy-benzophenones in water at 298 K (G^o_{sol} = total free energy in solution, kcal mol^{-1}; DM= dipole moment, Debye; dO$_1$-oHO= interaction distance between the carbonyl oxygen and the hydrogen of OH group at position 2 of aromatic ring A, Å; K$_C$: conformational equilibrium constant (Eq. (2)).

Optimization B3LYP/6-31G(d) with Tomasi's method (water)

| Benzophenone | Conformer 1 (with HIB) | | | K$_C$ |
	G^o_{sol}	DM$_1$	dO$_1$-oHO	
6	-409050	5.21	1.666	3.79 x 10^{-6}
7	-433722	5.28	1.664	2.62 x 10^{-6}
8	-480916	3.95	1.655	1.03 x 10^{-6}
9	-456256	3.60	1.652	9.44 x 10^{-7}

| Benzophenone | Conformer 2 (without HIB) | | |
	G^o_{sol}	DM$_2$	dO$_1$-oHO
6	-409043	3.84	-------
7	-433714	3.82	-------
8	-480908	5.06	-------
9	-456248	5.11	-------

TABLE 3. Calculated molecular magnitudes for the species involved in the conformational equilibrium of *o*-hydroxy-benzophenones in methanol at 298 K (G^o_{sol} = total free energy in solution, kcal mol^{-1}; DM= dipole moment, Debye; dO$_1$-*o*HO= interaction distance between the carbonyl oxygen and the hydrogen of OH group at position 2 of aromatic ring A, Å; K$_C$: conformational equilibrium constant (Eq. (2)).

Optimization B3LYP/6-31G(d) with Tomasi's method (methanol)

| Benzophenone | Conformer 1 (with HIB) | | | K$_C$ |
	G^o_{sol}	DM$_1$	dO$_1$-*o*HO	
6	-409054	5.13	1.666	3.87 x 10^{-6}
7	-433726	5.21	1.664	2.64 x 10^{-6}
8	-480921	3.89	1.655	1.14 x 10^{-6}
9	-456260	3.54	1.652	1.06 x 10^{-6}

| Benzophenone | Conformer 2 (without HIB) | | |
	G^o_{sol}	DM$_2$	dO$_1$-*o*HO
6	-409047	3.79	-------
7	-433719	3.54	-------
8	-480913	4.99	-------
9	-456252	5.03	-------

TABLE 4. Calculated molecular magnitudes for the species involved in the conformational equilibrium of *o*-hydroxy-benzophenones in ethanol at 298 K (G^o_{sol} = total free energy in solution, kcal mol^{-1}; DM= dipole moment, Debye; dO$_1$-*o*HO= interaction distance between the carbonyl oxygen and the hydrogen of OH group at position 2 of aromatic ring A, Å; K$_C$: conformational equilibrium constant (Eq. (2)).

Optimization B3LYP/6-31G(d) with Tomasi's method (ethanol)			
Benzophenone	Conformer 1 (with HIB)			K$_C$
	G^o_{sol}	DM$_1$	dO$_1$-*o*HO	
6	-409050	5.09	1.666	3.80 x 10^{-6}
7	-433722	5.18	1.664	2.57 x 10^{-6}
8	-480917	3.87	1.655	1.26 x 10^{-6}
9	-456256	3.51	1.652	1.01 x 10^{-6}
Benzophenone	Conformer 2 (without HIB)			K$_C$
	G^o_{sol}	DM$_2$	dO$_1$-*o*HO	
6	-409043	3.76	-------	
7	-433715	3.51	-------	
8	-480909	5.02	-------	
9	-456248	4.98	-------	

FIGURE 1. Structure of the benzophenones studied.
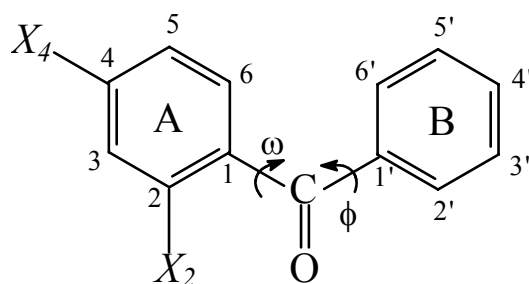
(1)	$X_2 = H$	$X_4 = H$	Benzophenone
(2)	$X_2 = H$	$X_4 = Cl$	4(Cl)-Benzophenone
(3)	$X_2 = H$	$X_4 = F$	4(F)-Benzophenone
(4)	$X_2 = H$	$X_4 = OH$	4(OH)-Benzophenone
(5)	$X_2 = H$	$X_4 = CH_3O$	4(CH_3O)-Benzophenone
(6)	$X_2 = OH$	$X_4 = H$	2(OH)-Benzophenone
(7)	$X_2 = OH$	$X_4 = CH_3$	2(OH),4(CH_3)-Benzophenone
(8)	$X_2 = OH$	$X_4 = CH_3O$	2(OH),4(CH_3O)-Benzophenone
(9)	$X_2 = OH$	$X_4 = OH$	2,4$(OH)_2$-benzophenone

FIGURE 2. Practical numbering system adopted in the calculations.
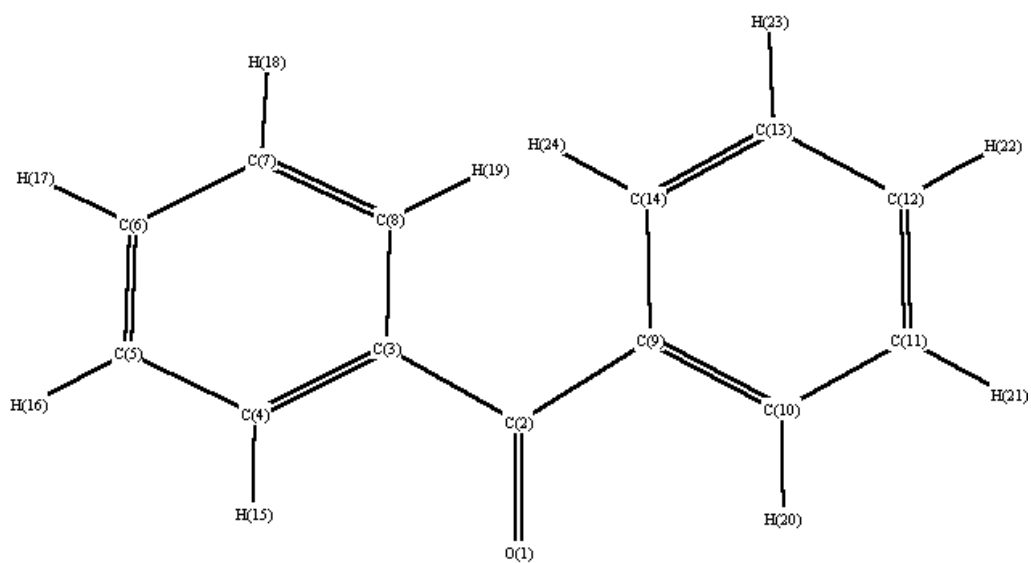
FIGURE 3. Potential energy curve for phenyl-ring A of unsubstituted benzophenone computed at HF/6-31G(d) level of theory in vacuum and water, at 298 K.
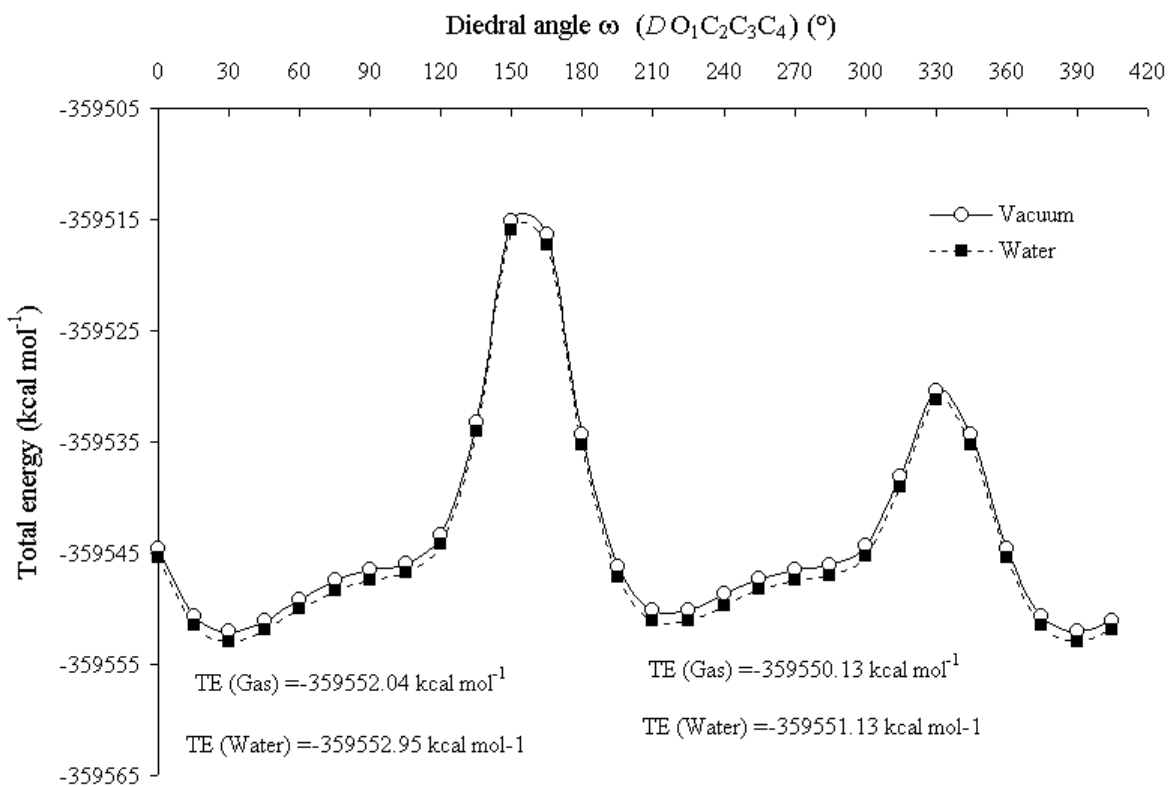
FIGURE 4. Changes of the ω torsional angles of *p*-substituted benzophenones computed at B3LYP/6-31G(d) with the Hammett's *p*-substituent constants.

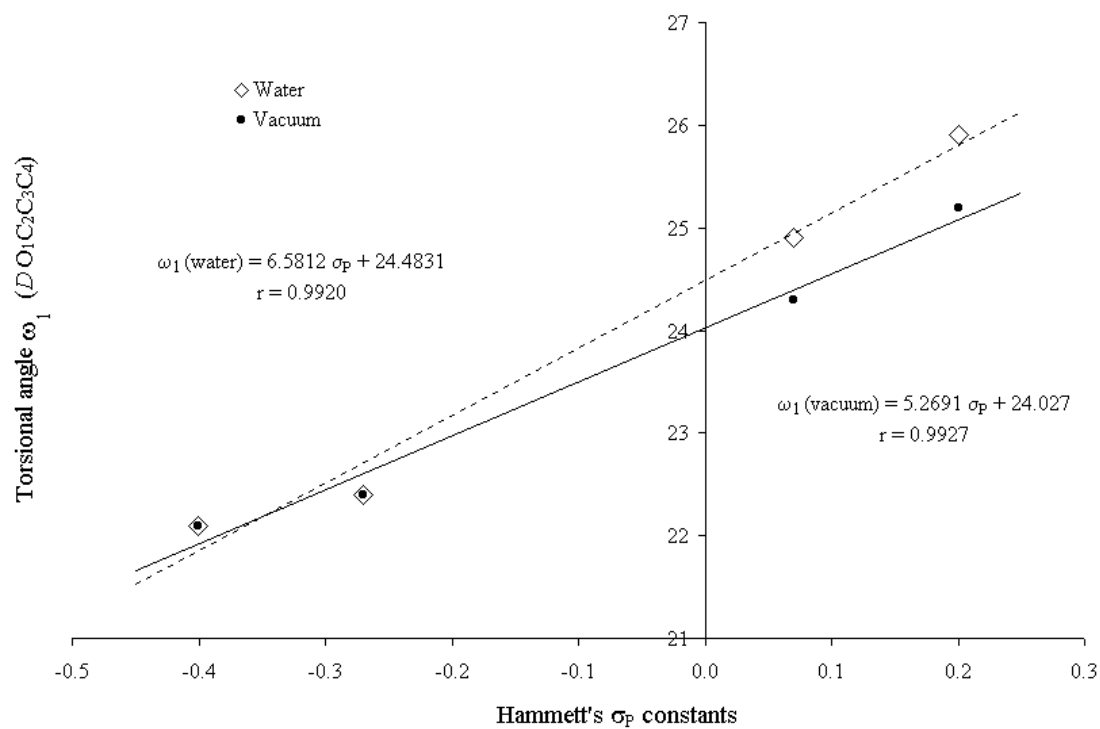FIGURE 5. Potential energy curve for phenyl-ring A of 2-hydroxy-benzophenone computed at HF/6-31G(d) level of theory in water, at 298 K.
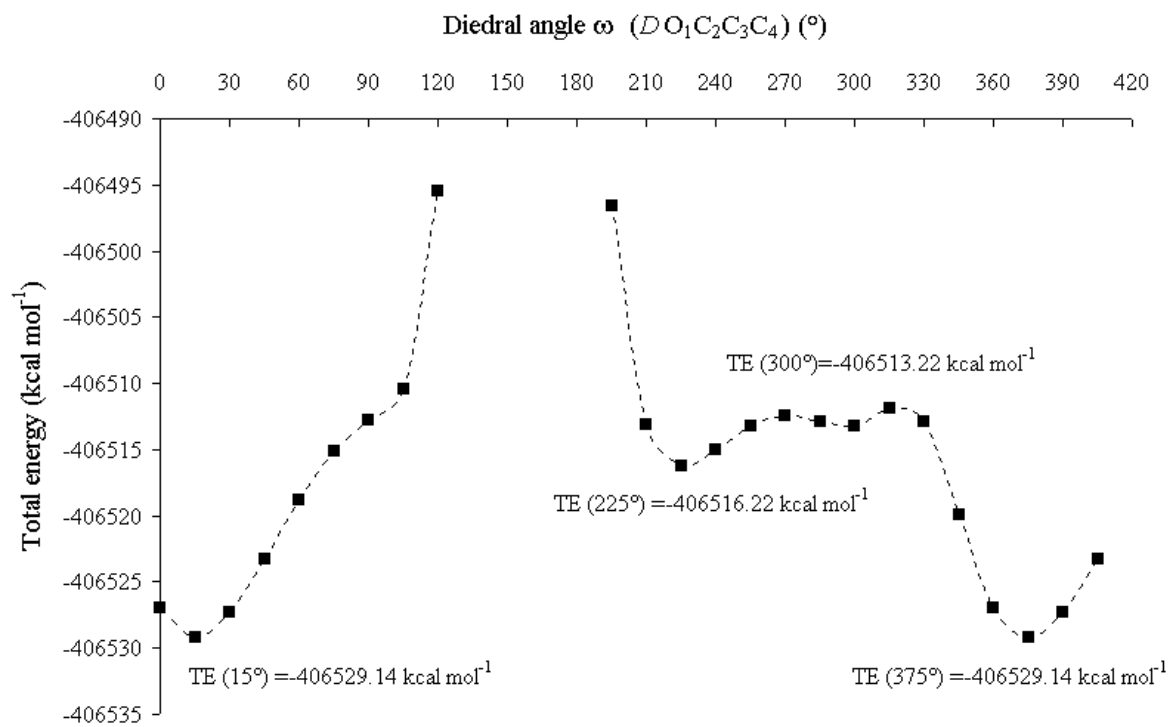
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FIGURE 6. Non-symmetrical conformers of 2-hydroxy-benzophenone optimized at B3LYP/6-31G(d). (a) Conformer 1 (with IHB); (b) Conformer 2 (without IHB).
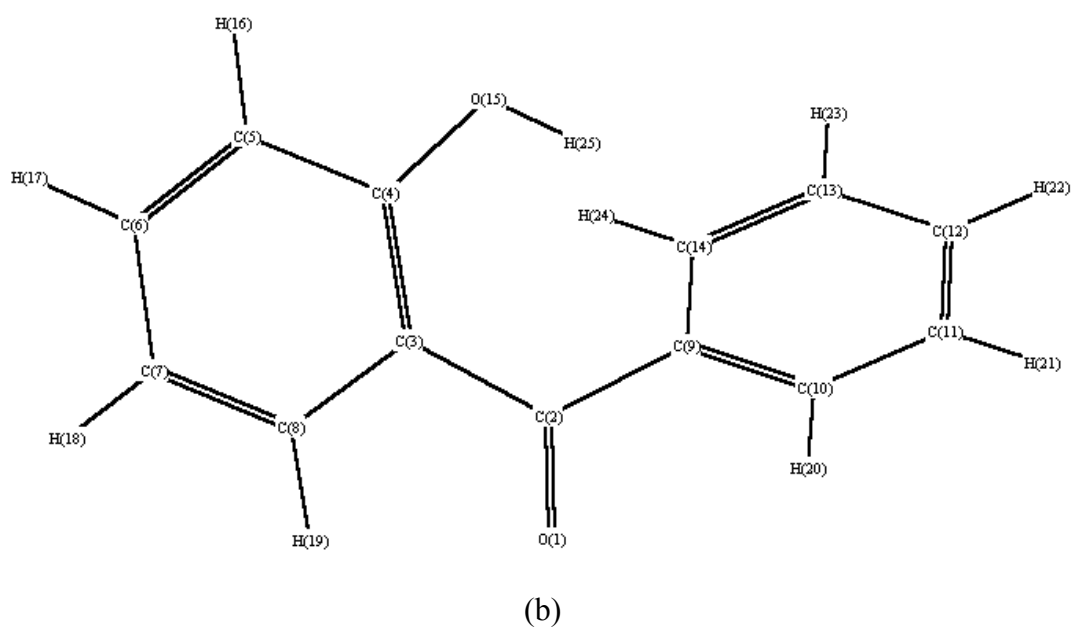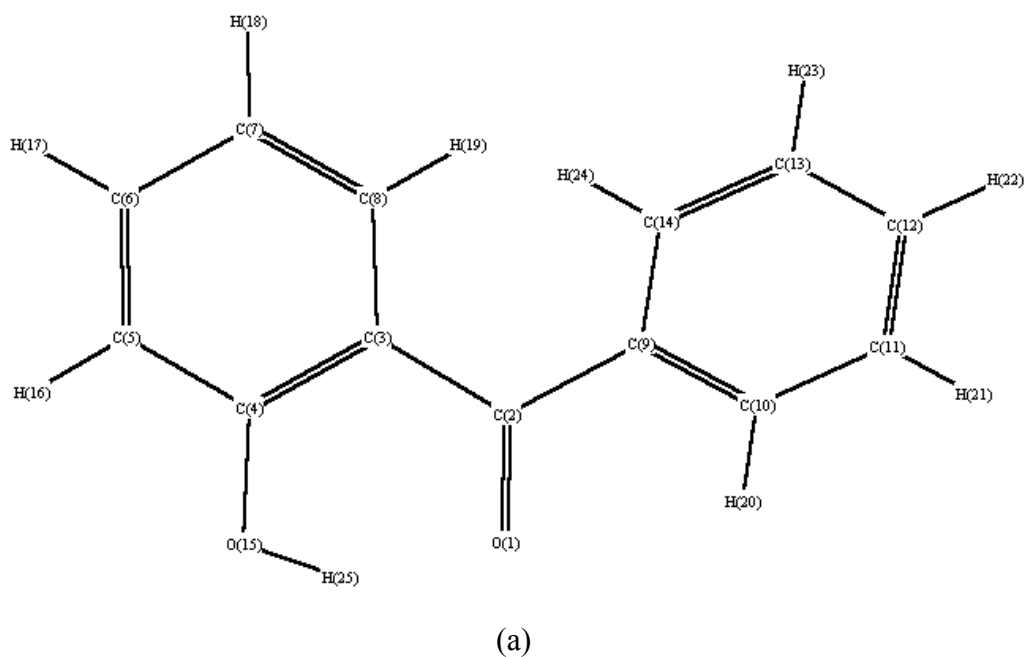

(a)

(b)

FIGURE 7. Relationships between the dipolar moments of *o*-hydroxy-benzophenones and *Acity* parameter of the solvating solvents.
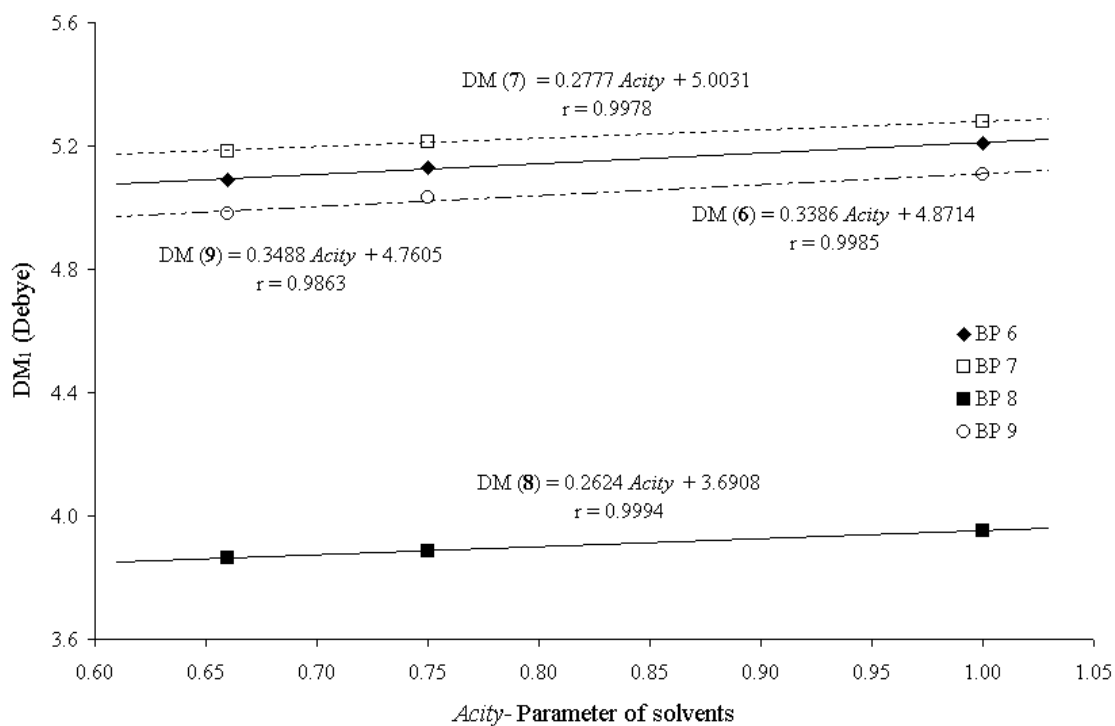
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FIGURE 8. Change of the conformational equilibrium constant of *o*-hydroxy-benzophenones with the Hammett's *p*-substituent constants.

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