

Solvent and substituent effects on the conformational equilibria and intramolecular hydrogen bonding of 4-substituted-2-hydroxybenzaldehydes

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Abstract—By applying the B3LYP/6-31G(d) method with the SCIPCM model on seven 4X substituted 2-hydroxybenzaldehydes, some structural characteristics related with their conformational equilibria and intramolecular hydrogen bonds have been clarified. The compounds are almost completely under the planar conformation characterized by a strong intramolecular hydrogen bond, which decreases in those solvents that possess a higher hydrogen bond donating capability and polarity. The substituents exert a marked influence on the conformational equilibrium constants and the strength of the IHB. Moreover, the excellent Hammett-type equations obtained support the proposed conformational reactions to quantify the IHB in the *o*-hydroxybenzaldehydes studied. © 2007 Elsevier Ltd. All rights reserved.

1. Introduction

Compounds with exceptional biological and physico-chemical properties are obtained by synthesis that involve 2-hydroxybenzaldehydes (2OHBz).^{1–3} Thus, the most recent methodology for preparing benzopyrans is based on base-catalyzed condensation of 2OHBz with α,β -unsaturated aldehydes.^{4,5} The formation of an intramolecular hydrogen bond (IHB) in a molecule, such as 4X substituted 2-hydroxybenzaldehydes (4X-2OHBz), plays a crucial role in the determination of its physico-chemical behavior.^{6–8} Although theoretical investigations of the parent molecule have been conducted, no investigations of substituted salicylaldehydes have been reported.^{9–11} With the aim of contributing to clarify the influence of solvents and substituents on the conformational equilibria and the IHB of 4X-2OHBz, in this work we carry out a structural study of these compounds in hydroxylic solvents by means of a B3LYP/6-31G(d) method (Becke hybrid three-parameter non-local exchange functional combined with the Lee–

Yang–Parr dynamic correlation functional)^{12,13} that makes use of the SCIPCM (self-consistent isodensity polarizable continuum model).¹⁴ In order to explain the strength of the IHB in 4X-2OHBz, we consider the occurrence of three conformational reactions between molecules with and without IHB.

Figure 1 shows the structure and practical numbering system adopted for carrying out the calculations, which were performed with known procedures.¹⁵ The studied compounds were (1) 2OH-Bz; (2) 2OH,4F-Bz; (3) 2OH,4Cl-Bz; (4) 2OH,4(NO₂)-Bz; (5) 2OH,4(CH₃O)-Bz; (6) 2,4(OH)₂-Bz, and (7) 2(OH),4(NH₂)-Bz. The potential energy surface minima obtained by the scan of 4X-2OHBz were optimized with GAUSSIAN 03¹⁶ program packages, using the B3LYP/6-31G(d) method

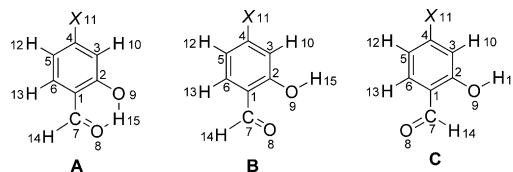


Figure 1. Structure and practical numbering system adopted in the calculations of the 4X substituted 2-hydroxybenzaldehydes studied. (A) Closed cis conformer; (B) open cis conformer; (C) trans conformer.^{7,8}

Keywords: 2-Hydroxybenzaldehydes; Conformational equilibria; Intramolecular hydrogen bond; Solvent and substituent effects; Acidity parameter; SCIPCM model; DFT method.

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and the default convergence criteria. The SCIPCM model¹⁴ was used to analyze the solvent effect on the 4X-2OHBz. Moreover, the equilibrium constants (K_{AB} , K_{AC} , K_{BC} , Eq. 2) between conformers having an IHB and those that lack this type of bond were calculated to analyze the IHB strength of the compounds in ethanol (EtOH), methanol (MeOH), and water. In the calculation of these equilibrium constants the zero-order vibrational energy contributions were considered.

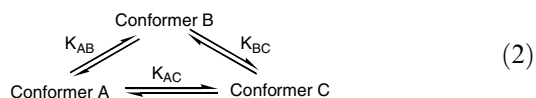
The number of conformers obtained in the scan of a compound, according to the number of rotatable bonds it possesses and the increment value adopted for rotating the involved dihedral angles can be calculated with Eq. 1,¹⁷

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

In the 4X-2OHBz analyzed the existence of three principal conformers with highest thermodynamic stability was detected (Fig. 1): (A) closed cis conformer; (B) open cis conformer; (C) trans conformer. Conformers A–C of each 4X-2OHBz have very different thermodynamic stabilities.

Table 1 reports the molecular parameters calculated for conformer A of 4X-2OHBz in hydroxylic solvents at 298 K. Due to the electron-donating groups increasing the π -electronic delocalization of the substituted aromatic ring, the simple bond nature of the C=O group and the electronic density of the carbonyl oxygen atom also increase. These facts favor the formation of a stronger IHB, which implies lower interaction distances between the carbonyl oxygen and the hydrogen of the hydroxyl group ($d_{O_8 \cdots H_{15}}$), and greater H-bond angles ($A-O_8H_{15}O_9$). An opposite behavior with electron-withdrawing groups was observed.

Taking into account the total free energy of the conformers A–C, calculated at B3LYP/6-31G(d) with SCIPCM model in EtOH, MeOH, and water at 298 K, it is inferred that the thermodynamic stability of the conformers of 4X-2OHBz in the solvents used decreases in the order, $A > C > B$. We proposed that these conformers are related by the conformational equilibria that follow,



Eq. 2 describes (a) two equilibria (K_{AB} and K_{AC}) between intramolecularly hydrogen bonded molecules (conformer A) and molecules lacking the internal hydrogen bond (conformers B and C); (b) an equilibrium (K_{BC}) between molecules not having an IHB. The values calculated for K_{AB} , K_{AC} , and K_{BC} are given in Table 2 together with Hammett's substituent constants.¹⁸ From Table 2, it can be observed that the K_{AB} , K_{AC} , and K_{BC} constants change significantly with the solvent. The

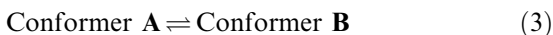
Table 1. Calculated molecular parameters for closed cis conformer of 4X-2-hydroxybenzaldehydes in hydroxylic solvents (optimization B3LYP/6-31G(d), SCIPCM model) at 298 K (C = compound; q = Mulliken's atomic charge of the indicated atom, au; $r_{C_7O_8}$ = bond length between the indicated atoms; $d_{O_8 \cdots H_{15}}$ = distance of the IHB between the indicated atoms (Å); $A-O_8H_{15}O_9$ = H-bond angle (°))

C	q_{O_8}	$r_{C_7O_8}$	$d_{O_8 \cdots H_{15}}$	$A-O_8H_{15}O_9$
<i>EtOH</i>				
1	-0.501	1.2379	1.7524	147.3
2	-0.503	1.2384	1.7394	147.5
3	-0.497	1.2371	1.7470	147.1
4	-0.481	1.2334	1.7588	146.2
5	-0.518	1.2426	1.7299	148.4
6	-0.518	1.2425	1.7312	148.3
7	-0.534	1.2467	1.7217	149.3
<i>MeOH</i>				
1	-0.501	1.2379	1.7523	147.3
2	-0.504	1.2384	1.7394	147.5
3	-0.498	1.2371	1.7470	147.1
4	-0.482	1.2333	1.7588	146.2
5	-0.519	1.2427	1.7298	148.4
6	-0.519	1.2426	1.7311	148.3
7	-0.534	1.2467	1.7218	149.3
<i>Water</i>				
1	-0.502	1.2379	1.7534	147.2
2	-0.505	1.2385	1.7393	147.6
3	-0.499	1.2372	1.7470	147.1
4	-0.483	1.2333	1.7588	146.2
5	-0.520	1.2428	1.7297	148.4
6	-0.520	1.2426	1.7305	148.4
7	-0.536	1.2467	1.7218	149.3

Table 2. Calculated equilibrium constants for conformational equilibria of 4X-substituted-2-hydroxybenzaldehydes in hydroxylic solvents at 298 K, and p -substituent constants (K_{AB} , K_{AC} , K_{BC} = conformational equilibrium constants, Eq. 2; σ_p = Hammett's p -substituent constants¹⁸)

Compound	Ethanol	Methanol	Water	σ_p
<i>Conformational equilibrium constant $K_{AB} \times 10^6$</i>				
1	3.452	4.014	5.113	0.00
2	3.528	4.176	5.547	0.07
3	4.702	5.483	6.744	0.20
4	12.75	14.61	18.72	0.78
5	1.562	1.860	3.711	-0.27
6	1.355	1.910	2.271	-0.40
7	0.8063	0.8904	1.240	-0.66
<i>Conformational equilibrium constant $K_{AC} \times 10^5$</i>				
1	6.072	6.793	8.524	0.00
2	4.990	6.062	7.403	0.07
3	6.893	7.696	8.700	0.20
4	19.64	21.49	25.21	0.78
5	1.746	2.010	2.743	-0.27
6	1.853	2.513	2.758	-0.40
7	1.232	1.383	1.698	-0.66
<i>Conformational equilibrium constant K_{BC}</i>				
1	17.588	16.921	16.670	0.00
2	14.144	14.518	13.345	0.07
3	14.660	14.035	12.901	0.20
4	15.402	14.708	13.468	0.78
5	11.181	10.804	7.3911	-0.27
6	13.672	13.155	12.142	-0.40
7	15.279	15.529	13.696	-0.66

$\text{Ln}K_{\text{AB}}$ values were plotted against the *Acity* parameter¹⁹ of the solvents used as shown in Figure 2. The parameter *Acity* is very useful for measuring the hydrogen bond donating ability (HBD capability) of a solvent, that is, the capability of the solvent to provide a proton. The values of *Acity* determined for EtOH, MeOH, and water are 0.66, 0.75, and 1.00,²⁰ respectively. The linear equations included in Figure 2 indicate that when the *Acity* increases the corresponding K_{AB} increases. This signifies that the solvents with greater HBD capability favor the conformational reaction,



In order to quantify the strength of the IHB in 4X-2OHBz, we consider that the free energy change of the reaction described by Eq. 3 is a reasonable quantification parameter (SIHB, kcal mol^{-1}).

Figure 3 plots the SIHB against the *Acity* parameter of the solvents. The linear equations of Figure 3 ($r > 0.99$) indicate that when the *Acity* increases the corresponding SIHB parameter decreases. This fact reveals that the strength of the IHB of 4X-2OHBz decreases in those solvents that possess higher HBD capability.

Besides, it should be noted that the values of K_{AB} and K_{AC} ranged between 8.063×10^{-7} – 1.872×10^{-5} and 1.232×10^{-5}

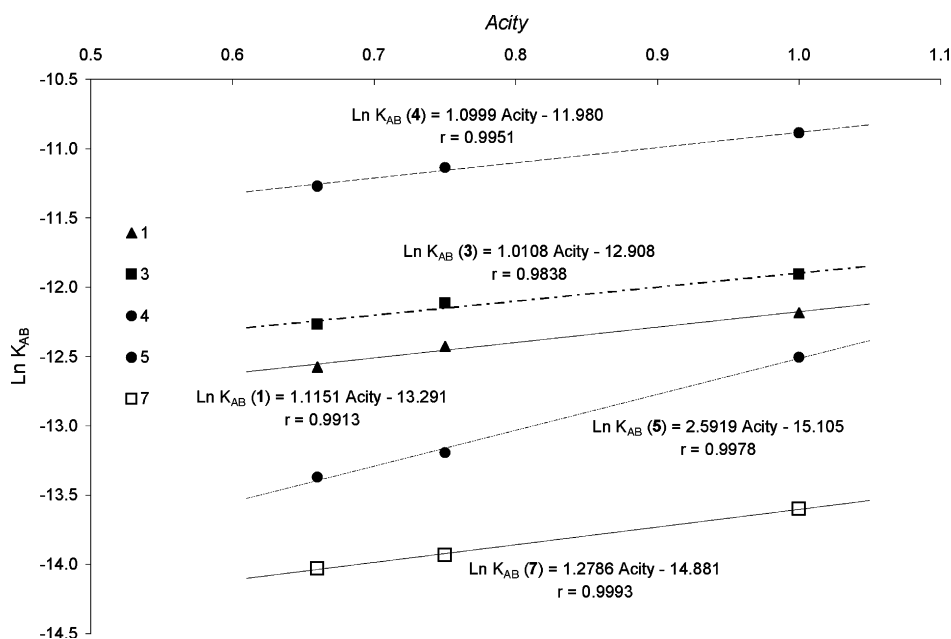


Figure 2. Influence of the solvent on the equilibrium constant of the conformational reaction of Eq. 3.

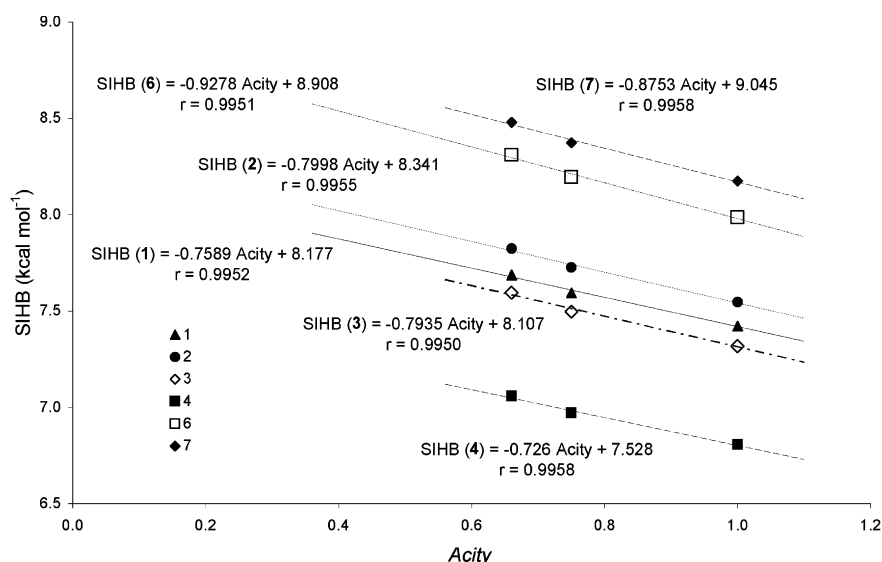


Figure 3. Plot of SIHB against the *Acity* parameter of solvents (SIHB = free energy change of the conformational reaction of Eq. 3).

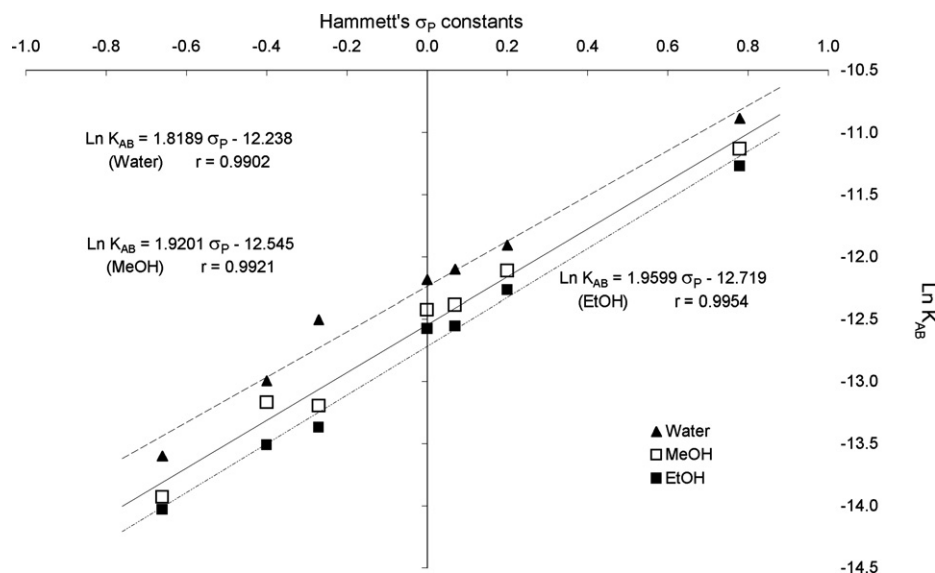


Figure 4. Changes of the conformational equilibrium constant K_{AB} of 4X-substituted-2-hydroxybenzaldehydes with the Hammett's p -substituent constants.

-2.521×10^{-4} , respectively. Since $K_{AB} \ll 1$ and $K_{AC} \ll 1$, the investigated 4X-2OHBz are almost completely under conformation A. For example, for compound **3** in water at 298 K, $K_{AB} = 6.744 \times 10^{-6}$ and $K_{AC} = 8.700 \times 10^{-5}$. In this way, the theoretical calculations predict 99.99097% of **3A**, 0.00051% of **3B**, and 0.00852% of **3C** in the equilibrium.

The substituents exert a strong influence on the K_{AB} , K_{AC} , and K_{BC} constants. For instance, Figure 4 depicts the $\text{Ln } K_{AB}$ changes with respect to Hammett's σ_p constants in EtOH, MeOH, and water. The linear equations slopes included in Figure 4 indicate that the effect of p -substituents decreases with the HBD capability of the reaction medium. It is also observed that the electron donating groups increase the occupancy fraction of conformation A. This is coherent with the linear relationship obtained between the $A\text{-O}_8\text{H}_{15}\text{O}_9$ H-bond angles of 4X-2OHBz (EtOH, Table 1) and σ_p experimental values

$$A\text{-O}_8\text{H}_{15}\text{O}_9 = -2.1219\sigma_p + 147.64 \quad (4)$$

The above equation suggests that the electron-withdrawing groups, by decreasing the $A\text{-O}_8\text{H}_{15}\text{O}_9$ H-bond angle, increase the corresponding $d\text{O}_8\text{-H}_{15}$ interaction distance and consequently, the strength of the IHB decreases. It was concluded that the establishment of Hammett-type equations, widely ensures the suitability of the conformational reactions proposed (Eq. 2) for a comparative study of the intramolecular hydrogen bond in 4X-2OHBz.

2. Conclusions

The influence of p -substituents and solvent effects on the conformational equilibria and the strength of the intramolecular hydrogen bond of 4X substituted 2-hydroxybenzaldehydes were studied by means of a B3LYP/6-31G(d) method that makes use of the SCI-

PCM model. The compounds studied have a planar structure and possess three important conformers with different thermodynamic stabilities. One of these conformers is characterized by a strong IHB while the other ones lack this type of bond. The compounds are almost completely under the planar conformation with IHB, but the solvents with greater HBD capability favor the formation of conformers without IHB. This signifies that the IHB strength of 4X-2OHBz decreases in those solvents that possess higher HBD ability. In addition, it was determined that the substituents exert a great influence on the conformational equilibrium constants. Furthermore, the effect of p -substituents decreases when the HBD capability of the solvent increases. It was concluded that the excellent Hammett-type relationships obtained, support the proposed conformational reactions described by Eqs. 2 and 3.

Acknowledgement

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