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Roxana A. Rudyk,<sup>1</sup> María A. A. Molina,<sup>1</sup> María I. Gómez,<sup>1</sup> Sonia E. Blanco,<sup>2</sup> and  
Ferdinando H. Ferretti<sup>2</sup>

<sup>1</sup> Cátedra de Química General, Facultad de Bioquímica, Química y Farmacia, Universidad Nacional  
de Tucumán, Ayacucho 491, 4000 Tucumán, República Argentina

<sup>2</sup> Area de Química–Física, Facultad de Química, Bioquímica y Farmacia, Universidad Nacional de  
San Luis, Chacabuco y Pedernera, 5700 San Luis, República Argentina

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## Structure and Dipole Moment of Catechol in Hydroxylic Solvents<sup>#</sup>

Roxana A. Rudyk,<sup>1</sup> María A. A. Molina,<sup>1</sup> María I. Gómez,<sup>1</sup> Sonia E. Blanco,<sup>2</sup> and  
Ferdinando H. Ferretti<sup>2,\*</sup>

<sup>1</sup> Cátedra de Química General, Facultad de Bioquímica, Química y Farmacia. Universidad Nacional de Tucumán. Ayacucho 491, 4000 Tucumán, República Argentina

<sup>2</sup> Area de Química-Física, Facultad de Química, Bioquímica y Farmacia, Universidad Nacional de San Luis, Chacabuco y Pedernera, 5700 San Luis, República Argentina

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### Abstract

**Motivation.** Various classes of flavonoids of great importance for medicine have a molecular structure containing a resorcinol in its A-ring whereas the B-ring is a catechol derivative. With a future view to establishing correlations between the physicochemical and biological properties of flavonoids and catechols and with the specific aim of explaining the dipole moment of catechol in water, we investigated the molecular conformations and solute–solvent interactions of catechol in ethanol, methanol and water.

**Method.** Basis sets at two levels of theory: HF/6–31G(d,p) and B3LYP/6–31G(d,p) were used for calculations. Onsager's method was used to analyze the solvent effects on the conformers of catechol.

**Results.** A conformational equilibrium between the two main conformers of non-solvated catechol was proposed. The total energies, dipole moments, structural molecular and reactivity parameters of the conformers and transition states involved were calculated. These theoretical magnitudes were correlated with properties of the solvating solvents. The properties of solute–solvent association complexes formed by a molecule of catechol and three molecules of water by means of intermolecular hydrogen bonds were also calculated.

**Conclusions.** The stability of the conformer that has one intramolecular hydrogen bond increases with the hydrogen–bond donor capability and polarity of the solvents. The dipole moment of catechol in water (11.45 D) is due to the solute–solvent association complexes, which are the predominant forms of the compound in aqueous solutions.

**Keywords.** Catechol; conformations; dipole moment; hydrogen bonding; solvent effects; association complexes; DFT calculations.

### Abbreviations and notations

DM, dipole moment	<i>TS</i> , transition state
D, Debye	IHB, intermolecular hydrogen bond
DFT, density functional method	HBD, hydrogen–bond donor capability
1A and 1B, conformers of catechol	HBA, hydrogen–bond–acceptor capability
RBE, rotation barrier energy	<i>D</i> , permittivity

<sup>#</sup> Dedicated to Professor Nenad Trinajstić on the occasion of the 65<sup>th</sup> birthday.

\* Correspondence author; phone: 54–2652–423789; fax: 54–2652–430224; E-mail: fferret@unsl.edu.ar.

## 1 INTRODUCTION

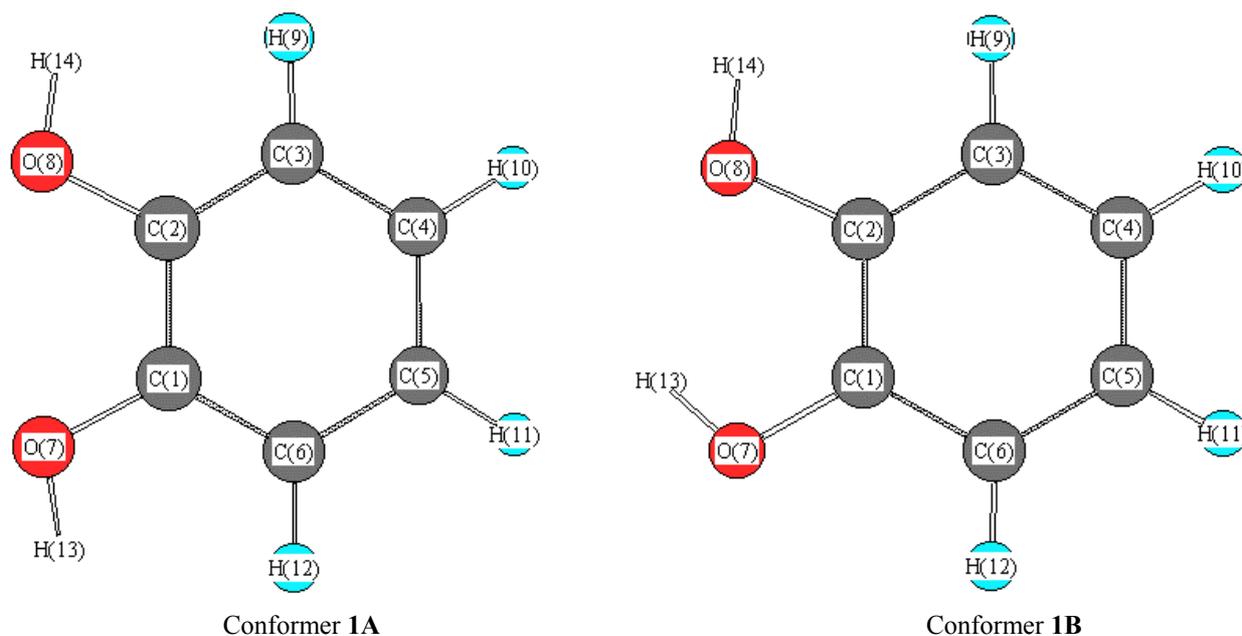
Among the numerous substances identified in medicinal plants, flavonoids [1] represent one of most interesting groups of biologically active compounds [2,3]. Inspection of the structures of various classes of flavonoids clearly shows that the A–ring in the majority of these compounds is a resorcinol, whereas the B–ring is a catechol derivative. It is known that several physicochemical parameters such as scavenging and decay rate constants, redox potentials and  $pK_a$  values, which are the most useful data to predict the antioxidative potential of flavonoids, basically depend of the presence of a B–ring catechol group [4,5]. The great importance of catechols or 1,2–benzenediols is fundamentally due to their varied biological and physicochemical properties. For this reason, these substances are object of continuous and dynamic investigations. Catechol and its derivatives like dopamine hydrochloride, levodopa, methyl dopa and adrenaline hydrochloride are widely used in important pharmaceutical formulations [6]. Recently, catechols from abietic acid were prepared by a short and good yielding chemical process and further evaluated for several biological activities, namely, antifungal, antitumoral, antimutagenic, antiviral, antiproliferative and inhibitory activity of nitric oxide production [7]. On the other hand, it has been determined that catechol readily forms complexes with aluminum (III) ions, under anhydrous conditions, to give a mixture of complexes with different stoichiometric composition metal–ligand [8]. The oxidation rate [9], spectroscopic [10] and acid–base [11] characteristics of catechol have also been investigated.

As part of a research program aimed at clarifying the stereochemical characteristics of compounds of biological importance, the dipole moments of catechol and flavone in hydroxylic solvents were previously determined by dielectric measurements [12]. The dipole moment (DM) of highly diluted solutions of catechol in water at 25°C was calculated using Buckingham’s equation [13], giving a DM average of 11.45 D [14]. With a future view to establishing correlations between the physicochemical and biological properties of flavonoids and 1,2–benzenediols, and with the specific objective of explaining the DM mentioned, in this paper we investigate the molecular conformations and solute–solvent interactions of catechol in ethanol, methanol and water by means of *ab initio* and density functional (DFT) methods.

## 2 MATERIALS AND METHODS

The structures of the conformers of catechol (**1**) and the practical numbering system adopted for carrying out the calculations are shown in Figure 1. The calculations were performed following known procedures [15]. The initial geometries of the molecules were modeled by the semiempirical AM1 method included in the CS Chem3D version 5.0 program [16]. For the determination of the potential energy surface minima of **1** in vacuum at the HF/6–31G(d,p) level of theory, energetic magnitudes of molecular structures were calculated as a function of dihedral angles ( $DH_{13O_7C_1C_2}$  and  $DH_{14O_8C_2C_1}$ ) using increments of 10° in the 0–180° interval. It was proposed that dihedral

angle  $DH_{13}O_7C_1C_2$  (or angle  $DH_{14}O_8C_2C_1$ ) is formed by the plane containing the OH group at position 1 (or position 2) and the plane containing the rest of the molecule. The two planes intersect along the single bond  $C_1-O_7$  (or single bond  $C_2-O_8$ ). The minima obtained by the scan of **1** were optimized with the Gaussian 98 [17] program packages, using basis sets at two levels of theory: HF/6–31G(d,p) and B3LYP/6–31G(d,p). Frequency calculations performed at the mentioned levels ensured that the critical points given as minima by the optimizations are indeed minima on the potential energy surface.



**Figure 1.** Structures of conformers of catechol and practical numbering system adopted for carrying out the calculations.

Onsager's method [18] was used to analyze the solvent effects (ethanol, methanol and water) on the rotamers of **1** (Figure 1), which we designate **1A** and **1B**, respectively. The conformational equilibrium constants ( $K_C$ ) between **1A**, which lacks intramolecular hydrogen bonding, and **1B**, which has this type of bond, were calculated. Furthermore, to determine the energies of the involved rotation barriers (RBEs) in the different solvents, the energies of the transition states were calculated at the B3LYP/6–31G(d,p) level of theory using the STQN method [19], QST2 option [20a]. This option requires the reactant and product structures as input, specified in two consecutive groups of title and molecule specification sections. It should be noted that the atoms must be specified in the same order in the two structures. To prove that the obtained structures were true transition states, it was determined if the structure connects the correct reactants and products by examining the imaginary frequency's normal mode. This implies that a true transition state only has one imaginary frequency [20b]. On the other hand, to explain the experimental DM of **1** in water, the formation of solute–solvent association complexes was proposed. Also, it was proposed that these complexes are formed by intermolecular hydrogen bonds that involve one molecule of **1** and

several molecules of water. The statistical calculations were carried out using a multiple regression analysis method [21]. It must be noted that straight lines were built using only three points. It is evident that a linear correlation with only 3 points is not too strong. However, using the correlation coefficient ( $r$ ) along with the standard deviation ( $sd$ ) of the straight line's slope, the confidence intervals were determined with 90% probability. Under these assumptions and with the above precautions, good relationships were obtained by linear regression between several calculated magnitudes and solvation parameters of the solvents used.

### 3 RESULTS AND DISCUSSION

#### 3.1 Selection of the calculation methods

It is well known that the basis-set has an influence on the results obtained with *ab initio* methods and that greater basis-sets gives the best results. However, it must be noted that to obtain the best possible results, besides selecting the optimal basis-set, it is necessary to start with the correct model, use methods for correcting the electronic correlation, such as the Møeller–Plesset (MP1–4) procedure and consider the basis-set superposition error (BSSE). Gould and Kollman [22] have given a good example of the effects of basis-set size, correlations and BSSE errors in calculating the hydrogen bonding energies in base pairs as guanine–cytosine and adenine–thymine.

It is generally recommended that, for the study of intramolecular and intermolecular hydrogen bonds, geometries optimized at the *ab initio* HF and MP2 levels using the 6–31G(d) basis set should be used. Then, the corresponding energies in single point calculations must be obtained using the 6–311+G(2d,p) basis set [23]. DFT methods also have been used for hydrogen–bond modeling by Breneman et al. [24].

However, is important to highlight that while the gas–phase calculations are invaluable for the insight they provide into intermolecular interactions, most chemistry, biochemistry, and molecular biology takes place in an aqueous medium. In water or a polar solvent, the molecules are subject to distortions or conformational changes due to diverse solute–solvent interactions. In this way, gas–phase calculations, by whatever method, are particularly academic for biological molecules, which do not exist in gas phase.

Therefore, and in order to choose the most appropriate method for carrying out studies in hydroxylic solvents, we performed preliminary calculations with reactions of formation of water and HF dimers, using the following levels and basis set: HF/6–31G(d), HF/6–31G(d,p), MP3/6–311+G(2d,p), B3LYP/6–31G(d) and B3LYP/6–31G(d,p). Surprisingly, the changes in the reaction free energy ( $\Delta G_r^\circ$ ) values calculated with the MP3/6–311+G(2d,p) method in aqueous medium were the most divergent from experimental observations. On the other hand, the  $\Delta G_r^\circ$  values calculated with the B3LYP/6–31G(d,p) method showed a good agreement with physicochemical properties of

flavonoids and benzophenones that we are currently investigating by spectroscopic methods. These studies, particularly of kinetic nature, imply acid base equilibria of OH groups that form part of strong intramolecular hydrogen bonds. Thus, the B3LYP/6–31G(d,p) method was selected to study catechol in hydroxylic solvents.

### 3.2 Conformational properties of catechol

Several authors have performed spectroscopic studies related with the structure of dihydroxy–derivatives of benzene [25,26]. Less attention, however, has been devoted to the study of the conformational equilibrium and dipole moment of **1** in solutions. It is well known that the number of conformers of a substance is related to the number of rotatable bonds it possesses [27]. In the analyzed compound, by rotation of the planes that involve the OH groups with respect to the plane containing the rest of the molecule around single bonds C–OH, the existence of two principal conformers of **1** was detected (Figure 1). In the same way as Mantas et al [28], it was proposed that **1A** and **1B** are related by the conformational equilibrium,



which is characterized by the conformational equilibrium constant  $K_C$ . Table 1 provide the calculated properties at the B3LYP/6–31G(d,p) level of theory for **1A**, **1B** and activated complex (*TS*) of **1** in vacuum.

**Table 1.** Calculated structural magnitudes at the B3LYP/6–31G(d,p) level of theory for the conformers (**1A**, **1B**) and activated complex (*TS*) of catechol in vacuum, at 25°C. TE = total energy (kcal mol<sup>-1</sup>);  $K_C$  = conformational equilibrium constant; RBE = energy of the involved rotation barrier (kcal mol<sup>-1</sup>); DM = dipolar moment (Debye);  $D-H_{13}O_7C_1C_2$  = dihedral angle  $H_{13}O_7C_1C_2$  (°);  $q$  = total atomic charge of Mulliken (au);  $dO_7-O_8$ ,  $dH_{13}-O_8$  = bond lengths between the indicated atoms (Å) (Figures 1 and 2);  $A-O_7H_{13}O_8$  = H–bond angle (°).

Magnitude	Vacuum		
	<b>1A</b>	<b>1B</b>	<i>TS</i>
TE	-240143.29	-240147.44	-240140.62
$K_C$		$1.10 \times 10^3$	
DM	1.11	2.49	2.02
RBE	2.67	6.82	–
$D-H_{13}O_7C_1C_2$	0	0	104.9
$qO_7$	-0.550	-0.568	-0.574
$qO_8$	-0.550	-0.595	-0.549
$qH_{13}$	0.316	0.334	0.320
$qH_{14}$	0.316	0.325	0.316
$dO_7-O_8$	2.653	2.675	2.710
$dH_{13}-O_8$	3.611	2.123	3.175
$A-O_7H_{13}O_8$	–	114.6	–

Tables 2, 3 and 4 summarize the calculated structural magnitudes using Onsager’s method at B3LYP/6–31G(d,p) for the conformers mentioned and *TS* of **1** in ethanol, methanol and water, respectively. Our determinations, performed at 298 K, indicate that **1A** and **1B** are totally planar. On the other hand, all the calculated *TS* have non–planar structures.

**Table 2.** Calculated structural magnitudes using the Onsager's method at the B3LYP/6–31G(d,p) level of theory for the conformers (**1A**, **1B**) and activated complex (*TS*) of catechol in ethanol, at 25°C. TE = total energy including solvent energy (kcal mol<sup>-1</sup>); K<sub>C</sub> = conformational equilibrium constant; RBE = energy of the involved rotation barrier (kcal mol<sup>-1</sup>); DM = dipolar moment (Debye); a<sub>0</sub> = molecular radius (Å); *D*–H<sub>13</sub>O<sub>7</sub>C<sub>1</sub>C<sub>2</sub> = dihedral angle H<sub>13</sub>O<sub>7</sub>C<sub>1</sub>C<sub>2</sub> (°); *q* = total atomic charge of Mulliken (au); *d*O<sub>7</sub>–O<sub>8</sub>, *d*H<sub>13</sub>–O<sub>8</sub> = bond lengths between the indicated atoms (Å) (Figures 1 and 2); *A*–O<sub>7</sub>H<sub>13</sub>O<sub>8</sub> = H–bond angle (°).

Magnitude	Ethanol		
	<b>1A</b>	<b>1B</b>	<i>TS</i>
TE	-240143.44	-240148.10	-240141.08
K <sub>C</sub>		2.62 × 10 <sup>3</sup>	
DM	1.39	2.96	2.34
RBE	2.36	7.02	–
a <sub>0</sub>	4.07	4.21	4.10
<i>D</i> –H <sub>13</sub> O <sub>7</sub> C <sub>1</sub> C <sub>2</sub>	0	0	106.8
<i>q</i> O <sub>7</sub>	-0.554	-0.575	-0.580
<i>q</i> O <sub>8</sub>	-0.554	-0.595	-0.552
<i>q</i> H <sub>13</sub>	0.315	0.335	0.319
<i>q</i> H <sub>14</sub>	0.315	0.331	0.318
<i>d</i> O <sub>7</sub> –O <sub>8</sub>	2.659	2.669	2.712
<i>d</i> H <sub>13</sub> –O <sub>8</sub>	3.617	2.110	3.200
<i>A</i> –O <sub>7</sub> H <sub>13</sub> O <sub>8</sub>	–	115.0	–

**Table 3.** Calculated structural magnitudes using the Onsager's method at the B3LYP/6–31G(d,p) level of theory for the conformers (**1A**, **1B**) and activated complex (*TS*) of catechol in methanol, at 25°C. TE = total energy including solvent energy (kcal mol<sup>-1</sup>); K<sub>C</sub> = conformational equilibrium constant; RBE = energy of the involved rotation barrier (kcal mol<sup>-1</sup>); DM = dipolar moment (Debye); a<sub>0</sub> = molecular radius (Å); *D*–H<sub>13</sub>O<sub>7</sub>C<sub>1</sub>C<sub>2</sub> = dihedral angle H<sub>13</sub>O<sub>7</sub>C<sub>1</sub>C<sub>2</sub> (°); *q* = total atomic charge of Mulliken (au); *d*O<sub>7</sub>–O<sub>8</sub>, *d*H<sub>13</sub>–O<sub>8</sub> = bond lengths between the indicated atoms (Å) (Figures 1 and 2); *A*–O<sub>7</sub>H<sub>13</sub>O<sub>8</sub> = H–bond angle (°).

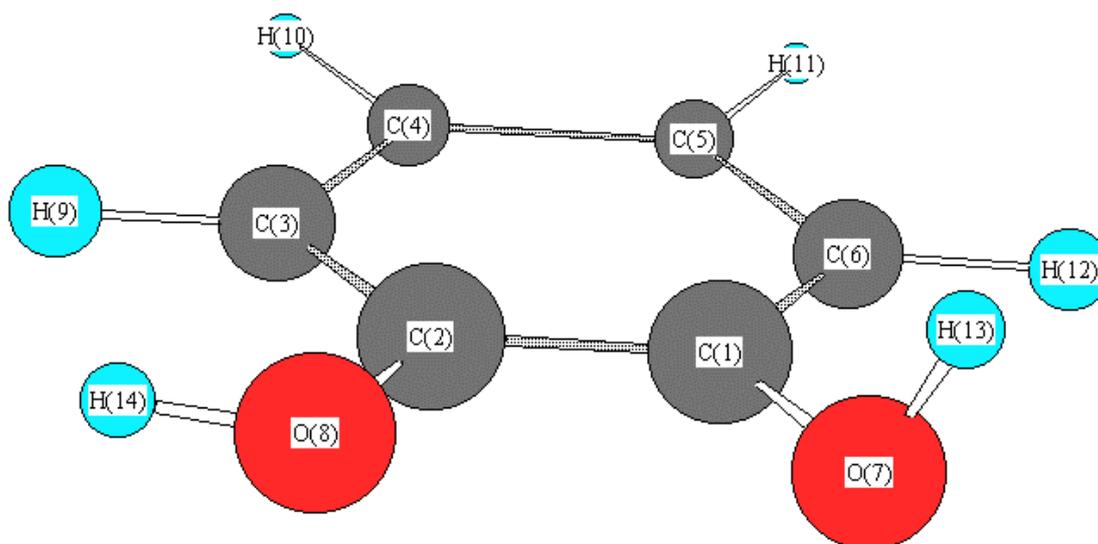
Magnitude	Methanol		
	<b>1A</b>	<b>1B</b>	<i>TS</i>
TE	-240143.46	-240148.23	-240141.18
K <sub>C</sub>		3.16 × 10 <sup>3</sup>	
DM	1.43	3.05	2.41
RBE	2.28	7.05	–
a <sub>0</sub>	3.98	4.03	3.90
<i>D</i> –H <sub>13</sub> O <sub>7</sub> C <sub>1</sub> C <sub>2</sub>	0	0	107.2
<i>q</i> O <sub>7</sub>	-0.555	-0.576	-0.581
<i>q</i> O <sub>8</sub>	-0.555	-0.594	-0.552
<i>q</i> H <sub>13</sub>	0.315	0.336	0.319
<i>q</i> H <sub>14</sub>	0.315	0.332	0.318
<i>d</i> O <sub>7</sub> –O <sub>8</sub>	2.660	2.668	2.713
<i>d</i> H <sub>13</sub> –O <sub>8</sub>	3.617	2.108	3.207
<i>A</i> –O <sub>7</sub> H <sub>13</sub> O <sub>8</sub>	–	115.1	–

For example, Figure 2 shows the structure of the *TS* computed in water. From the data in Tables 1–4 it can be observed that some of the calculated magnitudes significantly change with the solvent, while others show only slight variations. The values of dihedral angle *D*H<sub>13</sub>O<sub>7</sub>C<sub>1</sub>C<sub>2</sub>, which measures the non–planarity of the *TS* molecule, increase according to the following sequence:

$$104.9 \text{ (vacuum)} < 106.8 \text{ (ethanol)} < 107.2 \text{ (methanol)} < 107.8 \text{ (water)} \quad (2)$$

**Table 4.** Calculated structural magnitudes using the Onsager's method at the B3LYP/6–31G(d,p) level of theory for the conformers (**1A**, **1B**) and activated complex (*TS*) of catechol in water, at 25°C. TE = total energy including solvent energy (kcal mol<sup>-1</sup>); K<sub>C</sub> = conformational equilibrium constant; RBE = energy of the involved rotation barrier (kcal mol<sup>-1</sup>); DM = dipolar moment (Debye); a<sub>0</sub> = molecular radius (Å); *D*–H<sub>13</sub>O<sub>7</sub>C<sub>1</sub>C<sub>2</sub> = dihedral angle H<sub>13</sub>O<sub>7</sub>C<sub>1</sub>C<sub>2</sub> (°); *q* = total atomic charge of Mulliken (au); *d*O<sub>7</sub>–O<sub>8</sub>, *d*H<sub>13</sub>–O<sub>8</sub> = bond lengths between the indicated atoms (Å) (Figures 1 and 2); *A*–O<sub>7</sub>H<sub>13</sub>O<sub>8</sub> = H–bond angle (°).

Magnitude	Water		
	<b>1A</b>	<b>1B</b>	<i>TS</i>
TE	-240143.47	-240148.39	-240141.33
K <sub>C</sub>		3.99 × 10 <sup>3</sup>	
DM	1.45	3.15	2.52
RBE	2.14	7.06	–
a <sub>0</sub>	3.93	3.88	3.70
<i>D</i> –H <sub>13</sub> O <sub>7</sub> C <sub>1</sub> C <sub>2</sub>	0	0	107.8
<i>q</i> O <sub>7</sub>	-0.555	-0.577	-0.583
<i>q</i> O <sub>8</sub>	-0.555	-0.594	-0.554
<i>q</i> H <sub>13</sub>	0.315	0.336	0.319
<i>q</i> H <sub>14</sub>	0.315	0.333	0.319
<i>d</i> O <sub>7</sub> –O <sub>8</sub>	2.660	2.667	2.714
<i>d</i> H <sub>13</sub> –O <sub>8</sub>	3.617	2.106	3.215
<i>A</i> –O <sub>7</sub> H <sub>13</sub> O <sub>8</sub>	–	115.2	–



**Figure 2.** Calculated conformational transition state for catechol in water.

Even though these changes are small, it can be qualitatively concluded that the planarity of the structure of *TS* increases with the solvent polarity.

The greater thermodynamic stability of **1B** with respect to **1A** in vacuum and in the three solvents used (Tables 1–4) explains the values obtained for K<sub>C</sub>. It is clear that the value of this constant indicates the quantitative relationship between intramolecularly hydrogen bonded molecules (**1B**) and molecules lacking the internal hydrogen bond (**1A**). Intramolecular hydrogen bonding was firstly recognized by Sidgwick and Callow [29]. By means of these unions, the authors explained the significant differences in physical properties ortho vs meta and para hydroxy and

amino benzene derivatives. Intramolecular hydrogen bonds can be formed between donor and acceptor groups in the same molecule when the molecular configuration and conformation brings them within hydrogen bond geometry. Hydrogen bonds have been classified into strong, moderate and weak [30], according to their lengths, angles and energies. Thus, a moderate hydrogen bond has the following characteristics: (a) the two electronegative atoms ( $d_{O_7-O_8}$ ) are separated by 2.5–3.2 Å; (b) the distance between the donor–acceptor atoms ( $d_{H_{13}-O_8}$ ) varies between 1.5 and 2.2 Å; (c) the bonding energy ( $\cong TE \mathbf{1B} - TE \mathbf{1A}$ ) is in the 4–15 kcal mol<sup>-1</sup> range; (d) the bond angle ( $A-O_7H_{13}O_8$ ) changes in the 30–180° range. The intramolecular hydrogen bond of **1B** is formed by the H<sub>13</sub> atom of OH group bonded to C<sub>1</sub> and the O<sub>8</sub> atom of OH group at position 2. From Tables 1–4 it can be observed that our data completely satisfy properties (a), (b) and (c). However, it must be noted that the values obtained for the  $A-O_7H_{13}O_8$  bond angles ( $\cong 115^\circ$ ) are not within the 130–180° range. The hydrogen bond of **1B** is formed by OH groups attached to two adjacent carbon atoms, as occurs in the vicinal intramolecular hydrogen bondings of the carbohydrates. Consequently, a stabilization ring of five atoms (C<sub>1</sub>O<sub>7</sub>H<sub>13</sub>O<sub>8</sub>C<sub>2</sub>) is formed, while the formation of stabilization rings of six atoms, as in *o*-hydroxylated carbonylic compounds, is more common [31]. It is reasonable to assume that the bond angle in a ring of five members is smaller than in one of six members. This assumption explains why the calculated angles  $A-O_7H_{13}O_8$  are smaller than 130°. According to our calculations, it is concluded that the intramolecular hydrogen bond of **1B** is a moderate hydrogen bond. It must be noted that Kjaergaard *et al.* [10] recently determined the OH– and CH–stretching overtone spectra of **1** and explained their results proposing that the compounds presents a relatively weak intramolecular hydrogen bond.

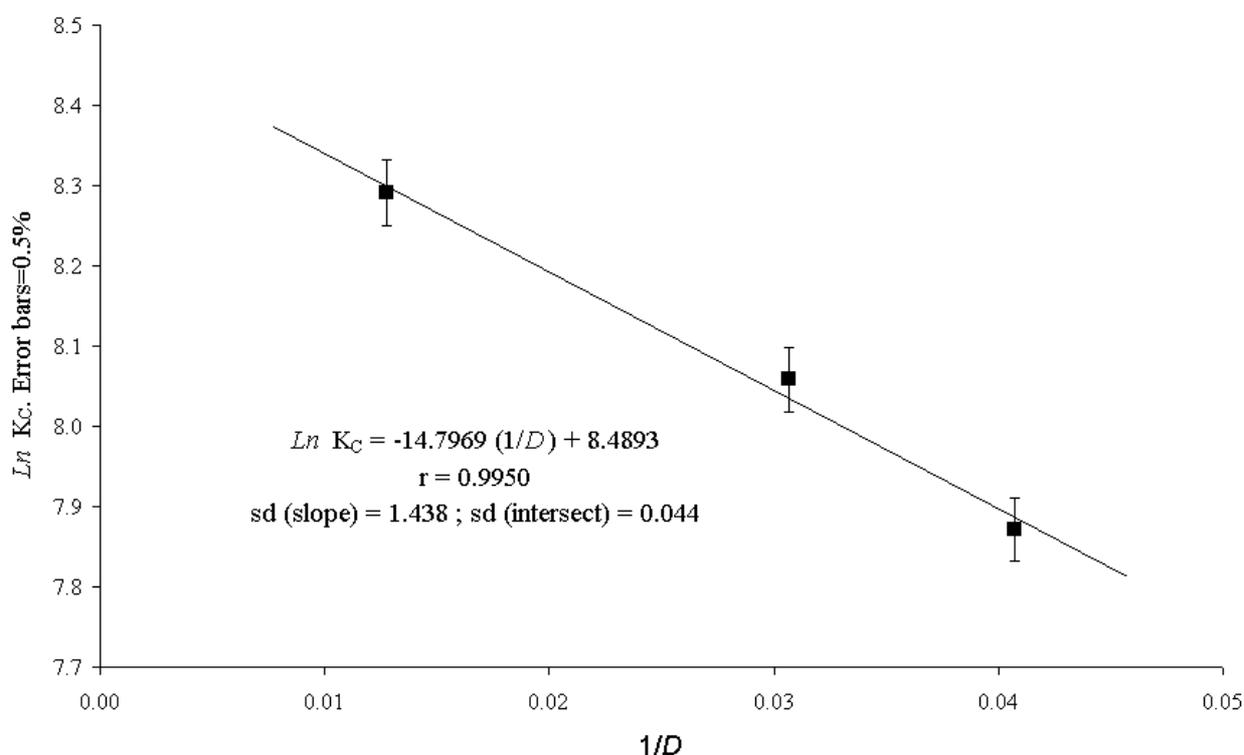
The structure of **1A** in vacuum (Tables 1–4) suffers slight changes with respect to their structures in solution; for example: (a) the  $d_{O_7-O_8}$  and  $d_{H_{13}-O_8}$  distances increase by 0.006 Å and 0.007 Å, respectively; (b) Mulliken's charges  $q_{O_7} = q_{O_8} = -0.550$  increase in absolute value up to  $q_{O_7} = q_{O_8} = -0.555$ , while  $q_{H_{13}} = q_{H_{14}} = 0.316$  practically remain constant; (c) the DMs also change significantly in the order 1.11 D (vacuum) < 1.39 D (ethanol) < 1.43 D (methanol) < 1.45 D (water); (d) the RBEs (kcal mol<sup>-1</sup>) decrease progressively as follows, 2.67 (vacuum) > 2.36 (ethanol) > 2.28 (methanol) > 2.14 (water). These results suggest that although both **1A** and *TS* increase their solvation with the solvent polarity, the solvation of *TS* is greater than that of **1A**. Consequently, forward reaction **1A** → **1B** is favored when the solvent polarity increases.

It must also be noted that the structure of **1B** in vacuum (Tables 1–4) also suffers slight changes as compared to their structures in solution. For example, (a) the  $d_{O_7-O_8}$  and  $d_{H_{13}-O_8}$  distances progressively decrease from 2.675 Å and 2.123 Å, respectively, to 2.667 Å and 2.106 Å, the values they exhibit in aqueous medium; (b) Mulliken's charge  $q_{O_7} = -0.568$  increases in absolute value up to  $q_{O_7} = -0.577$ , while  $q_{O_8} = -0.595$  practically remains constant; (c) H–bond angle  $A-O_7H_{13}O_8$  slightly increases from 114.6° to 115.2°; (d) as observed in **1A**, the DMs of **1B** increase significantly in the order 2.49 D (vacuum) < 2.96 D (ethanol) < 3.05 D (methanol) < 3.15 D (water); (e) the

RBEs for the reverse reaction **1B** → **1A** slightly increase from 6.82 kcal mol<sup>-1</sup> in vacuum to 7.06 kcal mol<sup>-1</sup> in water. In this case it can be inferred that the solvation of **1B** is greater than that of **TS**. Therefore, the occurrence of the above reaction decreases when the solvent polarity increases.

From Tables 1–4 it can be observed that the  $K_C$  values of **1** increase when the permittivity (or dielectric constant) of the reaction medium increases. The influence of the solvent upon the specific rate dipole–dipole reactions can be analyzed using the expression by Kirkwood [32,33]. Based on this expression, and considering our particular reaction system defined by Eq. (1), a relationship between the  $K_C$  of **1** and the permittivity ( $D$ ) of the medium was obtained,

$$\ln K_C = \ln K_\infty + \frac{3}{4kT} \left[ \frac{DM_{1A}^2}{r_{1A}^3} - \frac{DM_{1B}^2}{r_{1B}^3} \right] \frac{1}{D} \quad (3)$$



**Figure 3.** Relationship between the conformational equilibrium constant of catechol and the permittivity of hydroxylic solvents ( $r$  = coefficient correlation;  $sd$  = standard deviation).

In this equation,  $K_\infty$  is the conformational equilibrium constant for a medium with infinite  $D$ ;  $k$  is Boltzmann's constant;  $T$  is the absolute temperature;  $DM$  stands for the dipolar moments and  $r$  is the radius of the involved species. The  $K_C$  values calculated for **1** were plotted against  $1/D$  according to equation (3), as shown in Figure 3. The following expression was obtained,

$$\ln K_C = -14.7969 \frac{1}{D} + 8.4893 \quad r = 0.9950; \quad sd(\text{slope}) = 1.438 \quad (4)$$

where,  $r$  is the correlation coefficient and  $sd$  is the standard deviation. Eq. (4) indicates that  $D$  and

the corresponding  $K_C$  increase simultaneously. This implies that the solvents with highest polarity favor the conformational reaction described in Eq. (1). Analyzing Eqs. (3) and (4), it is inferred that in a solvent with  $D = \infty$ ,  $K_\infty$  is equal to  $4.86 \times 10^3$ .

On the other hand, using Eq. (3) and the data from Tables 2–4, the following  $K_\infty$  values were obtained,  $K_\infty$  (ethanol) =  $2.80 \times 10^3$ ,  $K_\infty$  (methanol) =  $3.36 \times 10^3$ ,  $K_\infty$  (water) =  $4.12 \times 10^3$ . From the mean of the three above values, we obtained  $K_\infty$  (average) =  $3.43 \times 10^3$ . The difference between the numerically calculated  $K_\infty$  constant and that obtained from Eq. (4) ( $K_\infty = 4.86 \times 10^3$ ) is lower than 30%. This shows the excellent match between Eq. (3) here proposed and the magnitudes calculated in ethanol, methanol and water, at 298 K.

On the other hand, it is obvious that, in solution, **1** undergoes specific solvent–solute interactions such as intermolecular hydrogen bonds (IHBs). Consequently, although  $D$  is an important physical property to measure the solvation abilities of solvents, we considered of great interest to relate the calculated  $K_C$  constants with other parameters of the solvents, which measure their specific interactions [34]. In this manner, to describe the solvent effects on the conformational equilibrium analyzed, we selected parameters  $\alpha$  [35] and  $\beta$  [36], and the solvation parameter *Acity* [37].

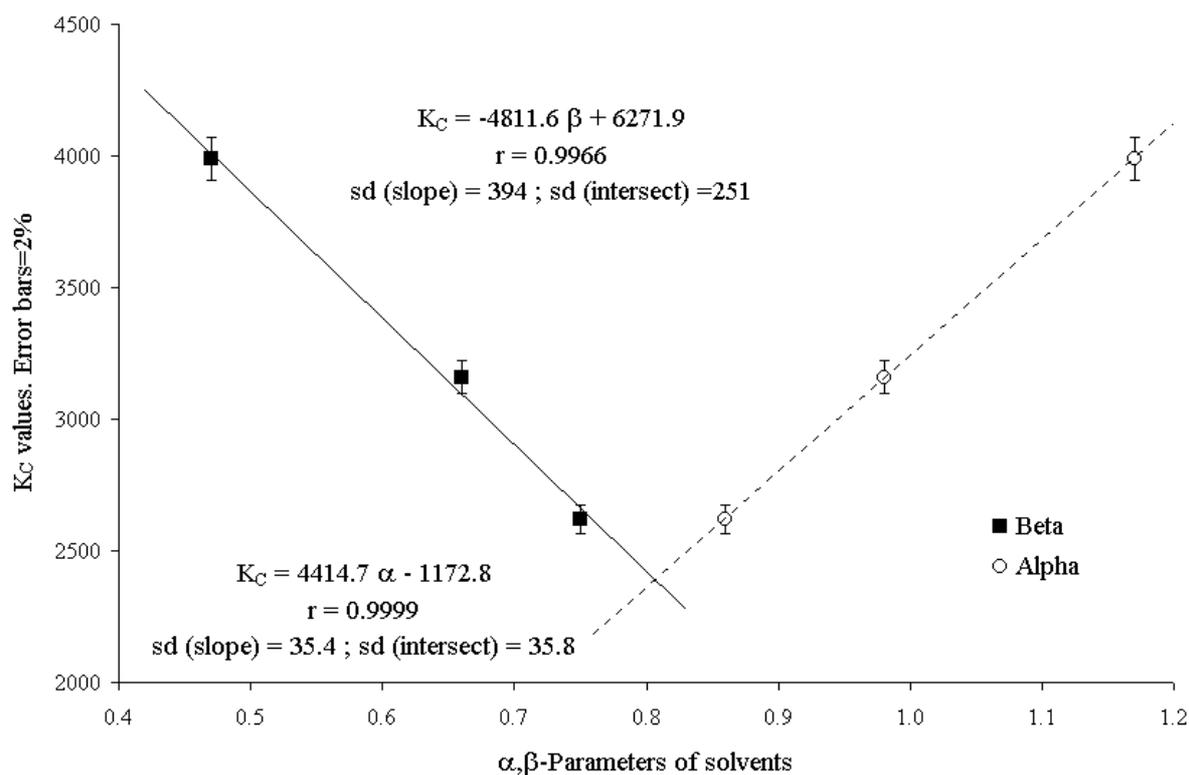
The  $\alpha$  scale measures the acidity of a hydrogen–bond–donor (capability to provide a proton) of the solvents. The  $\alpha$ –parameter measures exclusively the hydrogen–bond donor (HBD) properties of the solvents. The values of  $\alpha$  determined for ethanol, methanol and water are 0.86, 0.98 and 1.17 [38], respectively. The  $\beta$  scale measures the basicity of a hydrogen–bond–acceptor (capability to accept a proton) of the solvents. The  $\beta$ –parameter measures exclusively the hydrogen–bond–acceptor (HBA) properties of the solvents. The values of  $\beta$  determined for ethanol, methanol and water are 0.75, 0.66 and 0.47 [38], respectively.

It must be noted that parameters  $\alpha$  and  $\beta$  are not affected by other properties of the solvents, such as polarity, polarizability, tightness of cohesion, etc. Therefore, they are very useful for describing interactions that involve solute–solvent IHBs [38,39]. The *Acity* parameter developed by Swain [37], is as useful as the  $\alpha$  parameter of Taft for measuring the hydrogen bond donating ability of a solvent. According to Marcus [38], the *Acity* is related with  $\alpha$  in the following way:

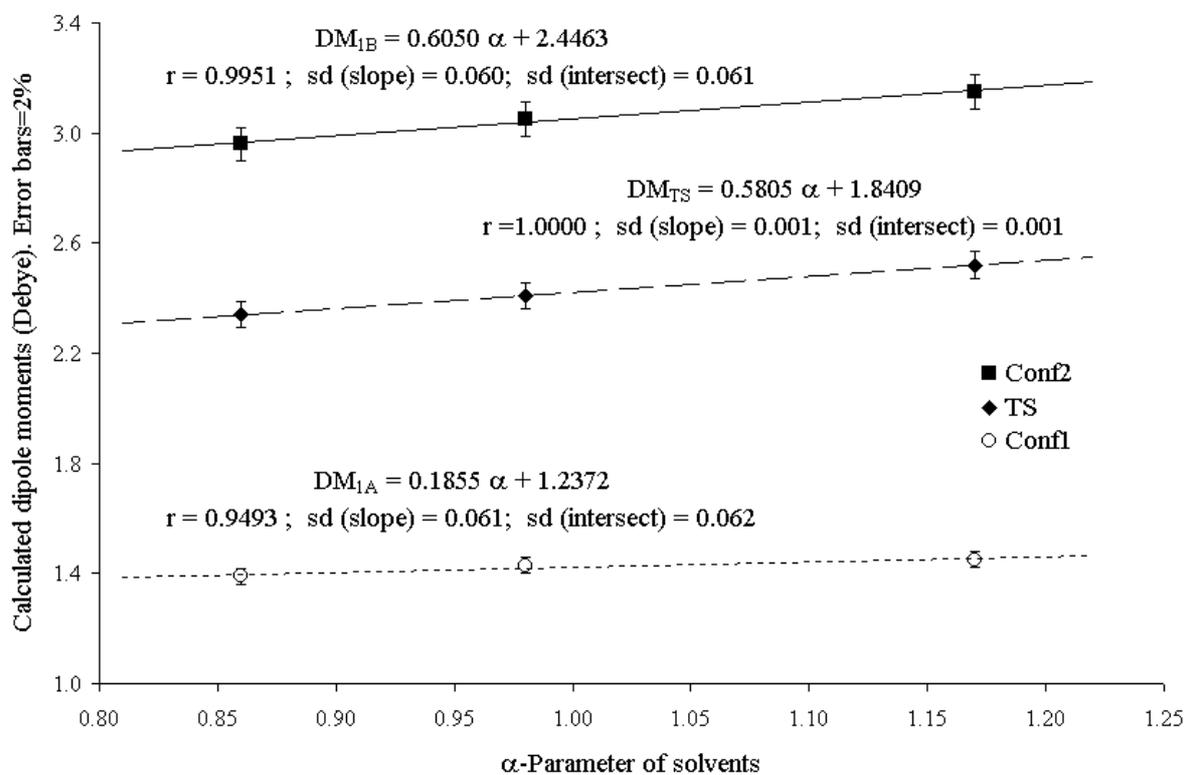
$$Acity = 0.03 + 0.64 \alpha + 0.25 \pi^* \quad (5)$$

where  $\pi^*$  is a solvatochromatic polarity–polarizability parameter [36]. The values of *Acity* determined for ethanol, methanol and water are 0.66, 0.75 and 1.00, respectively.

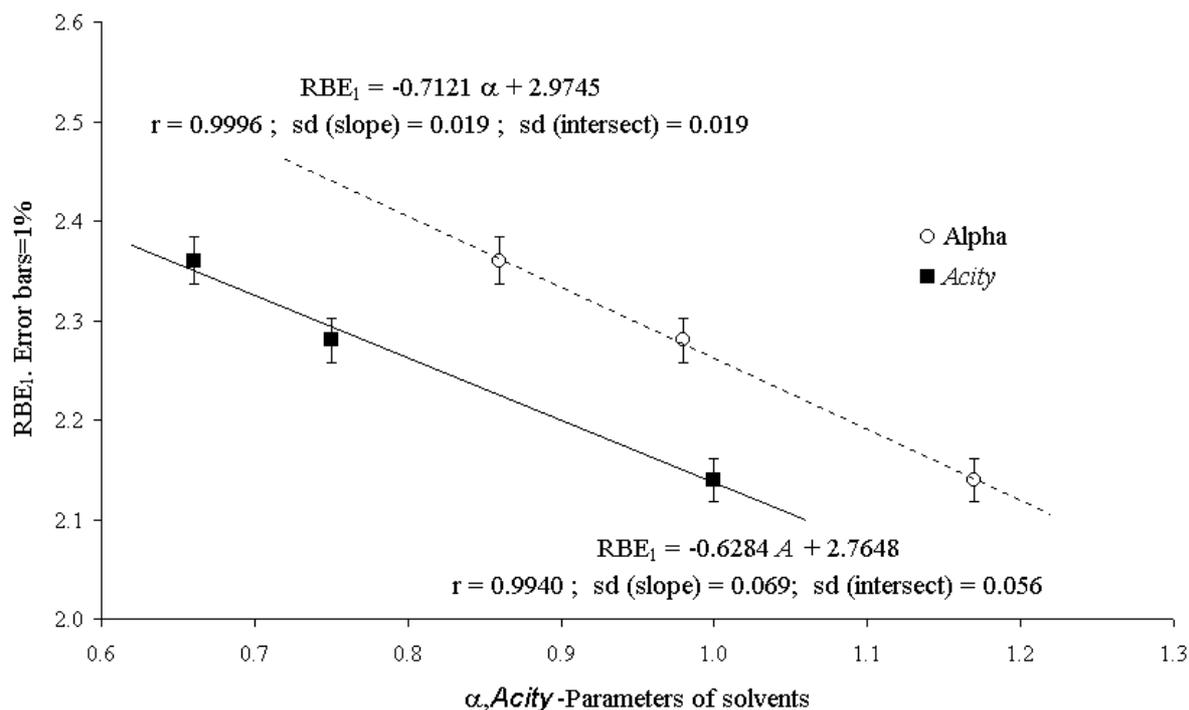
Good relationships were obtained between several theoretical magnitudes of the involved species in the conformational equilibrium of **1** and properties of solvating solvents. Figure 4 shows the increase and decrease of  $K_C$  with parameters  $\alpha$  and  $\beta$  of the solvents used, respectively.



**Figure 4.** Relationships between the  $K_C$  constants of catechol and the  $\alpha, \beta$ -parameters of solvents ( $r$  = coefficient correlation;  $sd$  = standard deviation).



**Figure 5.** Changes of the dipole moments of conformers and transition state of catechol with the  $\alpha$ -parameter of solvents ( $r$  = coefficient correlation;  $sd$  = standard deviation).



**Figure 6.** Variations of the rotation barrier energy of catechol with the  $\alpha$ , *Acity*-parameters of hydroxylic solvents ( $r$  = coefficient correlation;  $sd$  = standard deviation).

Similarly, Figure 5 shows the changes of the dipole moments of the conformers and transition state of **1** with the  $\alpha$ -parameter of the considered solvents. The variations of the rotation barrier energy (RBE) of **1** with the parameters  $\alpha$  and *Acity* of the solvents are shown in Figure 6. From Figures 4–6, it is observed that the linear equations obtained have very good correlation coefficients ( $r > 0.990$ ), with error bars of 1–2% and in general, low values for  $sd$  of slopes.

The equations of Figure 4 indicate that: (a) the increase of the HBD capability of the solvents favor a higher thermodynamic stability of **1B** with respect to **1A** and, therefore, an increase of the corresponding equilibrium constants; (b) The  $K_C$  constant increases when the HBA ability of the solvent decreases. The linear equations shown in Figure 5 reveal that the major HBD capability of a solvent favors the highest polarization of a species and consequently, increases its dipole moment. The equations of Figure 6 show that the RBEs vary inversely with the  $\alpha$ , *Acity*-parameters of the solvents. This fact implies that the solvents with highest polarity and HBD ability, decrease the corresponding RBEs and consequently, favor the conformational reaction described in Eq. (1).

As regards the conformational equilibrium of **1**, numerous lineal equations were obtained, which have been included in Figures 3–6. All these equations share the property of relating a theoretical magnitude of the involved species with experimental properties of the hydroxylic solvents. From an analysis of these equations it can be inferred that in solution the molecules of **1** undergoes several general and specific interactions with the solvent molecules. It is concluded that the degree of conversion **1A**  $\rightarrow$  **1B** increases with the HBD capability and polarity of the reaction medium.

Nevertheless, it must be pointed that, considering the DMs of the non-solvated conformers, it is not possible to explain the experimental DM of **1** in water. This is due to the fact that the values obtained for the DM of **1A** (1.45 D) and **1B** (3.15 D) were lower than the experimental DM of **1** (11.45 D) [14].

### 3.3 Solvent–solute association complexes

The solubility of a solid in a liquid cannot be predicted in a wholly satisfactory manner, except for ideal solutions, because of the various complicating factors that must be taken into account. This phenomenon has been previously analyzed by Hildebrand *et al.* [40], who demonstrated that a consideration of dipole moments alone is not adequate to explain the solubility of polar substances in hydroxylic solvents. These authors concluded that the capability of the solute to form hydrogen bonds is a more important factor than its own polarity to have interactions with the solvent and to form a solution.

Considering the important polarities of **1** and H<sub>2</sub>O, and also the hydrogen–bond–donor capacity of the solvent [38], the easy occurrence of significant solute–solvent interactions is understood. These interactions increase the respective molar polarizations of **1** and H<sub>2</sub>O, with the consequent increase in solution of the average DM. In the analyzed system, of all the interaction forces that can exist between the solute and the solvent, those that imply the formation IHBs are the most important.

It is clear that the principal sites of the molecule of **1** involved in these IHBs are those that have either high electronic densities such as oxygen atoms of hydroxyl groups, or electronic deficiencies such as the hydrogen atoms of hydroxyl groups (Figure 1). Therefore, proceeding as in a previous study on sulfamethoxazole [41], and with the specific objective of explaining the high experimental DM of **1** in H<sub>2</sub>O, the following solute–solvent association reactions were proposed,



In the above equations,  $n$  and  $m$  are the number of H<sub>2</sub>O molecules associated to **1A** and **1B**, respectively. Several calculations were performed by shifting the coefficients  $n$  and  $m$ . The most satisfactory results were obtained when  $n = m = 3$ . This fact implies that both complexes are formed by three molecules of solvent and one of solute. On the other hand, it must be noted that of the whole solute molecule only the regions that include the OH groups participate in the formation of the complex. Considering these complexes, the conformational equilibrium of Eq. (1) was reformulated as follows:



We will designate the equilibrium constant of the above reaction as  $K_{CW}$ . Table 5 gives optimized values of molecular properties of the proposed association complexes, obtained at the B3LYP/6–31G(d,p) level of theory with Onsager's method. Figures 7 and 8 show the structure of the association complexes  $(H_2O)_3-1A$  and  $(H_2O)_3-1B$ , respectively.

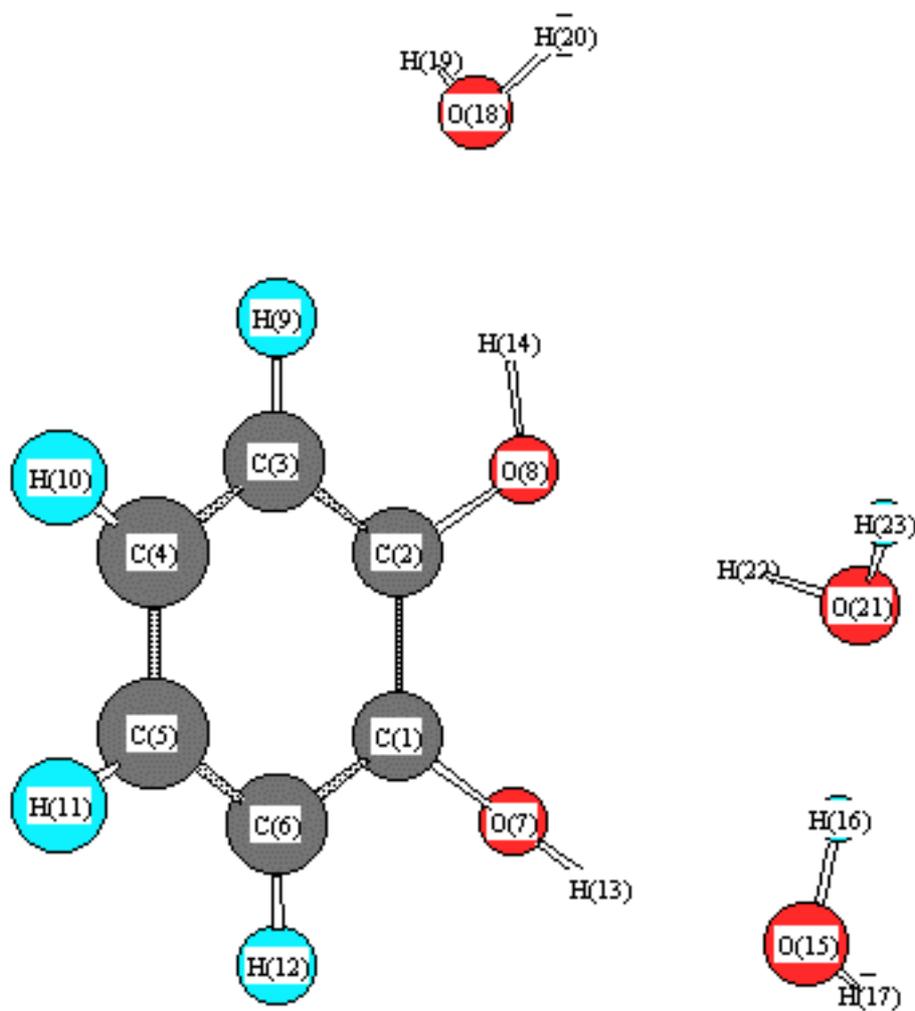
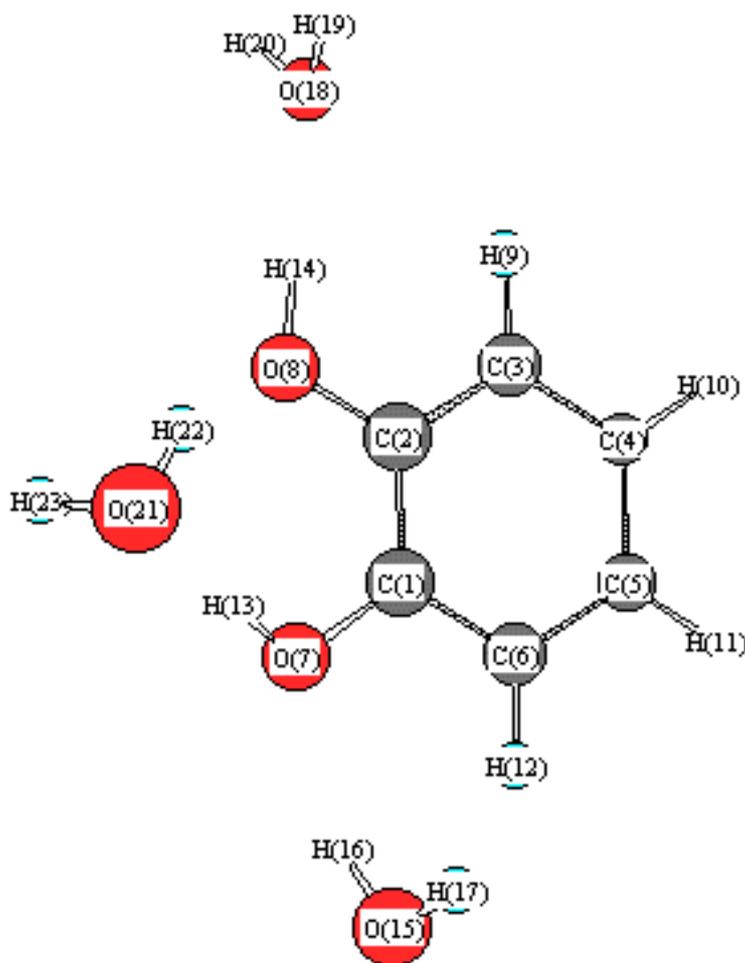


Figure 7. Structure of the association complex  $(H_2O)_3-1A$  of catechol.

In association complexes, the solute molecules do not have a planar structure, as is the case of non-solvated solute molecules (Table 4). In addition, when the molecules of **1A** and **1B** are solvated, the electronic densities of the oxygen atoms and the electronic deficiencies of the hydrogen atoms of their hydroxyl groups increase. Furthermore, in solvated molecules there is an increase of the  $d_{O_7-O_8}$  bond length and a decrease of the  $\angle A-O_7H_{13}O_8$  bond angle, as compared with non-solvated molecules. Consequently, the solvation of **1B** leads to the weakening of its own intramolecular hydrogen bond. On the other hand, it is important to highlight that in the formation of the association complexes, each atom of the two OH groups of the solute takes part in an IBH with the solvent molecules. This implies that the complexes are formed by 4 IBHs, which are of two

classes. In one of them the solvent acts as a hydrogen-bond donor (HBD capability), while in the other the solvent acts as a hydrogen-bond acceptor (HBA capability). For example, in the formation of the  $(\text{H}_2\text{O})_3\text{-1B}$  complex (Figure 8) IBHs  $\text{H}_{16}\text{-O}_7$  and  $\text{H}_{22}\text{-O}_8$  belong to the first class while IBHs  $\text{H}_{13}\text{-O}_{21}$  and  $\text{H}_{14}\text{-O}_{18}$  correspond to the second type. In this complex all the IBHs are moderate [30]. On the other hand, moderate and weak IBHs are observed in the  $(\text{H}_2\text{O})_3\text{-1A}$  complex (Figure 7).



**Figure 8.** Structure of the association complex  $(\text{H}_2\text{O})_3\text{-1B}$  of catechol.

Taking into account the value of  $K_{\text{CW}}$  we determined the fraction ( $F$ ) of each complex when the equilibrium in aqueous solution is reached. The values obtained were  $F_{1A} = 0.017$  and  $F_{1B} = 0.983$ . This implies that in aqueous solution at  $25^\circ\text{C}$ , there is 1.70% of complex  $(\text{H}_2\text{O})_3\text{-1A}$  and 98.3% of complex  $(\text{H}_2\text{O})_3\text{-1B}$ , in equilibrium. On the other hand, it is reasonable to propose that:

$$\text{DM } \mathbf{1} = F_{1A} \times \text{DM}_{\text{Theo}} (\text{H}_2\text{O})_3\text{-1A} + F_{1B} \times \text{DM}_{\text{Theo}} (\text{H}_2\text{O})_3\text{-1B} \quad (9)$$

where,  $\text{DM } \mathbf{1}$  is the total dipole moment of  $\mathbf{1}$  in aqueous solution, and  $\text{DM}_{\text{Theo}}$  stands for the theoretical DMs of the corresponding association complexes. Considering the values of these theoretical DMs (Table 5), using Eq. (9) it was determined that  $\text{DM } \mathbf{1} = 11.90 \text{ D}$ .

**Table 5.** Calculated structural magnitudes using the Onsager's method at the B3LYP/6–31G(d,p) level of theory for the solute–solvent association complexes of catechol in water, at 25°C. TE = total energy including solvent energy (kcal mol<sup>-1</sup>); K<sub>C</sub> = conformational equilibrium constant; DM = dipolar moment (Debye); a<sub>0</sub> = molecular radius (Å); *D*–H<sub>13</sub>O<sub>7</sub>C<sub>1</sub>C<sub>2</sub> = dihedral angle H<sub>13</sub>O<sub>7</sub>C<sub>1</sub>C<sub>2</sub> (°); *q* = total atomic charge of Mulliken (au); *d*O<sub>7</sub>–O<sub>8</sub>, *d*H<sub>13</sub>–O<sub>8</sub>, *d*H<sub>13</sub>–O<sub>15</sub>, *d*H<sub>13</sub>–O<sub>21</sub>, *d*H<sub>16</sub>–O<sub>7</sub>, *d*H<sub>22</sub>–O<sub>8</sub>, *d*H<sub>14</sub>–O<sub>18</sub> = bond lengths between the indicated atoms (Å) (Figures 7 and 8); *A*–O<sub>7</sub>H<sub>13</sub>O<sub>21</sub>, *A*–O<sub>7</sub>H<sub>16</sub>O<sub>15</sub>, *A*–O<sub>8</sub>H<sub>22</sub>O<sub>21</sub>, *A*–O<sub>8</sub>H<sub>14</sub>O<sub>18</sub>, *A*–O<sub>7</sub>H<sub>13</sub>O<sub>8</sub> = H–bond angles (°).

Magnitude	Water	
	(H <sub>2</sub> O) <sub>3</sub> – <b>1A</b> complex	(H <sub>2</sub> O) <sub>3</sub> – <b>1B</b> complex
TE	–384043.26	–384045.67
K <sub>CW</sub>		58.3
DM	8.01	11.97
a <sub>0</sub>	4.75	4.78
<i>D</i> –H <sub>13</sub> O <sub>7</sub> C <sub>1</sub> C <sub>2</sub>	114.6	19.0
<i>q</i> O <sub>7</sub>	–0.623	–0.632
<i>q</i> O <sub>8</sub>	–0.617	–0.648
<i>q</i> H <sub>13</sub>	0.322	0.343
<i>q</i> H <sub>14</sub>	0.358	0.373
<i>d</i> O <sub>7</sub> –O <sub>8</sub>	2.702	2.822
<i>d</i> H <sub>13</sub> –O <sub>8</sub>	3.293	2.453
<i>d</i> H <sub>13</sub> –O <sub>15</sub>	1.767	–
<i>d</i> H <sub>13</sub> –O <sub>21</sub>	2.943	1.723
<i>A</i> –O <sub>7</sub> H <sub>13</sub> O <sub>21</sub>	95.3	175.5
<i>d</i> H <sub>16</sub> –O <sub>7</sub>	2.724	1.919
<i>A</i> –O <sub>7</sub> H <sub>16</sub> O <sub>15</sub>	158.3	161.6
<i>d</i> H <sub>22</sub> –O <sub>8</sub>	1.870	1.856
<i>A</i> –O <sub>8</sub> H <sub>22</sub> O <sub>21</sub>	164.5	144.6
<i>d</i> H <sub>14</sub> –O <sub>18</sub>	1.770	1.732
<i>A</i> –O <sub>8</sub> H <sub>14</sub> O <sub>18</sub>	178.7	179.5
<i>A</i> –O <sub>7</sub> H <sub>13</sub> O <sub>8</sub>	–	101.5

Taking into account that the experimental dipole moment of **1** in water is 11.45 D [14], it is evident that there is excellent agreement between both values, their difference being under 4%. Therefore, we conclude that the association complexes are the predominant forms of **1** in aqueous solutions. It is also concluded that the experimental DM of **1** in aqueous medium is the result of the contribution of the dipolar moments of the two solvent–solute association complexes that are in equilibrium (Eq. (8)).

## 4 CONCLUSIONS

The solvent effects on the conformational equilibrium between the conformers of catechol **1A** (which lacks an intramolecular hydrogen bonding) and **1B** (which has this type of bond) were studied. These two conformers determine the major dielectric properties of aqueous solutions of **1**. We proposed an equation that explains in a highly satisfactory way the changes of K<sub>C</sub> with the medium permittivity. We also related different theoretical magnitudes of the solute (DMs, RBEs) with specific empirical parameters of the solvents ( $\alpha$ ,  $\beta$  and *Acity*). In this way, it was shown that **1** is a compound of high polarity and that its solubility in hydroxylic solvents is mainly determined by the capacity of the solvent to form hydrogen bonds and not by its dipole moment. In this paper, we

have demonstrated the possibility of explaining the dipole moment of **1** in water (11.45 D). To do this, it was necessary to propose that a conformational equilibrium takes place in aqueous solutions, which involves two association complexes that include the solvent and the solute. These complexes have 3:1 stoichiometry, *i.e.*, they are formed by three molecules of water and one of catechol. In their formation, there participate the regions of solute that include the hydroxyl groups. The calculations performed at the B3LYP/6–31G(d,p) level of theory using Onsager's method allowed to prove that the association complexes are formed by two types of IHBs. In one of them, the water acts as a hydrogen–bond donor, while in the other it acts as a hydrogen–bond acceptor. It was proposed that these association complexes are the predominant forms of **1** in aqueous medium. It was concluded that the dipole moment of **1** in water is due to a contribution of 1.70% of complex (H<sub>2</sub>O)<sub>3</sub>–**1A** and 98.3% of complex (H<sub>2</sub>O)<sub>3</sub>–**1B**. These results imply that the equilibrium constant characterizing the conformational reaction proposed is equal to 58.3, according to the calculation method used.

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