Solvent Effect on the Conformation of 2,6-Dimethoxyphenol Simulated with MOPAC2000

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(Received: May 24, 2002; Accepted for publication: November 15, 2002; Published on Web: December 6, 2002)

The conformation of 2,6-dimethoxyphenol (DMP), especially the solvent effect on the intra-molecular hydrogen bond was computed with semi-empirical molecular orbital calculation, MOPAC2000. In non-polar solvents (gaseous phase and benzene), the phenolic hydrogen oriented toward one of the methoxyl oxygens via an intra-molecular hydrogen bond. In polar solvents (chloroform, acetone and water), the phenolic hydroxyl group was sited between two methoxyl oxygens with balance of weak hydrogen bonds to them. This solvent effect on the optimum conformation was similar to guaiacol analyzed previously, and would be due to the split of the intra-molecular hydrogen bond caused by interaction from polar solvents. The rotational flexibilities of the hydroxyl and two methoxyl groups of DMP were high, because many of the low energy conformations were detected near the optimum conformation. The flexibilities of two methoxyl groups were lower in water than in gaseous phase. The cause may be complex interaction produced by polar solvents to the balance of intra-molecular hydrogen bonds among hydroxyl group and two methoxyl groups.

Keywords: 2,6-Dimethoxyphenol, Optimum conformation, Solvent effect, Hydrogen bond, Methoxyl group, Phenolic hydroxyl group

1 Introduction

In recent years, quite a number of reports were published on computer simulations on lignin, which is one of the polymers constituting the plant cell wall. These focused on aspects of molecular mechanics [1], molecular dynamics [2, 3], semi-empirical molecular orbital calculation [4–6] and an ab initio molecular orbital calculation [7, 8]. However, excluding those emphasizing molecular dynamics, others were limited to focusing on isolated molecules such as in gaseous phase. On the other hand, experimental evidence exists that the polarity of the reaction medium affects the polymerization of monolignols [9–11]. Therefore, it becomes important to consider the solvent effect and introduce this aspect to computer simulation of lignin chemistry.

For computer simulation of lignin reaction, suitable conformation of monolignols must be confirmed. This is appropriate since monolignols include many conformation-free functional groups (such as phenolic and alcoholic hydroxyls, methoxyl, carboxyl) and a double bond. Especially, it is important the solvent effect on the functional groups sited or neighbored at a reactive position, i.e., phenolic hydroxyl and methoxyl groups whose rotations are highly free. In our previous report [12], the optimum conformation of guaiacol (o-methoxyphenol) was determined by semi-empirical molecular orbital calculation, MOPAC2000, and the solvent effect on the conformation was analyzed. Since coniferyl alcohol that includes the guaiacyl aromatic ring such as guaiacol is the dominant precursor of softwood lignin, the calculation of the conformation of guaiacol is important. It has been found that the intra-molecular hydrogen bond between phenolic hydrogen and methoxyl oxygen observed in gaseous phase was ruptured by polar solvents.

However, hardwood lignin is mainly composed of coniferyl and sinapyl alcohols whose concentrations in the cell wall are almost half and half by weight. Sinapyl alcohol includes the syringyl aromatic ring such as DMP. The reactivity in dehydrogenative polymerization is so different from coniferyl alcohol [13]. Therefore, the op-
timum conformation of DMP must be considered predominantly to simulate the lignin chemistry of hardwood. Studies on computer simulation of hardwood lignin are meager. Russell et al. [6] reported the delocalization of radical electron in sinapyl alcohol and related molecules using the AM1 method, and positive correlation between the simulation and experimental data from electron spin resonance spectroscopy. However, the reported optimum conformations need re-evaluation since the AM1 method was developed a generation ago and neglected the effect of solvent.

In the present study, to clarify the conformation of monolignols dissolved in various solvents, we analyzed the conformation of DMP by using a computer simulation with semi-empirical molecular orbital calculation under the prevalence of solvent effect. For this protocol, the newest program MOPAC2000 was used.

2 Computational experiment

Calculation was performed with WinMOPAC ver.3.02 (served by Fujitsu Co. Ltd.) in a personal computer. This software combined a graphical user interface for Z-matrix and MOPAC2000 for calculating engine. The Eigenvector Following (EF) routine was used for optimizer, and the Gradient Normal (GNORM) was set at 0.05. The Parametric Method 3 (PM3) was used due to the high performance for hydrogen bond. Additionally, the Conductor-like Screening Model (COSMO) method was used for solvent effect. In the COSMO method, the relative dielectric constant (\( \varepsilon \)) of solvent (EPS) was set to the experimental value, and the number of geometrical segments per molecule (NSPA) was set at 200. Experimental values of \( \varepsilon \) used for benzene, chloroform, acetone and water were 2.274, 4.8, 20.7 and 78.4, respectively. For gaseous phase, the COSMO method was not applied whereas the \( \varepsilon \) corresponded to unity. For other parameters, default values programmed in MOPAC2000 were used.

The molecular structure of DMP and the definition of torsion angles of phenolic hydroxyl group (\( \phi \)) and two methoxyl groups (\( \psi_1 \) and \( \psi_2 \)) are illustrated in Figure 1. The torsion angle of the hydroxyl group was rotated toward the aromatic plane from 0° to 90° by 10° steps. Conformations at negative or over 90° of \( \phi \) were analogized from the symmetric conformations between 0° and 90° of \( \phi \). The torsion angles of two methoxyl groups were rotated toward aromatic plane from –180° to 180° by 10° steps, and the heat of formation (\( H_f \) in kcal/mol) of each conformation was calculated. All minimum \( H_f \) conformations detected in the preliminary scanning were further optimized to obtain the detail conformation of hydroxyl and methoxyl groups. Finally, the lowest \( H_f \) conformation in them was determined for final optimum conformation. The \( H_f \) of the final optimum conformation was called \( H_{f}^{\text{opt}} \) in this study.

![Figure 1. Molecular structure of 2,6-dimethoxyphenol and the definition of torsion angles of phenolic hydroxyl (\( \phi \)) and two methoxyl groups (\( \psi_1 \) and \( \psi_2 \)).](image)

3 Results and discussion

3.1 Optimum conformations of DMP in gaseous phase and in water

From preliminary scan of low energy conformation of DMP, the minimum values of \( H_f \) appeared at \( \phi = 0° \), \( \psi_1 = 70° \) and \( \psi_2 = 30° \) in gaseous phase, and at \( \phi = 30° \), \( \psi_1 = 110° \) and \( \psi_2 = 30° \) in water. By further optimization of these conformations, the values of \( H_{f}^{\text{opt}} \) and torsion angles of finally optimum conformations were detected as shown in Table 1 and graphically in Figure 2. These conformations were different from each other in the points of combination between \( \phi \) and \( \psi_1 \). The difference would be caused by rupture of intra-molecular hydrogen bond by water molecules. Decided optimum conformations were different from previous results obtained by Russell et al. [6]. They have reported that one of the methoxyl groups in sinapyl alcohol radical molecule is directed toward phenolic oxygen (\( \psi_1 = 180° \)). The cause of disagreement would be different calculating methods, AM1 for Russell et al. and PM3 for us. We believe that the results obtained in this study have higher accuracy due to the newer method PM3.
Table 1. Optimum conformation of 2,6-dimethoxyphenol in gaseous phase and in water calculated by PM3 with COSMO method in MOPAC2000.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>ε</th>
<th>$H_f^{opt}$ (kcal/mol)</th>
<th>$\phi$ (degree)</th>
<th>$\psi_1$ (degree)</th>
<th>$\psi_2$ (degree)</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Gaseous phase)*</td>
<td>1</td>
<td>-92.77</td>
<td>-1.80</td>
<td>74.11</td>
<td>26.42</td>
<td>A</td>
</tr>
<tr>
<td>Water</td>
<td>78.4</td>
<td>-105.12</td>
<td>32.91</td>
<td>109.93</td>
<td>24.96</td>
<td>B</td>
</tr>
</tbody>
</table>

* absence of solvent.

In gaseous phase, the values of $\phi$ and $\psi_1$ of DMP were quite similar to those of guaiacol ($\phi = -2.54^\circ$ and $\psi = 73.95^\circ$) [12], because of the similar situation made by intra-molecular hydrogen bond between these groups. The reason for methoxyl carbon slant toward the aromatic ring may be hydrogen bond between hydroxyl hydrogen and lone electron-pair of methoxyl oxygen. The conformation of another methoxyl group ($\psi_2$) was similar to the methoxyl group of anisole ($\psi = 0^\circ$) [12]. This means that the influences of hydroxyl and methoxyl groups of DMP upon the conformation of another methoxyl group are weak.

In water, $\phi$ and $\psi_1$ of DMP were different from those of guaiacol ($\phi = -179.65^\circ$ and $\psi = 25.69^\circ$) [12]. It is a matter of course, because hydroxyl group of DMP approaches another methoxyl group at $\phi < -90^\circ$ or $90^\circ < \phi$. Consequently, the hydroxyl group is sited between two methoxyl oxygens with balance of hydrogen bonds among these groups and polar solvent. The rotational position of another methoxyl group ($\psi_2$) was similar to that of anisole (about 16°), the same as in gaseous phase.

Considering the interaction between hydroxyl hydrogen and methoxyl oxygen, the optimum conformations in gaseous phase and in water are identified as Form-A and Form-B, respectively, in this report.

The energy difference of $H_f^{opt}$ in water from that in gaseous phase corresponds to the solvation energy. The value was $-12.35$ kcal/mol in DMP and $-9.33$ kcal/mol in guaiacol; the larger exothermic energy indicating the higher affinity to water. These calculated values qualitatively correspond to experimental results of larger solubility of sinapyl alcohol than coniferyl alcohol in water [14]. It is seen that methoxyl group works as a hydrophilic group.

### 3.2 Flexibility of optimum conformations

Figure 3A shows the energy surface maps of DMP in gaseous phase as functions of $\psi_1$ and $\psi_2$ at constant $\phi$. The value of heat of formation in the maps is shown as the difference of $H_f$ from $H_f^{opt}$, i.e., $\Delta H_f = H_f - H_f^{opt}$. At 25°C, the increase of 0.5 kcal/mol of $\Delta H_f$ corresponds to about 10% reduction of statistical possibility of the conformation. As shown in the figure, a number of distinctly spread low energy islets appeared in the maps from 0° to 40° of $\phi$. The existence of many low-energy points indicates that many conformations exist statistically. However, low-energy islet was limited at approximately -120° < $\psi_1$ < 120° as typically shown in the map at $\phi = 0^\circ$. It suggests that the rotation of methoxyl group expressed by $\psi_1$ is restricted by intra-molecular hydrogen bonding and steric hindrance from hydroxyl group. In contrast, the possibility of rotation of another methoxyl group expressed by $\psi_2$ is comparatively free due to less restriction by hydrogen bond from phenolic hydroxyl group, which is far from the methoxyl oxygen.
Figure 3. Energy surface maps of 2,6-dimethoxyphenol in gaseous phase (A) and in water (B). Arrows indicate the global minimum energy conformation in each solvent. Energy surface maps at negative or over 90° of \( \phi \) can be analogized from the symmetric conformation between 0° and 90° of \( \phi \).

Figure 3B shows the energy surface maps in water phase. Similar to those in gaseous phase, many low energy islets are visible. In contrast with gaseous phase, low energy islets appeared in all ten maps. This means that the freedom of rotation of hydroxyl group expressed by \( \psi \) is statistically higher in water than in gaseous phase. Reduction of intra-molecular hydrogen bonding between hydroxyl and methoxyl groups perturbed by polar solvent molecules appears as a cause for this. However, the low energy islets existing in \( \psi_1-\psi_2 \) maps were smaller in water than in gaseous phase. The small islets in \( \psi_1-\psi_2 \) maps mean low possibility of rotation of two methoxyl groups. The cause may be that both methoxyl groups are restricted from hydroxyl group, and the balance of the hydrogen bonds is simultaneously occurring to one hydroxyl group.

3.3 Solvent effect on the optimum conformation of DMP

From the results in gaseous phase and water, the conformations in other solvents were estimated. With the assumption that the optimum conformation in other solvents is similar to either optimum conformation in gaseous phase or in water, the optimum conformations in other solvents were decided by further optimization from the optimum conformations in gaseous phase and in water. Figure 4A shows the \( H_f \) of DMP in various solvents optimized from Form-A or -B decided in gaseous phase or in water, respectively. In gaseous phase and in benzene, Form-A was more suitable than Form-B due to its lower \( H_f \). In chloroform, the \( H_f \)'s of two forms were almost identical. In acetone and water, Form-B gave lower \( H_f \) and then changed to suitable conformation. These solvent effects with increase of \( \epsilon \) are similar to guaiacol. However, the difference between \( H_f \)'s of the two formations of DMP was small and limited within 0.5 kcal/mol in all solvents, whereas 1.9 kcal/mol for guaiacol [12]. The small difference observed in DMP indicates that the statistical probabilities of two conformations were almost equivalent. It can be analogized from the spread low energy islets in energy surface maps.
Figure 4. Heat of formation (A) and bond order between phenol hydrogen and methoxyl oxygen (B) of 2,6-dimethoxyphenol in various solvents. Abscissa indicates the relative dielectric constant of the solvent; in gaseous phase (\(\varepsilon = 1\)), in benzene (\(\varepsilon = 2.274\)), in chloroform (\(\varepsilon = 4.8\)), in acetone (\(\varepsilon = 20.7\)) and in water (\(\varepsilon = 78.4\)). Closed and open symbols denote Form-A and -B, respectively. Circles and triangles in B denote the bond orders of hydroxyl hydrogen to proximal and other methoxyl oxygens, respectively.

Table 2. Optimum conformation of 2,6-dimethoxyphenol in various solvents calculated by PM3 with COSMO method in MOPAC2000.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>(\varepsilon)</th>
<th>(H_f^{\text{opt}}) (kcal/mol)</th>
<th>(\phi) (degree)</th>
<th>(\psi_1) (degree)</th>
<th>(\psi_2) (degree)</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>2.274</td>
<td>-97.72</td>
<td>1.66</td>
<td>78.22</td>
<td>26.77</td>
<td>A</td>
</tr>
<tr>
<td>Chloroform</td>
<td>4.8</td>
<td>-100.95</td>
<td>25.43</td>
<td>110.14</td>
<td>26.63</td>
<td>B</td>
</tr>
<tr>
<td>Acetone</td>
<td>20.7</td>
<td>-104.23</td>
<td>31.59</td>
<td>109.94</td>
<td>25.40</td>
<td>B</td>
</tr>
</tbody>
</table>

Note: These optimum conformations were obtained by further optimization from the optimum conformations determined in gaseous phase or in water, with the assumption that the optimum conformation in other solvents is similar to that in either gaseous phase or water. Then, the lower energy conformation in two optimum conformations, as shown in Figure 4A, was determined for final optimum conformation in the solvent.

Figure 4B shows the bond order between hydroxyl hydrogen and methoxyl oxygens in DMP molecule. The bond order can be regarded as an indicator of strength of intra-molecular hydrogen bond between the two atoms. The bond order to the nearest methoxyl oxygen, shown as circles, was higher than that of the other methoxyl oxygen, shown as triangles. This is because the strength of the hydrogen bond depends on the distance between two atoms. The bond order in gaseous phase was higher than in water, because of the higher degree of hydrogen bonding in gaseous phase as described previously. As for guaiacol, the bond order to proximal methoxyl oxygen (circles in Figure 4B) decreased with increase of \(\varepsilon\). This behavior is expressed in the interaction of hydroxyl hydrogen with polar solvents. Contrastingly, the bond order to the other methoxyl oxygen (triangles in Figure 4B) was insignificant because of the long distance between them.

Table 2 shows the numerical expression of optimum conformations in various solvents, which are decided to lower energy conformation in Form-A and -B shown in Figure 4A. As shown in Table 1 in the comparison between the gaseous and water phases, \(H_f^{\text{opt}}\) values decreased with increase in \(\varepsilon\). Since the energy difference of \(H_f^{\text{opt}}\) in solvent from that in gaseous phase corresponds to the solvation energy for the solvent, the affinity of the DMP molecule for solvent is higher in more polar solvent. Concerning the rotational positions of optimum conformations, Form-A in benzene, and Form-B in chloroform or in acetone were quite similar to the optimum conformations in gaseous phase and in water, respectively.

4 Conclusion

The optimum conformation of DMP was transformed from Form-A to -B by an increase of the \(\varepsilon\) of the solvent. The solvent effect on the optimum conformation would be due to the split of intra-molecular hydrogen bond caused by perturbation from polar solvents. The rotational flexibilities of the hydroxyl and methoxyl groups of DMP were higher than those of guaiacol, and those in water were higher than those in the gaseous phase. It means that the optimum conformation of DMP is governed by the balance of intra-molecular hydrogen bonds among hydroxyl and two methoxyl groups. Consequently, the obtained conformations of DMP with different kinds of solvents can be used to construct the initial conforma-
tion of sinapyl alcohol for computer simulation on lignin chemistry.

We thank to Dr. Sachi Sri Kantha, Gifu University, for help in the preparation of the manuscript. This study was supported by a Grant-in-Aid (No.11760120) from the Ministry of Education of Japan.

References