Solvent Effect on the Conformations of Phenol, Anisole and Guaiacol Simulated with MOPAC2000

Mikiji SHIGEMATSU, Takayuki KOBAYASHI* and Mitsuhiko TANAHASHI
Faculty of Agriculture, Gifu University, Gifu 501-1193, Japan
*The United Graduate School of Agricultural Science, Gifu University, Gifu 501-1193, Japan

Received 12 May 2001; accepted 25 May 2001

Abstract
The conformations of phenol, anisole and guaiacol, especially solvent effect on the intra-molecular hydrogen bond were computed with semi-empirical molecular orbital calculation, MOPAC2000. Solvent effect on the conformations of phenol and anisole appears minimal. However, the optimum conformation of guaiacol was transformed from cis- to trans-forms by increase of specific conductivity of the solvent. This effect would be due to the break of intra-molecular hydrogen bond between phenolic hydroxyl and methoxyl groups caused by perturbation from polar solvents.

Introduction
In recent years, quite a number of reports were published on the computer simulations on lignin which is one of the polymers constituting plant cell wall. These focused on aspects of molecular mechanics (Simon and Eriksson 1995), molecular dynamics (Houtman and Atalla 1995, Houtman 1999), semi-empirical molecular orbital calculation (Gravitis and Erins 1983, Elder et al 1988, Russell et al 1996) or ab initio molecular orbital calculation (Simon and Eriksson 1996, 1998). However, excluding those emphasizing molecular dynamics, others were limited to focusing on isolated molecule such as gas phase. On the other hand, experimental evidence exists that the polarity of reaction medium affects the polymerization of monolignols (Tanahashi et al 1976, 1990, Terashima and Atalla 1995). Therefore, it becomes important to consider the solvent effect and introduce this aspect to computer simulation of lignin chemistry.

To simulate the reactions of lignin with computer, suitable conformation of monolignols must be considered. This is appropriate since monolignols contain many conformation-free functional groups (e.g., phenolic and alcholic hydroxyls, methoxyl, carboxyl) and a double bond. Especially, it is important to consider the solvent effect on the functional groups sited or neighbored at reactive position, i.e., phenolic hydroxyl and methoxyl groups whose rotations are highly free.

Previously, Remko and Polčin had investigated diligently intra- and inter-molecular hydrogen bond of phenolic substances related to monolignols. In particular, they paid attention to guaiacol, which constitutes the basic structural unit of lignin. For example, Remko and Polčin (1976) conducted CNDO/2 calculation on the

Fig. 1 Analyzed molecular structures.
intra-molecular hydrogen bond between phenolic hydroxyl and methoxyl groups of guaiacol in gas phase. Furthermore, CNDO/2 calculation for the inter-molecular hydrogen bond between phenolic hydroxyl and single molecule of polar solvents (Remko and Polčin 1977), PCILO calculation for the optimum conformation considered intra-molecular hydrogen bond in absence of solvent (Remko 1979), and PCILO calculation for the optimum conformation perturbed by polar solvents (Remko 1983) have been reported subsequently. Unfortunately, in their investigations, the perturbation from solvent was simulated by approaching of single molecule of polar solvents but not multiple molecules.

In the present report, to obtain the information on the conformation of monolignols dissolved in various solvents, we analyzed the conformation of guaiacol by using a computer simulation with semi-empirical molecular orbital calculation under existence of solvent effect. For this protocol, the newest program MOPAC2000 was used. In this study, the solvent effect on the conformation of phenol and anisole was analyzed preliminarily, and on the interaction between phenolic hydroxyl and methoxyl groups of guaiacol was followed. The structures of calculated molecules are illustrated in Fig. 1.

**Computational experiment**

The calculation was conducted with WinMOPAC ver.3.02 (served by Fujitsu Co. Ltd.) in a personal computer (OS: Windows2000, cpu: Pentium II/333MHz, memory: 384MB). This software has a graphical user interface for Z-matrix and MOPAC2000 ver.1.11 for calculating engine. The Eigenvector Following (EF) routine was used for optimizer, and the Gradient Normal (GNORM) was set to 0.05. The Parametric Method 3 (PM3) was used because of the high performance for hydrogen bond. Additionally, Conductor-like Screening Model (COSMO) method was used for solvent effect, because the solvent effect is simulated as the perturbation of solvents acting from all direction toward target molecule. In COSMO method, the specific conductivity (\(\varepsilon\)) of solvent (EPS) was set to the experimental value, and the number of geometrical segments per molecule (NSPA) was set to 200. Used experimental values of \(\varepsilon\) were 2.274 in benzene, 4.8 in chloroform, 20.7 in acetone, and 78.4 in water. For gas phase, COSMO method was not applied whereas the \(\varepsilon\) corresponded to unity. For other parameters, default values programmed in MOPAC2000 were used.

In case of phenol, the heat of formation (\(H_f\) in kcal/mol) was calculated at torsion angle of phenol hydrogen (\(\phi\)) toward ortho-carbon of aromatic ring from \(-180^\circ\) to \(180^\circ\) by \(10^\circ\) of step. In case of anisole, \(H_f\) was calculated at torsion angle of methoxyl carbon (\(\psi\)) toward ortho-carbon of aromatic ring from \(-180^\circ\) to \(180^\circ\) by \(10^\circ\) of step. In case of guaiacol, both torsion angles of hydroxyl hydrogen (\(\phi\)) and methoxyl carbon (\(\psi\)) were rotated toward aromatic plane from \(-180^\circ\) to \(180^\circ\) by \(10^\circ\) of steps, and the \(H_f\) was expressed as two-dimensional energy surface map. All conformations indicating energy minimum were further optimized to obtain the final optimum conformations. The definition of torsion angles is illustrated in Fig. 2.

![Fig. 2 Definition of torsion angles of phenolic hydroxyl and methoxyl groups in guaiacol.](image-url)
Results and discussion

Conformations of phenol and anisole

Figure 3A shows the $H_f$ of phenol as a function of $\phi$. In all solvents, the phenolic hydroxyl group was stable at 0° and 180° (both symmetric) to aromatic plane. It is presumed that the stability of these optimum conformations is high because of deep valley appeared in $H_f$ curves. The change of $H_f$ on $\phi$ in solvent was slightly flat than in gas phase, and this flatness was increased by $\epsilon$ of solvents. The decrease of rotation barrier at $\phi=90°$ indicated that the hydrogen bond of solvent affects the heat of formation. However, the hydrogen bond between hydroxyl group of phenol and solvents would be weak and could not influence the optimum conformation.

Figure 3B shows the $H_f$ of anisole as a function of $\psi$. The methoxyl group was stable at 0° and 180° (both symmetric) in gas phase and benzene. In contrast with these milieus, the optimum conformation in other solvents was observed at about -164°, -16°, 16° and 164° (all symmetric), indicating the methoxyl group slanted slightly away from the aromatic plane. However, the rotation of methoxyl group is comparatively free as presumed by shallow valley in $H_f$ curve. Consequently, the different optimum conformations by the circumstance of solvent were predicted in methoxyl group but not observed in phenolic hydroxyl group. However, the difference was minimal because of high freedom.

Simon and Eriksson (1996) computed the effect of perturbation from single water molecule on the rotation of methoxyl group of anisole with ab initio molecular orbital method. The result of solvent effect was that the rotational barrier of methoxyl group from 0° (equatorial on aromatic plane) to 90° (axial) is reduced by the approach of water molecule. This indicates that the freedom of rotation of methoxyl group is increased by inter-molecular hydrogen bond with polar solvent. Our findings based on semi-empirical molecular orbital method qualitatively concur with that of Simon and Eriksson (1996). Unfortunately, change of torsion angle of methoxyl group at optimum conformation by presence of water molecules was not provided in their report.

Conformation of guaiacol

As shown in the previous section, the interaction of solvent on optimum conformations of phenol and anisole was minimal. However, in the case of guaiacol, the perturbation from solvent on intra-molecular hydrogen bond between the phenol hydrogen and methoxyl oxygen is predicted. When the solvent effect is low, strong hydrogen bond between phenol hydrogen and methoxyl oxygen governs the optimum conformation, and vice versa.
The heat of formation of optimum conformation \( (H_{f}^{opt}) \) and its structure of guaiacol in each solvent are shown in Table 1. The difference of \( H_{f}^{opt} \) between in each solvent and in gas phase corresponds to heat of solvation, and indicates occurrence of affinity of solvent with guaiacol.

In gas phase and benzene, \( \phi \approx 0^\circ \) and \( \psi \approx 75^\circ \), respectively. \( 40^\circ \) corresponds to the optimum conformation of phenolic hydroxyl group of phenol, but \( 45^\circ \) was different to methoxyl of anisole. The cause of difference in methoxyl group may be electrical influence based on the hydrogen bond between hydroxyl hydrogen and methoxyl oxygen. Previously, Vokin et al (1993) reported the methoxyl group of guaiacol was optimum at \( \psi=0^\circ \) by calculation with AM1 in gas phase. The difference between the results of Vokin et al (1993) and ours would be caused by different calculation methods, i.e., AM1 and PM3.

On the other hand, in chloroform, acetone and water, \( \phi \approx 180^\circ \) and \( \psi \approx 25^\circ \) were observed in the optimum conformations. The values of \( \phi \) and \( \psi \) approximately corresponded to the optimum conformations of phenol and anisole, respectively. In this, the influence of hydrogen bond to the torsion of methoxyl group may disappear because of long distance between hydrogen and oxygen. In these solvents, phenolic hydroxyl group may associate with the solvents whose \( \epsilon \) are higher than gas and benzene. Consequently, it was simulated that the intra-molecular hydrogen bond may be broken by polar solvents.

As already shown, two conformations were predicted with difference of solvents. One is the conformation that phenolic hydroxyl group directs to methoxyl one (called cis-form in this report), and another is phenolic hydroxyl group opposite (called trans-form). These conformations are illustrated in Fig. 4.

Figure 5 shows the two-dimensional energy surface map of guaiacol as functions of \( \phi \) and \( \psi \). In this figure, the heat of formation is indicated by the difference from \( H_{f}^{opt} \) in each solvent, i.e., \( \Delta H_{f} = H_{f} - H_{f}^{opt} \). In all solvents, low energy conformations were located around cis- and trans-forms. In gas phase and benzene, low energy conformations were located around cis-form, but \( H_{f} \) around trans-form was comparatively high. In chloroform, low energy conformations were located around not only cis-form but also trans-one. This means that both cis- and trans-forms are suitable because of weak hydrogen bond with chloroform whose polarity is low. In the cases of acetone and water, \( H_{f} \) around cis-form was no longer low, and trans-form was predominant for the suitable conformation. As shown in the maps (Figs. 5A, 5B and 5C), low energy island at cis-form spread with increase of \( \epsilon \). This indicates that the rotational freedom of phenolic hydroxyl and methoxyl groups became increasing by break of intra-molecular hydrogen bond.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>( H_{f}^{opt} ) (kcal/mol)</th>
<th>( \phi ) (degree)</th>
<th>( \psi ) (degree)</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Gas phase)*</td>
<td>-58.23</td>
<td>-2.54</td>
<td>73.95</td>
<td>cis</td>
</tr>
<tr>
<td>Benzene</td>
<td>-61.72</td>
<td>-0.28</td>
<td>78.41</td>
<td>cis</td>
</tr>
<tr>
<td>Chloroform</td>
<td>-63.96</td>
<td>-179.25</td>
<td>25.89</td>
<td>trans</td>
</tr>
<tr>
<td>Acetone</td>
<td>-66.81</td>
<td>-179.43</td>
<td>25.77</td>
<td>trans</td>
</tr>
<tr>
<td>Water</td>
<td>-67.56</td>
<td>-179.65</td>
<td>25.69</td>
<td>trans</td>
</tr>
</tbody>
</table>

* absence of solvent.
Intra-molecular hydrogen bond of guaiacol

Figure 6A shows the solvent effect on the $H_f$ of cis- and trans-forms of guaiacol. The meta-stable conformation, i.e., trans- for gas phase and benzene, and cis- for others, was carefully optimized from an initial structure obtained in Fig. 5. The lower value of $H_f$ in each solvent shown in Fig. 6A corresponds to the $H_{f, \text{opt}}$ values shown in Table 1. In low $\varepsilon$ solvents such as gas phase and benzene, $H_f$ of cis-form was lower than that of trans-form.

Fig. 5 Two-dimensional energy surface map of differential $H_f$ ($\Delta H_f = H_f - H_{f, \text{opt}}$) of guaiacol in various solvents as functions of $\phi$ and $\psi$: (A) in gas phase, (B) in benzene, (C) in chloroform, (D) in acetone and (E) in water. Arrows indicate the global minimum energy conformation in each solvent. In all figures, all the symmetric minimum points have not been shown.

Fig. 6 Heat of formation ($H_f$) and bond order between phenol hydrogen and methoxyl oxygen in guaiacol molecule. Abscissa indicates the specific conductivity of solvent ($\varepsilon$). Closed and open symbols denote the cis- and trans-forms shown in Fig. 4, respectively.

Intra-molecular hydrogen bond of guaiacol

Figure 6A shows the solvent effect on the $H_f$ of cis- and trans-forms of guaiacol. The meta-stable conformation, i.e., trans- for gas phase and benzene, and cis- for others, was carefully optimized from an initial structure obtained in Fig. 5. The lower value of $H_f$ in each solvent shown in Fig. 6A corresponds to the $H_{f, \text{opt}}$ values shown in Table 1. In low $\varepsilon$ solvents such as gas phase and benzene, $H_f$ of cis-form was lower than that of trans-form.
trans-one because of predominant intra-molecular hydrogen bond. Then, trans-form was meta-stable in these circumstances. However, lower Hfs in cis- and trans-forms were opposite at above 4.8 of ε, and trans-form changed to lower Hf and optimum conformation in chloroform, acetone and water.

The intra-molecular hydrogen bond in guaiacol could be expressed as the bond order between phenol hydrogen and methoxyl oxygen. Figure 6B shows the solvent effect on the bond order between them in guaiacol molecule. The bond order in trans-form was very small, because of long distance between hydrogen and oxygen. On the other hand, the bond order in cis-form was comparatively large, but decreased by increase of ε. This decrease implies that the intra-molecular hydrogen bond was broken by polar solvent as predicted in the previous section. Therefore, the optimum conformation was finally transformed from cis- to trans- by increase of ε by break of intra-molecular hydrogen bond, as discussed in Fig. 6A.

Remko (1983) reported no transformation of optimum conformation from cis- to trans-forms in presence of polar solvents (water, methanol, phenol and acetic acid) by using PCILO calculation, whereas finding of decrease of intra-molecular hydrogen bond in guaiacol. In the calculation, he set geometrical complex of guaiacol and single polar molecule, which sited neighbor phenolic hydroxyl group of guaiacol. The difference in his and our results about transformation of optimum conformation may be caused by different approach system of polar solvents and/or different calculating methods.

Conclusion
Preliminarily, solvent effect on the conformations of phenol and anisole was minimal. However, the optimum conformation of guaiacol was transformed from cis- to trans-forms by increase of ε. This effect would result from the break of intra-molecular hydrogen bond between phenolic hydroxyl and methoxyl groups by perturbation from polar solvent. From these results, we conclude that the solvent effect is important in the computer simulation of lignin reaction.

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

References