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# Conformational Preferences of Glycerol in the Gas Phase and in Water†

**Keunhong Jeong, Byung Jin Byun,‡ and Young Kee Kang‡,***

*Department of Chemistry, Korea Military Academy, Seoul 139-799, Republic of Korea*
*‡Department of Chemistry, Chungbuk National University, Cheongju, Chungbuk 361-763, Republic of Korea*
**E-mail: ykkang@chungbuk.ac.kr*
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The conformational study of glycerol has been carried out using the M06-2X/cc-pVTZ level of theory in the gas phase and the SMD M06-2X/cc-pVTZ level of theory in water in order to understand its conformational preferences and solvation effects. Most of the preferred conformers of glycerol have two $C_5$ hydrogen bonds in the gas phase, as found by the analysis of calorimetric data. It has been known that the solvation drove the hydrogen bonds of glycerol to be weaker and its potential surface to be fatter and that glycerol exists as an ensemble of many feasible local minima in water. The calculated populations of glycerol in the gas phase and in water are consistent with the observed values, which are better than the previously calculated ones at the G2(MP2), CBS-QB3, and SM5.42 HF/6-31G(d) levels of theory.

**Key Words :** Glycerol, Conformations, Hydrogen bonds, Density functional calculations, Solvation effects

## Introduction

Glycerol (1,2,3-propanetriol), which is formed by synthetic production and byproduct in manufacturing biodiesel, is one of the most valuable substances with a wide range of versatile uses and applications.[1-4] It has many unique physical and chemical properties including gravity, boiling point, and decomposition. Therefore, it is used in many commercial products like food ingredients, cosmetics, personal care products, and pharmaceutical uses. Biologically, glycerol has been the object of many investigations for its crucial role in biological reactions. Furthermore, in terms of bio-industry, researchers have recently paid attention to the capability of the glycerol to maintain biological molecules without any transformations and promote protein self-assembly through hydration.

Since glycerol has three hydroxyl groups and is a highly flexible molecule, it can form both intramolecular and intermolecular hydrogen bonds. Since the properties of glycerol show a peculiar dependence on variations in temperature or pressure, not only a study on the glycerol provides exact glycerol properties, which is valuable matter, but also the understanding of the energies involved in hydrogen bonding of hydroxyl groups is useful in modeling sugars and related macromolecules. The investigation of conformational equilibriums in polyfunctional alcohols would supply information for this purpose. Bastiansen defined the relative orientations of the two groups $H_2(OH)C$- and -CH(OH)C- by α, β, and γ (Fig. 1).[5] In the α conformation, the oxygen of the $H_2(OH)C$- group is nearly trans to the carbon atom of the -CH(OH)C- group. In the β conformation, the oxygens of the two groups are trans. In the γ conformation, the oxygen of the $H_2(OH)C$- group is nearly trans to the hydrogen atom of the -CH(OH)C- group. Hence, glycerol can have six different backbone conformations such as αα, αβ, αγ, ββ, βγ, and γγ, irrespective of the hydroxyl hydrogen orientations, where the heterogeneous pairs, for example αβ and βα, are counted as the same conformer because of the indistinguishability in this definition.

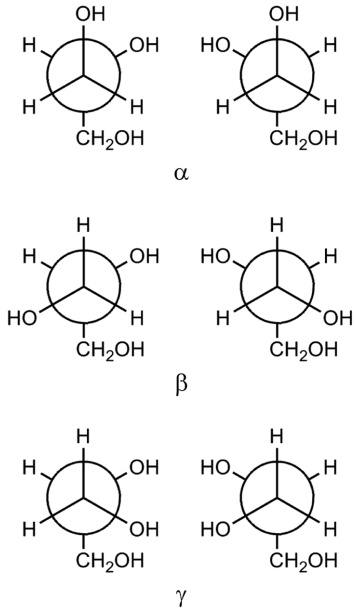



**Figure 1.** Definition of backbone conformations α, β, and γ.[5]

In order to understand the conformational preferences of glycerol in gas phase and water, considerable experimental[5-12] and theoretical[12-19] studies have been carried out. In the gas phase, the electron diffraction experiments indicated that the two conformations αα and αγ are major conformations of glycerol,[5] whereas the microwave spectroscopic studies

†This paper is to commemorate Professor Kook Joe Shin's honourable retirement.

reported that γγ and αγ are dominating conformations.[11] However, the symmetrical αα conformation was identified as the preferred structure in the solid state.[6] For the liquid and glassy state, neutron diffraction studies suggested the αα and αγ conformers to be dominated in explaining the observed structural factors.[8,9] The recent neutron diffraction study of glycerol in the liquid state combined with the empirical potential structure refinement technique suggested that the αβ conformation provided the best fit of the ensemble-averaged structural factors to the measured data and no evidence for intramolecular hydrogen bonds was found.[12] In aqueous solution of glycerol, the conformations αγ, αβ, and αα were found to be more populated and followed by the conformation βγ than the conformations ββ and γγ from $^1$H NMR experiments in $D_2O$.[7]

Several *ab initio* HF and MP2 calculations[13-15,18,19] and density functional B3LYP studies[16-18] have been carried out in order to investigate the conformational preferences of glycerol in the isolated state (i.e., gas phase) and/or in water using various basis sets. Most of the previous works[13-17] took only the relatively small numbers (i.e., 8-13) of feasible conformers into account in interpreting the conformational distributions obtained from the electron diffraction,[5] microwave measurement,[11] and infrared spectra.[16] Although Law *et al.* identified the 84 local minima from the 576 starting structures generated by the combination of the possible torsion angles, they optimized the structures at the relatively lower HF/3-21G level of theory in the gas phase and no comparison was made with the observed results.[19] In particular, Callam *et al.* studied the 126 possible conformations of glycerol by *ab initio* MO and density functional theory calculations in the gas phase and in water at various levels of theory and basis sets.[18] Boltzmann distributions have been determined from the G2(MP2) and CBS-QB3 levels of theory in the gas phase and the B3LYP/6-31+G(d,p)//SM5.42/HF/6-31G(d) level of theory in water, which are reasonably consistent with those of the available experimental data. However, the structures were optimized at the somewhat lower levels of theory such as HF/6-31G(d), MP2/6-31G(d), B3LYP/6-31G(d), and B3LYP/6-31G†. In particular, all local minima were located using the *ab initio* HF and density functional B3LYP methods with lacking the dispersion effects or the MP2 method with the overestimated dispersion energies. In order to make up these deficiencies, the conformational preferences of glycerol have been reinvestigated in the gas phase and in water using the dispersion-corrected density functional and the recently improved solvation model with the larger basis set.

## Computational Methods

Atomic numberings used for gylcerol are defined in Figure 2, as in ref 18. Each conformation of glycerol can be described in terms of five torsion angles: two for the C-C bonds and three for the C-O bonds. By assuming typical staggered conformations for these bonds having minima near 180°, 60°, and −60° for two different orientations of the

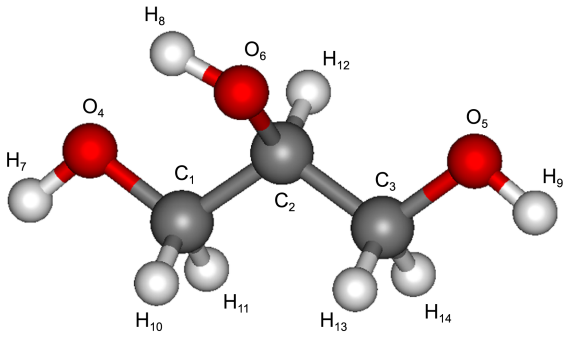



**Figure 2.** Atomic numbering used for glycerol.

OH group attached to the C2 atom, the 486 possible structures can be generated, which are reduced to the 126 symmetrically non-redundant structures.[18] Following the notation of ref 18, each backbone conformation was designated by T, G, and G' for trans, gauche+, and gauche- of the C-C bond, respectively, and the conformation of each OH group was designated by t, g, and g' for the C-O bond, respectively, analogous to the backbone. For example, the conformation gGg',gG'g corresponds to the structure with g, G, g' for the $C_2$-$C_1$-$O_4$-$H_7$, $O_4$-$C_1$-$C_2$-$O_6$, and $C_1$-$C_2$-$O_6$-$H_8$ sequences, respectively, and with g, G', g for the $C_3$-$C_2$-$O_6$-$H_8$, $O_6$-$C_2$-$C_3$-$O_5$, and $C_2$-$C_3$-$O_5$-$H_9$ sequences, respectively. In addition, this conformation gGg',gG'g equals to γγ, according to the definition of Bastiansen.[5]

All DFT calculations were carried out using the Gaussian 09 package.[20] The starting points for optimization were taken from the 126 symmetrically non-redundant structures obtained by Callam *et al.*[18] In the gas phase, full geometry optimizations were carried out at the hybrid-meta-GGA M06-2X functional[21] with the 6-31G(d) basis set, from which the 106 local minima were obtained. These local minima were further optimized with the cc-pVTZ basis set. In water, the same 126 non-redundant structures were optimized at the M06-2X/6-31G(d) level of theory using the Solvation Model based on Density (SMD) method[22] and the 106 local minima were identified. Then, the further optimizations were followed for the local minima at the SMD M06-2X/cc-pVTZ level of theory in water.

For all local minima, the vibrational frequencies were calculated at the M06-2X/cc-pVTZ level of theory in the gas phase and the SMD M06-2X/cc-pVTZ level of theory in water at 25 °C and 1 atm. The scale factor used for frequency calculations is 0.9466 that is obtained to reproduce experimental frequencies for the amide I band of *N*-methylacetamide in Ar and $N_2$ matrixes.[23] The zero-point energy correction and the thermal energy corrections were employed in calculating the Gibbs free energy of each conformation, from which the populations of all local minima were estimated at 25 °C in the gas phase and in water. The ideal gas, rigid rotor, and harmonic oscillator approximations were used for the translational, rotational, and vibrational contributions to the Gibbs free energy, respectively.[24,25] Recently, the M06-2X/cc-pVTZ//SMD M06-2X/6-31+G(d) level of theory reproduced the observed conformational preferences of the proline and

4-methylproline dipeptides in water.[26]

## Results and Discussion

**Conformational Preferences in the Gas Phase.** We obtained the 78 local minima for glycerol at the M06-2X/cc-pVTZ level of theory in the gas phase, whose 15 local minima have the enantiomers. The number of local minima obtained by us is similar to those obtained at the HF/6-31G(d) and B3LYP/6-31G(d) levels of theory, which are 75 and 76, respectively.[18] The torsion angles and thermodynamic properties of the 37 local minima for glycerol with the relative Gibbs free energy ($\Delta G$) <3 kcal/mol obtained at the M06-2X/cc-pVTZ level of theory in the gas phase are listed in Table 1 and the preferred optimized structures with $\Delta G$ <1 kcal/mol are shown in Figure 3. The torsion angles and thermodynamic properties of other local minima are listed in Table S1 of the Supporting Information. In particular, the number of intramolecular hydrogen bonds for each structure is listed in those Tables. When the distance $d$(O-H···O) <2.5 Å, such a contact was considered as a hydrogen bond.

In the gas phase, the conformation **g1** (gGg',gG'g) with the backbone conformation γγ is found to be lowest in energy, enthalpy, and Gibbs free energy, which has one six-membered ($C_6$) and two five-membered ($C_5$) hydrogen bonds with the distances of $d$($O_4$-$H_7$···$O_5$) = 2.11 Å, $d$($O_6$-$H_8$···$O_4$) = 2.16 Å, and $d$($O_5$-$H_9$···$O_6$) = 2.46 Å, respectively. The corresponding angles of $\theta$($O_4$-$H_7$···$O_5$), $\theta$($O_6$-$H_8$···$O_4$), and $\theta$($O_5$-$H_9$···$O_6$) are 132°, 117°, and 101°, respectively, which indicate that the second and third hydrogen bonds are relatively more distorted and weaker than the first one.

The second preferred conformations are **g2** (tG'g,tG'g) and **g2'** (tGg',tGg') with the backbone conformation αγ, which are enantiomers, having the relative energy ($\Delta E$) of 0.85 kcal/mol but $\Delta G$ of 0.11 and 0.16 kcal/mol, respectively. Each of the two conformers has two $C_5$ hydrogen bonds with the distances of $d$($O_6$-$H_8$···$O_4$) = 2.17 Å and $d$($O_5$-$H_9$···$O_6$) = 2.26 Å and the angles of $\theta$($O_6$-$H_8$···$O_4$) = 113° and $\theta$($O_5$-$H_9$···$O_6$) = 110°, as found for the conformation **g1**. In particular, the strongest hydrogen bond of $O_4$-$H_7$···$O_5$ in the conformation **g1** is lost for the conformers **g2** and **g2'**, to which the higher electronic energy of the latter may be ascribed. The third preferred conformations are enantiomers **g3** (g'G'g,tG'g) and **g3'** (gGg',tGg') with the backbone conformation αγ having $\Delta E$ of 1.19 kcal/mol but $\Delta G$ of 0.75 and 0.76 kcal/mol, respectively. Each of the two conformers has two $C_5$ hydrogen bonds with the distances of $d$($O_6$-$H_8$···$O_4$) = 2.20 Å and $d$($O_5$-$H_9$···$O_6$) = 2.27 Å and the angles of $\theta$($O_6$-$H_8$···$O_4$) = 115° and $\theta$($O_5$-$H_9$···$O_6$) = 109°, as found for the conformers **g2** and **g2'**. Although the conformers **g3** and **g3'** have the similar hydrogen bonds as for the conformers **g2** and **g2'**, the values of $\Delta E$ for the former are higher by 0.34 kcal/mol than the latter, which can be ascribed to the unfavored contact between $H_7$ and $H_8$ with the distances of 2.66 and 2.93 Å for the former and latter, respectively.

Although the fourth preferred enantiomers **g4** (tGg',gG'g') and **g4'** (gGg',gG't) have the same backbone conformation γγ as for the most preferred conformer **g1**, they have $\Delta E$ of 1.16 kcal/mol and $\Delta G$ of 1.05 kcal/mol, which are similar to and higher by 0.3 kcal/mol than those of the conformers **g3** and **g3'**, respectively. The conformers **g4** and **g4'** have one $C_6$ and one $C_5$ hydrogen bonds with the distances of $d$($O_5$-$H_9$···$O_4$) and $d$($O_4$-$H_7$···$O_5$) = 2.00 Å and $d$($O_6$-$H_8$···$O_5$) and $d$($O_6$-$H_8$···$O_4$) = 2.17 Å and the angles of $\theta$($O_5$-$H_9$···$O_4$) and $\theta$($O_4$-$H_7$···$O_5$) = 132° and $\theta$($O_6$-$H_8$···$O_5$) and $\theta$($O_6$-$H_8$···$O_4$) = 116°, respectively, whereas the conformers **g3** and **g3'** have two $C_5$ hydrogen bonds, as described above.

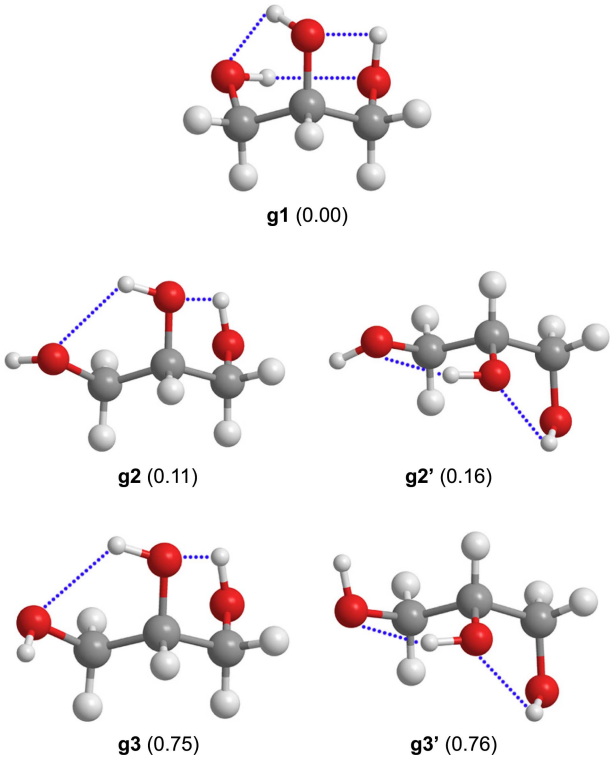



**Figure 3.** Preferred conformations of glycerol in the gas phase. The relative Gibbs free energies (kcal/mol) are shown in parentheses.

The fifth preferred conformers **g5** (g'Gt,gG't) and **g5'** (tGg',tG'g) have the backbone conformation αα, whose $\Delta E$ and $\Delta G$ are 1.91 and 1.10 kcal/mol, respectively. Although conformers **g5** and **g5'** have two $C_5$ hydrogen bonds, as found for the conformers **g2**, **g2'**, **g3**, and **g3'**, they are unstable by 1.06 and 0.72 kcal/mol in $\Delta E$ than those of the conformers **g2** and **g2'** and the conformers **g3** and **g3'**, respectively, but their $\Delta G$ values are comparable to those of the conformers **g4** and **g4'**.

In particular, it should be noted that the conformations with one or two β backbone structures such as the conformers **g9**, **g14**, and **g28**, which have one $C_5$, $C_5$, and $C_6$ hydrogen bond, respectively, have higher $\Delta E$ of 3.31, 3.77, and 4.12 kcal/mol and $\Delta G$ of 1.62, 2.34, and 3.09 kcal/mol, respectively, compared with the most preferred conformation **g1** with three hydrogen bonds. The data for the conformer **g28** are listed in Table S1 of the Supporting Information.

By the comparison of the populations calculated from the

$\Delta G$ values, the first three preferred conformations **g1**, **g2**, and **g2'** exist dominantly by ~55% with the populations of 21, 18, and 16%, respectively, which indicates that the number of hydrogen bonds strongly contributes to the overall stability of glycerol in the gas phase. According to the analysis of thermodynamic properties, the zero-point and thermal energies contributed to lower the electronic energies of all local minima on average by 0.3 kcal/mol, whereas the mean entropic term was calculated to be –0.79 kcal/mol. In particular, the mean contributions of the zero-point and thermal energies and the entropic terms were calculated to be –0.14 and –0.38 kcal/mol, respectively, for the second to fifth preferred conformations. This indicates that the populations of conformers are more dependent of the entropic term than the zero-point and thermal energies.

Callam *et al.*[18] reported the conformational energies calculated at the G2(MP2) and CBS-QB3 levels of theory, in which the geometries were optimized at the MP2/6-31G(d) and B3LYP/6-31G† levels of theory, respectively. The most preferred conformation was identified to be γγ by $\Delta E$ with the zero-point correction, i.e., the conformation **g1** in this work, at both the levels of theory and followed by the conformation αγ, which is the conformation **g2** in this work. We recalculated the values of $\Delta E$, $\Delta H$, and $\Delta G$ for the αγ structure at the same levels of theory. The calculated values of $\Delta E$, $\Delta H$, and $\Delta G$ are 0.61, 0.37, and –0.03 kcal/mol at the G2(MP2) level of theory and 0.55, 0.35, and –0.13 kcal/mol at the CBS-QB3 level of theory, respectively, whereas the corresponding values are 0.85, 0.65, and 0.11 kcal/mol at the M06-2X/cc-pVTZ level of theory (Table 1). The values obtained at the G2(MP2) and CBS-QB3 levels of theory are similar to those at the M06-2X/cc-pVTZ level of theory, even though there are some deviations. In particular, the distances of hydrogen bonds for the two conformers γγ and αγ obtained at the G2(MP2) level of theory are a little shorter on average by 0.07 Å than those at the M06-2X/cc-pVTZ level of theory, but those obtained at the CBS-QB3 level of theory are quite similar to those at the M06-2X/cc-pVTZ level of theory.

**Conformational Preferences in Water.** We obtained the 94 local minima for glycerol at the SMD M06-2X/cc-pVTZ level of theory in water, whose 16 local minima have the enantiomers. The number of local minima obtained by us is larger than the 75 local minima obtained at the SM5.42 HF/6-31G(d) level of theory in water.[18] The difference in the number of local minima might be caused by the differences in the density functional, the solvation model, and the basis set used. The increase of the number of local minima in water may indicate that the potential surface of glycerol becomes flatter by the solvation and the difference in relative energy becomes smaller from conformation to conformation (Table 2). The torsion angles and thermodynamic properties of the 34 local minima for glycerol with $\Delta G < 1$ kcal/mol obtained at the SMD M06-2X/cc-pVTZ level of theory in water are listed in Table 2 and the preferred optimized structures with $\Delta G < 0.3$ kcal/mol are shown in Figure 4. The torsion angles and thermodynamic properties of other local minima are listed in Table S2 of the Supporting Information. In addition, the number of intramolecular hydrogen bonds with the distance *d*(O-H···O) <2.5 Å for each structure is listed in those Tables.

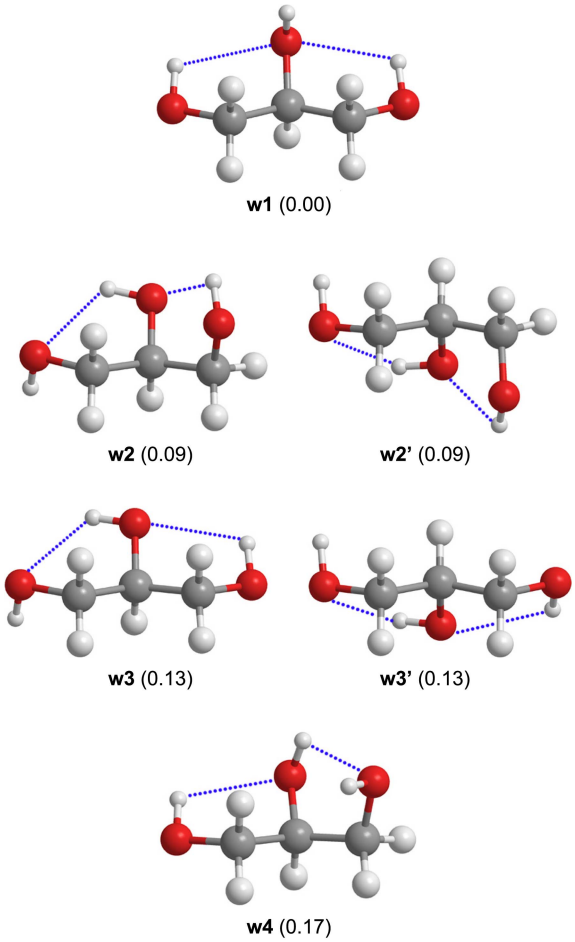



**Figure 4.** Preferred conformations of glycerol in water. The relative Gibbs free energies (kcal/mol) are shown in parentheses.

Most of all local minima in the gas phase exist as local minima in water, except the conformers **g57** and **g59** with high $\Delta G$ values of 4.95 and 5.40 kcal/mol, respectively (see Table S1 of the Supporting Information). In particular, there are the 18 local minima additionally located in water and two of them, i.e., the conformers **w9** (g'G'g,tGg) with the αα backbone and **w22** (tG'g,tG't) with the αγ backbone, have the lower $\Delta G$ values of 0.50 and 0.91 kcal/mol, respectively. Because of the flattened potential surface of glycerol in water, there are the 34 local minima with $\Delta G < 1$ kcal/mol. Almost of the local minima have the lower $\Delta G$ values < 3 kcal/mol in water.

Although the most preferred conformation **g1** in the gas phase, which is the conformation **w12** in water, also has the lowest energy and enthalpy in water, its $\Delta G$ value becomes 0.60 kcal/mol in water due to the entropic terms. Instead, the conformation **w1** (g'Gg,g'G'g) with the backbone conformation αα is found to be most preferred by $\Delta G$, although its $\Delta E$ and $\Delta H$ values are 0.47 and 0.27 kcal/mol, respectively, against the conformation **w12**. It should be noted that the values of

**Table 1.** Torsion angles and thermodynamic properties of glycerol calculated at the M06-2X/cc-pVTZ level of theory in the gas phase[a]

| | Conf[c] | | HB[d] | Torsion angles[b] | | | | | | Therm. properties | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | $\chi^1$ | $\chi^2$ | $\chi^3$ | $\chi^4$ | $\chi^5$ | $\chi^6$ | $\Delta E^e$ | $\Delta H^f$ | $\Delta G^g$ | $p^h$ |
| **g1** | gGg',gG'g | γγ | 3 | 58.2 | 48.3 | -19.6 | 104.0 | -58.7 | 64.3 | 0.00 | 0.00 | 0.00 | 0.21 |
| **g2** | tG'g,tG'g | αγ | 2 | 166.4 | -54.4 | 41.6 | 163.1 | -56.5 | 49.9 | 0.85 | 0.65 | 0.11 | 0.18 |
| **g2'** | tGg',tGg' | αγ | 2 | -165.7 | 54.4 | -41.7 | -163.2 | 56.5 | -50.0 | 0.85 | 0.65 | 0.16 | 0.16 |
| **g3** | g'G'g,tG'g | αγ | 2 | -74.8 | -51.3 | 35.1 | 156.8 | -57.0 | 50.2 | 1.19 | 1.05 | 0.75 | 0.06 |
| **g3'** | gGg',tGg' | αγ | 2 | 74.4 | 51.3 | -35.1 | -156.8 | 57.0 | -50.2 | 1.19 | 1.05 | 0.76 | 0.06 |
| **g4** | tGg',gG'g' | γγ | 2 | -169.9 | 72.4 | -89.8 | 35.2 | -47.7 | -61.1 | 1.16 | 1.17 | 1.04 | 0.04 |
| **g4'** | gGg',gG't | γγ | 2 | 61.0 | 47.7 | -35.3 | 89.7 | -72.4 | 169.6 | 1.16 | 1.17 | 1.05 | 0.04 |
| **g5** | g'Gt,gG't | αα | 2 | -48.2 | 57.7 | 172.9 | 50.7 | -58.2 | 169.2 | 1.91 | 1.67 | 1.10 | 0.03 |
| **g5'** | tGg',tG'g | αα | 2 | -169.2 | 58.2 | -50.7 | -172.9 | -57.7 | 48.2 | 1.91 | 1.67 | 1.10 | 0.03 |
| **g6** | g'Gg,g'Gt | αγ | 2 | -44.5 | 54.4 | 81.0 | -43.3 | 55.5 | -169.6 | 1.91 | 1.73 | 1.30 | 0.02 |
| **g7** | gGg',tG'g | αα | 2 | 75.4 | 54.5 | -41.9 | -164.3 | -57.2 | 49.5 | 2.14 | 1.93 | 1.43 | 0.02 |
| **g7'** | g'G'g,tGg' | αα | 2 | -75.5 | -54.4 | 41.8 | 164.1 | 57.2 | -49.5 | 2.14 | 1.94 | 1.44 | 0.02 |
| **g8** | g'Gg,tGg' | γα | 2 | -45.2 | 53.9 | 80.3 | -157.9 | 59.0 | -52.9 | 2.31 | 2.04 | 1.52 | 0.02 |
| **g9** | g'Tg,g'Gg | βγ | 1 | -71.2 | -170.5 | 77.8 | -45.2 | 63.3 | 81.3 | 3.31 | 3.05 | 1.62 | 0.01 |
| **g10** | g'Gg,g'Gg | αγ | 2 | -42.0 | 52.2 | 86.7 | -37.6 | 51.1 | 80.7 | 2.25 | 2.09 | 1.68 | 0.01 |
| **g11** | gG'g,tGg' | αα | 1 | 72.8 | -54.9 | 86.8 | -151.4 | 59.6 | -50.9 | 2.96 | 2.80 | 2.09 | 0.01 |
| **g12** | g'Tg,tG'g | βγ | 1 | -74.9 | 164.2 | 52.6 | 173.0 | -71.3 | 58.1 | 3.04 | 2.92 | 2.13 | 0.01 |
| **g12'** | gTg',tGg' | βγ | 1 | 74.9 | -164.2 | -52.6 | -173.0 | 71.3 | -58.1 | 3.04 | 2.92 | 2.13 | 0.01 |
| **g13** | tTg,g'Gg | βγ | 1 | -169.4 | -167.8 | 78.0 | -44.8 | 64.9 | 80.3 | 3.07 | 3.00 | 2.27 | 0.00 |
| **g14** | tG'g,tTt | αβ | 1 | 174.5 | -57.1 | 45.7 | 167.4 | 178.5 | -177.7 | 3.77 | 3.43 | 2.34 | 0.00 |
| **g14'** | tGg',tTt | αβ | 1 | -174.5 | 57.1 | -45.8 | -167.4 | -178.5 | 177.7 | 3.77 | 3.43 | 2.34 | 0.00 |
| **g15** | tGg',tTg | αβ | 1 | -172.0 | 58.4 | -45.3 | -167.3 | -176.6 | 70.6 | 3.67 | 3.30 | 2.40 | 0.00 |
| **g15'** | tG'g,tTg' | αβ | 1 | 172.0 | -58.4 | 45.3 | 167.3 | 176.6 | -70.6 | 3.67 | 3.30 | 2.40 | 0.00 |
| **g16** | g'Gg,tTg | γβ | 2 | -51.6 | 66.6 | 76.0 | -163.9 | -161.8 | 74.3 | 3.04 | 2.93 | 2.40 | 0.00 |
| **g17** | gGg',tTt | αβ | 1 | 76.5 | 55.0 | -38.9 | -160.9 | -175.8 | 179.6 | 3.67 | 3.34 | 2.44 | 0.00 |
| **g17'** | g'G'g,tTt | αβ | 1 | -76.5 | -55.0 | 38.9 | 160.9 | 175.8 | -179.6 | 3.67 | 3.34 | 2.44 | 0.00 |
| **g18** | g'Gg,g'G'g | αα | 2 | -40.6 | 56.8 | 62.7 | -62.7 | -56.8 | 40.6 | 3.12 | 2.94 | 2.50 | 0.00 |
| **g19** | gTg,g'Gt | βγ | 1 | 77.2 | -169.0 | 68.4 | -55.2 | 70.4 | -168.1 | 3.44 | 3.35 | 2.54 | 0.00 |
| **g20** | gGg',tTg | αβ | 1 | 76.7 | 55.3 | -38.4 | -160.6 | -174.7 | 74.8 | 3.95 | 3.54 | 2.59 | 0.00 |
| **g20'** | g'G'g,tTg' | αβ | 1 | -76.7 | -55.3 | 38.4 | 160.6 | 174.7 | -74.8 | 3.95 | 3.54 | 2.59 | 0.00 |
| **g21** | tGg',gTg' | γβ | 1 | -177.6 | 54.3 | -42.7 | 81.0 | 174.0 | -73.1 | 3.58 | 3.38 | 2.61 | 0.00 |
| **g22** | tTg,tG'g | βγ | 1 | -159.9 | -172.3 | 57.3 | 178.4 | -56.5 | 52.4 | 3.68 | 3.43 | 2.62 | 0.00 |
| **g23** | tGg',gTt | γβ | 1 | -174.7 | 55.1 | -42.6 | 81.1 | 173.6 | 177.6 | 3.42 | 3.32 | 2.63 | 0.00 |
| **g24** | gTg,tGg' | βα | 1 | 65.8 | -179.1 | 71.1 | -167.3 | 61.3 | -52.1 | 4.35 | 3.88 | 2.83 | 0.00 |
| **g25** | tTg,tGg' | βα | 1 | -176.1 | -177.3 | 77.0 | -161.7 | 60.1 | -51.0 | 4.23 | 3.85 | 2.90 | 0.00 |
| **g25'** | gG't,g'Tt | αβ | 1 | 51.0 | -60.1 | 161.7 | -77.0 | 177.3 | 176.1 | 4.23 | 3.85 | 2.90 | 0.00 |
| **g26** | g'Gg,tTt | γβ | 1 | -45.0 | 54.0 | 74.8 | -163.9 | 174.5 | 167.2 | 3.99 | 3.77 | 2.95 | 0.00 |

[a]Only the conformations with $\Delta G$ < 3 kcal/mol. [b]Torsion angles are defined in Figure 1; units in degrees. [c]See the text for definition. [d]The number of hydrogen bonds. [e]Relative electronic energies in kcal/mol. [f]Relative enthalpies in kcal/mol at 25 °C. [g]Relative free energies in kcal/mol at 25 °C. [h]Population (%) for each local minimum calculated by its $\Delta G$ at 25 °C.

$\Delta E$, $\Delta H$, and $\Delta G$ for the conformation **w1** (i.e., the conformation **g18**) are 3.12, 2.94, and 2.50 kcal/mol in the gas phase (Table 1). The conformer **w1** has two symmetrical $C_5$ hydrogen bonds with the distances of $d(O_4\text{-}H_7\cdots O_6) = d(O_5\text{-}H_9\cdots O_6) = 2.39$ Å and the angles of $\theta(O_4\text{-}H_7\cdots O_6) = \theta(O_5\text{-}H_9\cdots O_6) = 107^o$, whose distances and angles become longer by 0.08 Å and narrower by 5°, respectively, compared with those of the conformer **g18** due to the solvation.

The second preferred conformations are the enantiomers **w2** (gGg',tGg') and **w2'** (g'G'g,tG'g) with the backbone conformation αγ and $\Delta G$ = 0.09 kcal/mol, which is almost isoenergetic to the conformer **w1**. These two conformers have two $C_5$ hydrogen bonds with the distances of $d(O_6\text{-}H_8\cdots O_4) = 2.27$ Å and $d(O_5\text{-}H_9\cdots O_6) = 2.39$ Å and the angles of $\theta(O_6\text{-}H_8\cdots O_4) = 113^o$ and $\theta(O_5\text{-}H_9\cdots O_6) = 106^o$. These distances and angles are longer by 0.07 and 0.12 Å and narrower by 2° and 3°, respectively, compared with those of the similar conformers **g3** and **g3'** in the gas phase. The third preferred conformers **w3** (gGg',tG'g) and **w3'** (g'G'g,tGg') have the backbone conformation αα with $\Delta G$ = 0.13 kcal/mol, which is quite similar to those of the conformers **w2** and **w2'**. The conformers **w3** and **w3'** have also two $C_5$ hydrogen bonds with the distances of $d(O_6\text{-}H_8\cdots O_4) = 2.38$ Å and $d(O_5\text{-}H_9\cdots O_6) = 2.39$ Å and the angles of $\theta(O_6\text{-}H_8\cdots O_4)$

**Table 2.** Torsion angles and thermodynamic properties of glycerol calculated at the SMD M06-2X/cc-pVTZ level of theory in water[a]

| | | | | | Torsion angles[b] | | | | | | Therm. properties | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Conf[c] | | HB[d] | $\chi^1$ | $\chi^2$ | $\chi^3$ | $\chi^4$ | $\chi^5$ | $\chi^6$ | $\Delta E^e$ | $\Delta H^f$ | $\Delta G^g$ | $p^h$ |
| **w1** | **g18** | g'Gg,g'G'g | αα | 2 | -52.2 | 57.3 | 61.9 | -61.9 | -57.3 | 52.2 | 0.47 | 0.27 | 0.00 | 0.05 |
| **w2** | **g3'** | gGg',tGg' | αγ | 2 | 65.8 | 54.3 | -40.2 | -162.9 | 60.5 | -53.9 | 0.44 | 0.12 | 0.09 | 0.05 |
| **w2'** | **g3** | g'G'g,tG'g | αγ | 2 | -65.8 | -54.3 | 40.2 | 162.9 | -60.5 | 53.9 | 0.44 | 0.12 | 0.09 | 0.05 |
| **w3** | **g7** | gGg',tG'g | αα | 2 | 67.6 | 56.9 | -52.2 | -173.9 | -60.3 | 56.4 | 0.70 | 0.32 | 0.13 | 0.04 |
| **w3'** | **g7'** | g'G'g,tGg' | αα | 2 | -67.6 | -56.9 | 52.2 | 173.9 | 60.3 | -56.4 | 0.70 | 0.32 | 0.13 | 0.04 |
| **w4** | **g10** | g'Gg,g'Gg | αγ | 2 | -51.9 | 56.0 | 76.3 | -48.4 | 53.7 | 78.8 | 0.53 | 0.25 | 0.17 | 0.04 |
| **w5** | **g6** | g'Gg,g'Gt | αγ | 2 | -52.1 | 56.9 | 74.4 | -50.1 | 59.6 | -164.0 | 0.99 | 0.59 | 0.31 | 0.03 |
| **w6** | **g4** | tGg',gG'g' | γγ | 2 | 177.5 | 65.8 | -79.4 | 46.4 | -52.3 | -54.6 | 0.76 | 0.42 | 0.38 | 0.03 |
| **w6'** | **g4'** | gGg',gG't | γγ | 2 | 54.6 | 52.3 | -46.5 | 79.3 | -65.7 | -177.4 | 0.76 | 0.42 | 0.38 | 0.03 |
| **w7** | **g8** | g'Gg,tGg' | γα | 2 | -52.7 | 56.5 | 71.9 | -165.9 | 60.6 | -55.3 | 0.74 | 0.44 | 0.39 | 0.03 |
| **w8** | **g11** | gG'g,tGg' | αα | 1 | 70.3 | -61.3 | 80.1 | -158.8 | 60.7 | -53.0 | 0.77 | 0.64 | 0.49 | 0.02 |
| **w9** | | g'G'g,tGg | αα | 1 | -68.0 | -54.8 | 47.3 | 169.1 | 62.7 | 63.8 | 1.34 | 0.92 | 0.50 | 0.02 |
| **w10** | **g2'** | tGg',tGg' | αγ | 2 | -162.3 | 57.4 | -40.9 | -163.5 | 60.1 | -53.6 | 0.90 | 0.56 | 0.52 | 0.02 |
| **w10'** | **g2** | tG'g,tG'g | αγ | 2 | 162.3 | -57.4 | 40.9 | 163.5 | -60.1 | 53.6 | 0.90 | 0.56 | 0.52 | 0.02 |
| **w11** | **g5'** | tGg',tG'g | αα | 2 | -172.0 | 60.4 | -54.4 | -176.1 | -60.3 | 55.9 | 1.13 | 0.77 | 0.60 | 0.02 |
| **w11'** | **g5** | g'Gt,gG't | αα | 2 | -55.9 | 60.3 | 176.1 | 54.4 | -60.4 | 172.0 | 1.13 | 0.77 | 0.60 | 0.02 |
| **w12** | **g1** | gGg',gG'g | γγ | 2 | 53.9 | 52.5 | -40.8 | 84.6 | -64.4 | 68.3 | 0.00 | 0.00 | 0.60 | 0.02 |
| **w13** | **g29** | gGg',tTg' | αβ | 1 | 69.7 | 55.5 | -43.5 | -165.4 | -172.9 | -77.5 | 1.77 | 1.41 | 0.64 | 0.02 |
| **w13'** | **g29'** | g'G'g,tTg | αβ | 1 | -69.7 | -55.5 | 43.5 | 165.4 | 172.9 | 77.5 | 1.77 | 1.41 | 0.64 | 0.02 |
| **w14** | **g51** | g'Gg,tGg | γα | 1 | -51.4 | 58.9 | 66.4 | -171.4 | 64.2 | 63.0 | 1.43 | 1.00 | 0.70 | 0.02 |
| **w15** | **g31** | gTg,tG'g | βγ | 1 | 64.1 | -177.9 | 54.3 | 177.0 | -60.5 | 54.1 | 1.42 | 1.12 | 0.75 | 0.01 |
| **w16** | **g34** | g'Gg,g'Tg | αβ | 1 | -51.9 | 58.8 | 62.3 | -61.8 | -174.7 | 65.8 | 1.38 | 1.12 | 0.78 | 0.01 |
| **w17** | **g12** | g'Tg,tG'g | βγ | 1 | -75.9 | -176.6 | 56.0 | 178.6 | -61.9 | 54.4 | 1.41 | 1.20 | 0.86 | 0.01 |
| **w17'** | **g12'** | gTg',tGg' | βγ | 1 | 75.9 | 176.6 | -56.0 | -178.6 | 61.9 | -54.4 | 1.41 | 1.20 | 0.86 | 0.01 |
| **w18** | **g37** | g'Gg,tGt | γα | 1 | -54.1 | 60.9 | 67.0 | -170.7 | 67.7 | -174.4 | 1.78 | 1.32 | 0.87 | 0.01 |
| **w19** | **g21** | tGg',gTg' | γβ | 1 | -169.5 | 60.3 | -51.4 | 73.3 | 176.8 | -64.4 | 1.74 | 1.41 | 0.88 | 0.01 |
| **w20** | **g36** | g'Gg,tTg' | γβ | 1 | -51.0 | 58.3 | 64.0 | -173.6 | 179.0 | -65.0 | 1.40 | 1.21 | 0.89 | 0.01 |
| **w21** | **g24** | gTg,tGg' | βα | 1 | 65.0 | -174.9 | 68.3 | -170.3 | 63.3 | -56.4 | 1.50 | 1.22 | 0.91 | 0.01 |
| **w22** | | tG'g,tG't | αγ | 1 | 163.5 | -60.7 | 44.5 | 168.2 | -65.4 | 178.6 | 2.16 | 1.66 | 0.91 | 0.01 |
| **w23** | **g9** | g'Tg,g'Gg | βγ | 1 | -64.5 | 178.5 | 74.3 | -50.2 | 58.0 | 76.2 | 1.11 | 1.02 | 0.93 | 0.01 |
| **w24** | **g25'** | gG't,g'Tt | αβ | 1 | 56.5 | -63.1 | 168.9 | -69.8 | 174.3 | 178.3 | 2.00 | 1.57 | 0.95 | 0.01 |
| **w24'** | **g25** | tTg,tGg' | βα | 1 | -178.3 | -174.3 | 69.8 | -168.9 | 63.1 | -56.5 | 2.00 | 1.57 | 0.95 | 0.01 |
| **w25** | **g27** | g'Tg,tGg' | βα | 1 | -78.8 | -171.7 | 69.2 | -169.2 | 63.1 | -55.8 | 1.67 | 1.38 | 1.00 | 0.01 |
| **w25'** | **g27'** | gG't,g'Tg | αβ | 1 | 55.8 | -63.1 | 169.2 | -69.2 | 171.7 | 78.8 | 1.67 | 1.38 | 1.00 | 0.01 |

[a]Only the conformations with $\Delta G$ < 1 kcal/mol. [b-h]See footnotes *b-h* of Table 1.

= 107° and $\theta$($O_5$-$H_9$···$O_6$) = 105°, which are longer by 0.12 Å and narrower by 5°, respectively, compared with those of the similar conformers **g7** and **g7'** in the gas phase. The conformer **w4** (g'Gg,g'Gg) has the backbone conformation αγ with $\Delta G$ = 0.17 kcal/mol, which is quite similar to those of the conformers **g3** and **g3'**. The conformer **w4** has two $C_5$ hydrogen bonds with the distances of $d$($O_6$-$H_8$···$O_4$) = 2.33 Å and $d$($O_5$-$H_9$···$O_6$) = 2.35 Å and the angles of $\theta$($O_6$-$H_8$···$O_4$) = 110° and $\theta$($O_5$-$H_9$···$O_6$) = 108°, which are longer by 0.12 Å and narrower by 5°, respectively, compared with those of the similar conformer **g10** in the gas phase.

Hence, these first six local minima have in common two $C_5$ hydrogen bonds and their distances and angles become longer by ~0.1 Å and narrower by ~4° than those of the corresponding local minima in the gas phase, which indicates the hydrogen bonds being weaker in water. Contrary to the findings in the gas phase, the differences in relative free energies for these first six preferred conformers are decreased and result in the smaller populations in water. The sum of the populations for these preferred conformers is only 27% in water, whereas it is 55% for the first three conformers in the gas phase, as described above. It should be noted that the population of the most preferred conformer **w1** is 5%. The same magnitudes of the changes in distances and angles for hydrogen bonds and the smaller differences in conformational free energies are also found for other local minima in water. In particular, the conformers with one or two β backbone structures such as the conformers **w23**, **w46**, and **w73** with the backbone structures βγ, αβ, and ββ, respectively, have lower $\Delta G$ by 0.8 kcal/mol, compared with those of the corresponding conformers **g9**, **g14**, and **g28** in the gas phase. Therefore, these results indicate that the solvation drove the hydrogen bonds of glycerol to be weaker and its potential surface to be fatter and that glycerol exists

**Table 3.** Population of backbone structures of glycerol in the gas phase and in water[a]

| | Gas phase | | | Water | | |
|---|---|---|---|---|---|---|
| | M06-2X[b] | G2(MP2)[c] | CBS-QB3[c] | SMD M06-2X[d] | SM5.42[e] | exptl[f] |
| αα | 11.4 | 19 | 21 | 24.4 | 18 | 20 ± 4 |
| αγ | 50.9 | 31 | 33 | 31.8 | 27 | 29 ± 3 |
| αβ | 4.1 | 12 | 9 | 20.0 | 23 | 21 ± 4 |
| ββ | 0.4 | 2 | 2 | 1.2 | 3 | 6 ± 2 |
| βγ | 4.8 | 18 | 17 | 13.4 | 24 | 15 ± 2 |
| γγ | 28.5 | 18 | 19 | 9.2 | 4 | 11 ± 3 |

[a]Units in %. Each population was calculated by the values of Δ*G* at 25 °C, except for the values at the SM5.42 HF/6-31G(d) level of theory in water, which were calculated by the values of Δ*E*. [b]Calculated at the M06-2X/cc-pVTZ level of theory. [c]Taken from ref 18. [d]Calculated at the SMD M06-2X/cc-pVTZ level of theory. [e]Calculated at the SM5.42 HF/6-31G(d) level of theory; taken from ref 18. [f]Mean values obtained by $^1$H NMR experiments in $D_2O$; taken from ref 7.

as an ensemble of many feasible local minima in water.

Callam *et al*.[18] identified the 75 local minima at the SM5.42 HF/6-31G(d) level of theory in water, in which there are the 19 local minima with Δ*E* <1 kcal/mol and the 69 local minima with Δ*E* < 3 kcal/mol. The most preferred conformation was identified to be the conformation **95** (tG'g,tG'g) with the backbone structure αγ by Δ*E* and followed by the conformation **46** (gGg',tGg') with the same structure αγ with Δ*E* = 0.17 kcal/mol, which corresponds to the conformations **w10'** and **w2** with Δ*E* = 0.90 and 0.44 kcal/mol, respectively, at the SMD M06-2X/cc-pVTZ level of theory in water. At the SM5.42 HF/6-31G(d) level of theory, the conformer **45** with the γα and Δ*E* = 0.36 kcal/mol is third preferred and followed by the conformer **109** with the αα and Δ*E* = 0.43 kcal/mol. The former corresponds to the conformer **w7** with Δ*E* = 0.74 kcal/mol, but the latter is not a local minimum at the SMD M06-2X/cc-pVTZ level of theory. In particular, the conformer **w12** (g'Gg,g'G'g) with the backbone structure γγ by Δ*E* is most preferred at the SMD M06-2X/cc-pVTZ level of theory (Table 2), whereas its corresponding conformer **100** has Δ*E* = 0.60 kcal/mol at the SM5.42 HF/6-31G(d) level of theory. These comparison of the local minima and their Δ*E* values indicate that the different conformational preferences of glycerol were obtained at the SM5.42 HF/6-31G(d) and SMD M06-2X/cc-pVTZ levels of theory in water.

**Populations of Backbone Structures.** At the M06-2X/cc-pVTZ level of theory in the gas phase and the SMD M06-2X/cc-pVTZ level of theory in water, the populations of backbone structures were calculated using the Δ*G* values at 25 °C, which are listed in Table 3. In the gas phase, the populations of the backbone structures αγ, γγ, and αα are calculated to be 50.9, 28.5, and 11.4%, respectively. The sum of the populations of these three structures is 90.8% and other structures appear to be negligible. According to the electron diffraction experiments, the two conformations αα and αγ are major conformations of glycerol in the gas phase,[5] whereas the microwave spectroscopic studies reported that γγ and αγ are dominating conformations.[11] Therefore, our calculated populations are reasonably consistent with these observed results. Callam *et al*. reported these populations to be 31, 18, and 19%, respectively, at the G2(MP2) level of theory and 33, 19, and 21%, respectively, at the CBS-QB3 level of theory.[18] However, the population of the structure βγ was suggested to be 18 and 17% at these levels of theory, which seem to be overestimated. In particular, most of the preferred conformers of glycerol obtained by us have two $C_5$ hydrogen bonds, as described above, which is in good agreement with the observed results by the analysis of calorimetric data.[5]

In water, the most preferred backbone structures are calculated to be αγ, αα, and αβ, whose populations are 31.8, 24.4, and 20.0%, respectively, and followed by the structures βγ and γγ with the populations of 13.4 and 9.2%, respectively. The sum of the populations of the first three structures is 76.2% and the structure ββ appears to be negligible. These calculated populations are in good agreement with the mean values obtained by $^1$H NMR experiments in $D_2O$, which are 29 ± 3, 20 ± 4, 21 ± 4, 15 ± 2, 11 ± 3, and 6 ± 2% for the structures αγ, αα, αβ, βγ, γγ, and ββ, respectively.[7] Although the populations calculated at the SM5.42 HF/6-31G(d) level of theory[18] are reasonably consistent with these NMR data, the population of 24% for the structure βγ appears to be overestimated.

## Conclusions

The preferred conformations of glycerol and the populations of their backbone structures were calculated at the M06-2X/cc-pVTZ level of theory in the gas phase and the SMD M06-2X/cc-pVTZ level of theory in water. Most of the preferred conformers of glycerol have two $C_5$ hydrogen bonds in the gas phase, as found by the analysis of calorimetric data. It has been known that the solvation drove the hydrogen bonds of glycerol to be weaker and its potential surface to be fatter and that glycerol exists as an ensemble of many feasible local minima in water. The calculated populations of glycerol in the gas phase and in water are consistent with the observed values, which are better than the previously calculated ones at the G2(MP2), CBS-QB3, and SM5.42 HF/6-31G(d) levels of theory. These results may imply that the M06-2X/cc-pVTZ level of theory and/or the solvation model SMD can be successfully used for the conformational analysis of other molecules with polyfunctional alcohols.

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**Supporting Information Available.** Torsion angles, thermodynamic properties, and the number of hydrogen bonds of local minima with higher values of $\Delta G$ at the M06-2X/cc-pVTZ level of theory in the gas phase and at the SMD M06-2X/cc-pVTZ level of theory in water. This material is available free of charge *via* the Internet at http://www.kcsnet.or.kr/bkcs.

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