Theoretical Study of Mutarotation of Glucose

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I. Introduction

Glucose has the molecular formula $C_6H_{12}O_6$ and crystalline α and β anomers. When dissolved in water, these equilibrate both with an open aldehyde form and with each other (Scheme 1). Glucose is a very fundamental organic compound and has been studied enormously.[1] Theoretical studies have been concerned mainly with conformations of glucose in gas and aqueous phases.[2]

Although Scheme 1 is familiar to every chemist, the mechanism of the mutarotation is still unsettled. It is a structural question how the ether and its adjacent hydroxyl groups in the α and β forms interact with water molecules. Hydrogen bonds require the O−H···O linearity generally. The above question is directed to the way of constructing a strain-free hydrogen-bond network (as in ice). There have been many theoretical studies of proton transfers and relays between a water molecule and a proton donor (or an acceptor).[3] The unusually high capability of water molecules for the exchange of O−H covalent bonds and O···H hydrogen bonds has been demonstrated.

In this work, isomerizations in Scheme 1 were examined with ab initio calculations. Of course, reactions in the aqueous media cannot be described accurately. But, molecule-level analyses are expected to shed light on the distinction between reactant and solvent water molecules. The number of water molecules for the good network will be scrutinized.

II. Method of Calculations

Ab initio calculations were performed using the GAUSSIAN 94[4] program on the CONVEX SPP 1200/XA com-

puter at the Information Processing Center of Nara University of Education. All of the geometries were optimized using the Becke3lyp[5]/6-31G* method with the SCRF[6] solvent effect (the dielectric constant of water, ϵ = 76.55). For transition states (TSs), B3-LYP(SCRF)/6-31G* vibrational analyses were carried out to check whether the sole imaginary frequencies were correctly obtained. TS structures were first sought by a semiempirical MO method (PM3). After they were optimized with PM3, their force constants were obtained by vibrational analyses. By the use of those PM3 force constants, opt = (readfc, TS, noeig), TS geometries were determined by B3-LYP/6-31G* with SCRF solvent effect throughout. The criterion for convergence of the transition state is the same as that of stable states.

III. Results of Calculations and Discussions

Figure 1 shows the geometries of mutarotation without water molecules. Those of the α and β forms are of trans gauche (TG) conformers, where CH_2−OH groups are directed to the oxygen atoms in the left-end O−H groups as intramolecular hydrogen bonds. When the proton (a shaded circle) moves to the ether oxygen atom, a four-centered TS, TS1, is generated. TS1 has a proton-movement character and a small (unfavorable) hydrogen-bond angle of 125.3°.

After TS1, the aldehyde form is obtained. The proton is involved in the intramolecular hydrogen bond with a distance of 2.17 Å. However, this bond is specific (i.e., artificial) only in the gas phase. In any medium, the intramolecular bond would disappear and the intermolecular bond will be formed. From the aldehyde form, a ring closure takes place via the four-centered TS, TS2, leading to the β form. The geometry of TS2 is close to that of TS1.

(1) See, for instance: Cram, D. J.; Hammond, G. S. *Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1964; Chapter 27.

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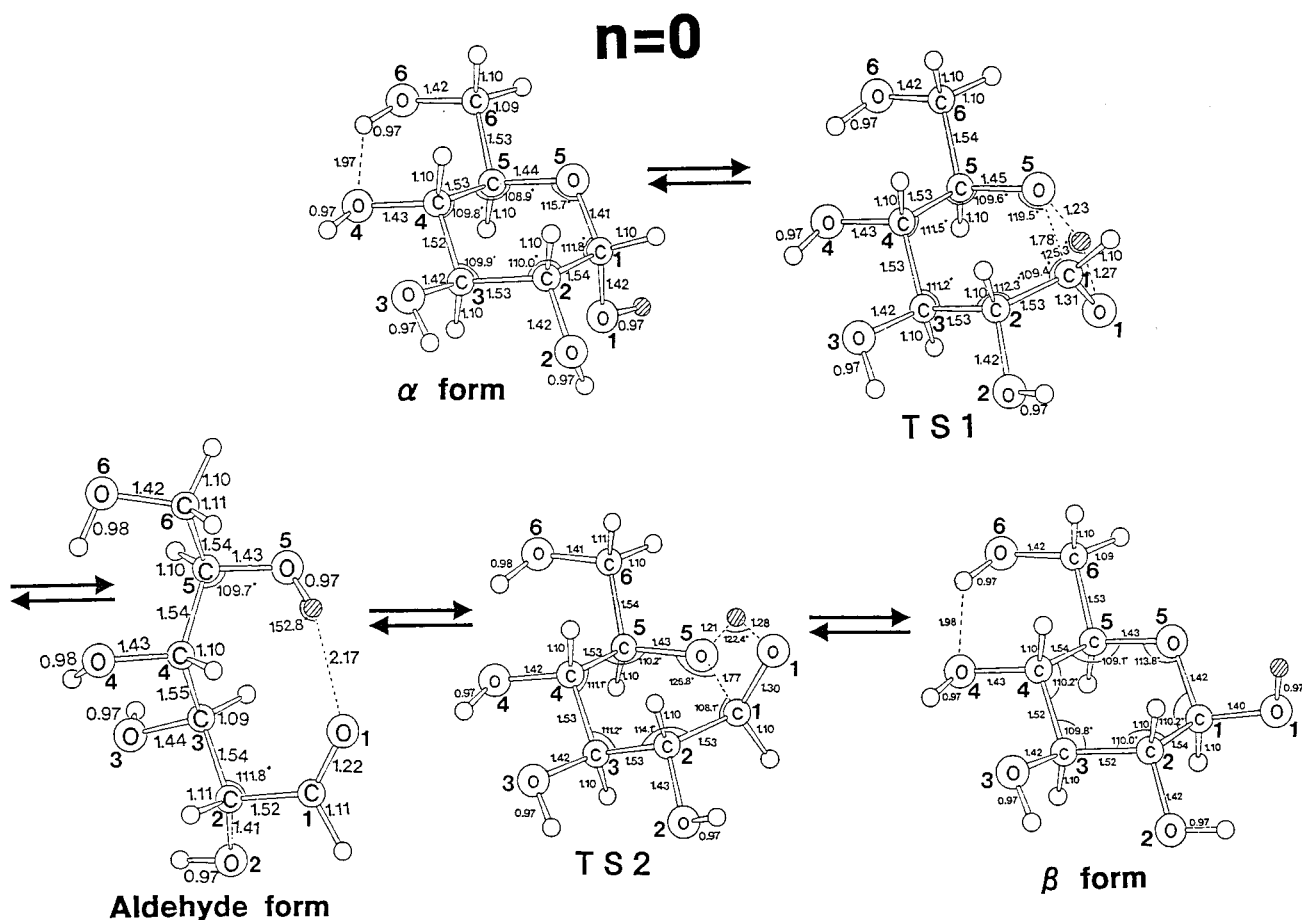
(4) *Gaussian 94*, Revision D.4; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.: Ayala, P. Y.: Chen, W.: Wong, M. W.: Andres, J. L.: Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc.: Pittsburgh, PA, 1995.

(5) (a) Becke, A. D. *Phys. Rev.* **1988**, *A38*, 3098. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

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Figure 1. Isomerization of three forms of glucose without water molecules ($n = 0$) via two transition states, TS1 and TS2. Empty circles denote hydrogen atoms, and the shaded circle represents a reaction center. Distances are in angstroms.

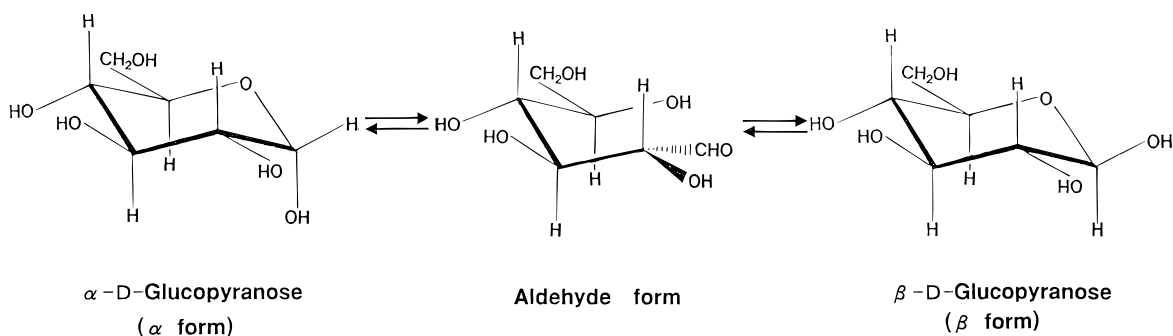**Scheme 1.   Mutarotation of Glucose with an Aldehyde Form in Aqueous Solution**

Figure 1 has demonstrated that the water-free isomerization is possible but suffers from large ring strain in TS geometries. Isomerizations assisted by water molecules are required to relax the ring strain of the hydrogen-bond network.

Figure 2 exhibits geometries of isomerizations including one water molecule. In the precursor, α form···H_2O, two hydrogen bonds denoted by broken lines are formed. Hydrogen-bond angles are 140.8° and 147.3°, which are too small for ready proton transfers.[7] However, by inclusion of H_2O, slight distortion of the pyranose skeleton toward the aldehyde form is caused. In TS1, hydrogen-bond angles of 150.7° and 153.1° are favorably larger than those of the precursor, 140.8° and 147.3°, respec-

tively. The resultant geometry is that of aldehyde form···H_2O. By rotating the aldehyde group, the hydrogen-bond network moves to the reverse side of the alkyl chain.

TS2 stands for the transition state of the pyranose ring closure along with proton transfers. TS2 also has a strained network with hydrogen-bond angles of 152.2° and 153.1°. After TS2, β form···H_2O is formed. One water

(7) In our previous study, a correlation between proton affinities (PAs) and angles of intramolecular hydrogen bonds in bifunctional organic compounds was examined. As the angle increases, PA values grow large. A protonated 2,4-pentadione has the angle 141.9°, which corresponds to a small PA value, 207.8 kcal/mol. A protonated 2,5-hexanedione has the angle 160.4°, which corresponds to a large PA value, 213.2 kcal/mol. Yamabe, S.; Hirao, K.; Wasada, H. *J. Phys. Chem.* **1992**, *96*, 10261.
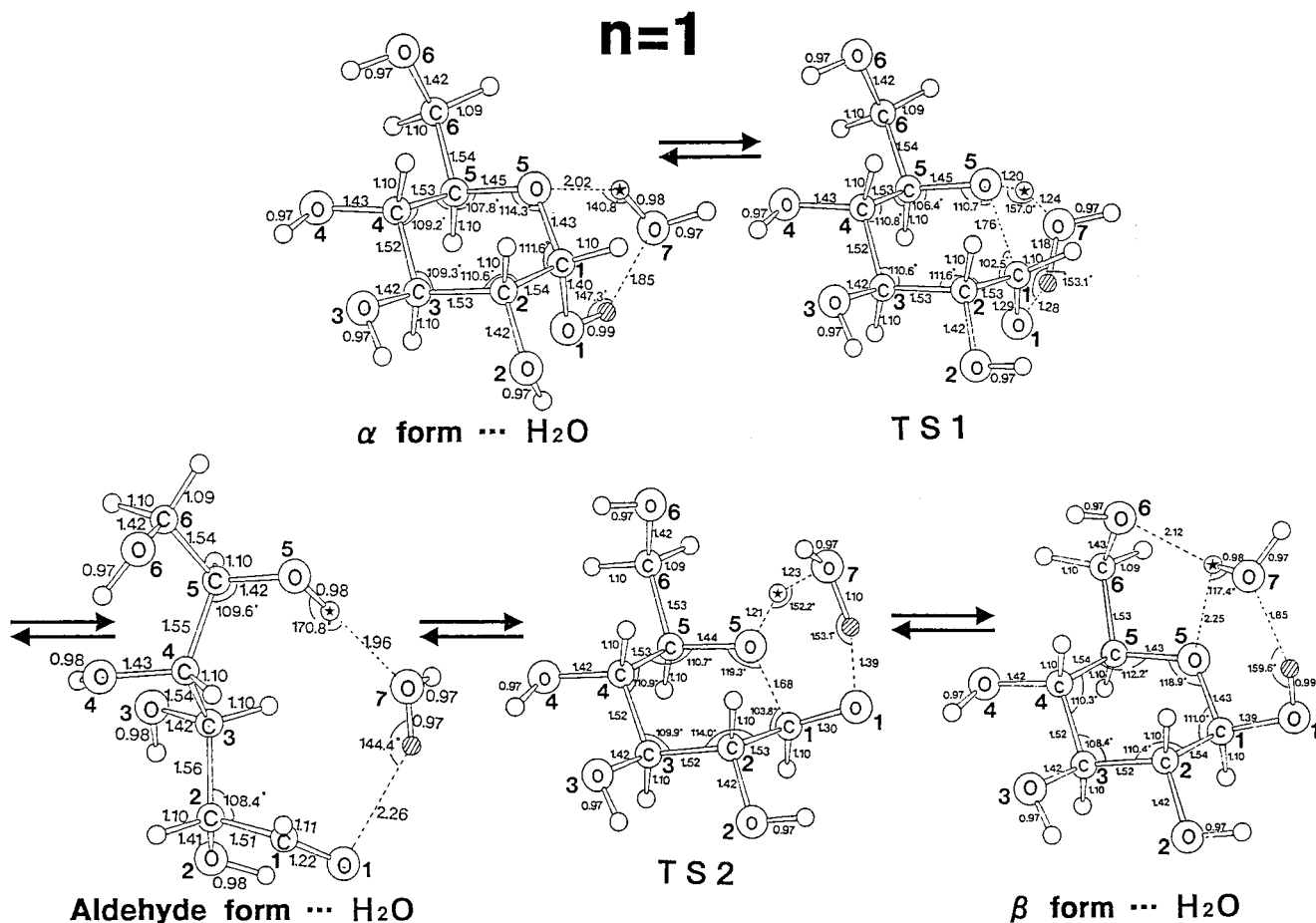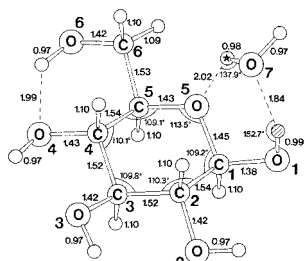
Figure 2. Isomerization including one water molecule ($n = 1$). Same notations as in Figure 1 are used.

molecule is linked with the O(6) and the O(1)−H hydrogen atoms. These hydrogen bonds are transient. According to internal rotation of the −CH$_2$OH group around the C(5)−C(6) axis, one hydrogen bond O(7)−H···O(6) disappears.[8] Figure 2 indicates that participation of one water molecule is still insufficient for ready proton transfers.

Figure 3 shows geometries of isomerizations of glucose with two water molecules. In the precursor, α form···2H$_2$O, an almost strain-free beautiful network is established. Hydrogen-bond angles are 167.0°, 161.5°, and 170.4°. A C−O distance of 1.39 Å means there is a slight contribution of the carbonyl bond. When the proton relay is initiated, TS1 is brought about. Hydrogen-bond angles of TS1 are close to 180.0°.
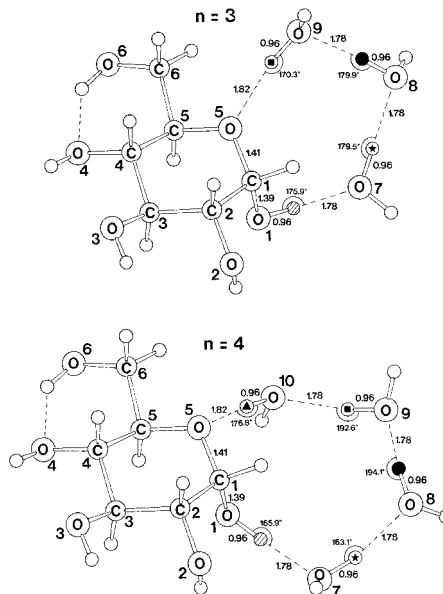
After TS1, aldehyde form···2H$_2$O is generated. When the aldehyde group rotates and proton transfers are caused, TS2 is arrived at. TS2 has also a good network.

(9) Participations of water trimer ($n = 3$) and tetramer ($n = 4$) were tested by means of PM3 calculations. The $n = 3$ precursor geometry of PM3 was found to be similar to that of B3-LYP(SCRF)/6-31G* in Figure 4. The PM3 calculation is, at least, applicable to precursor geometries. The $n = 4$ geometry involves four hydrogen bonds, and their linearities become worse than those in $n = 3$. Thus, the $n = 4$ geometry is unfavorable, and the water tetramer would not cause the mutarotation.

(8) As an isomer of the β form···H$_2$O species, the following geometry has been obtained.
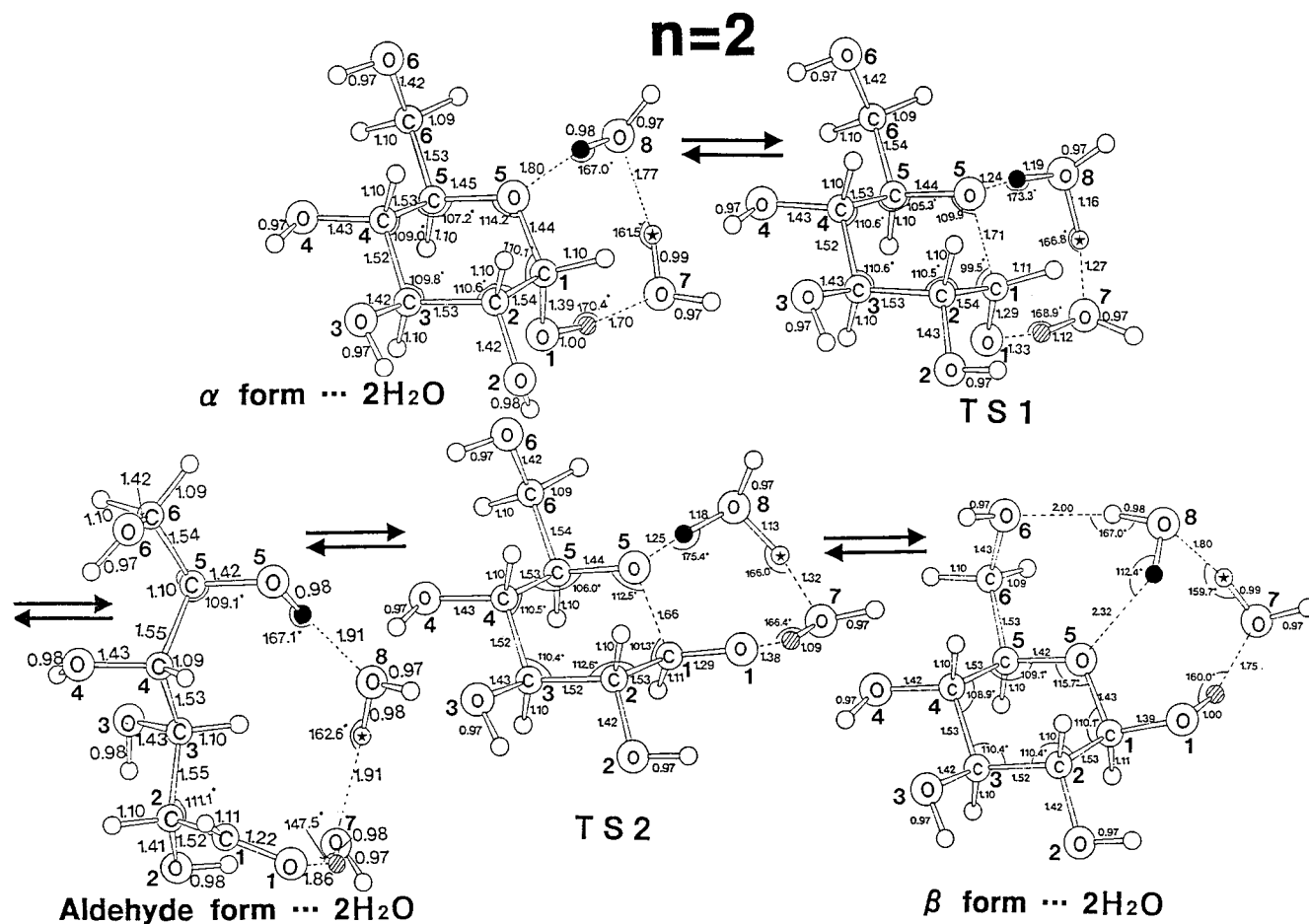

The above structure is by 0.2 kcal/mol more stable than that in Figure 2. The energy difference is very small, which indicates that inter- and intramolecular hydrogen bonds are formed and cleaved instantaneously under the thermal condition.
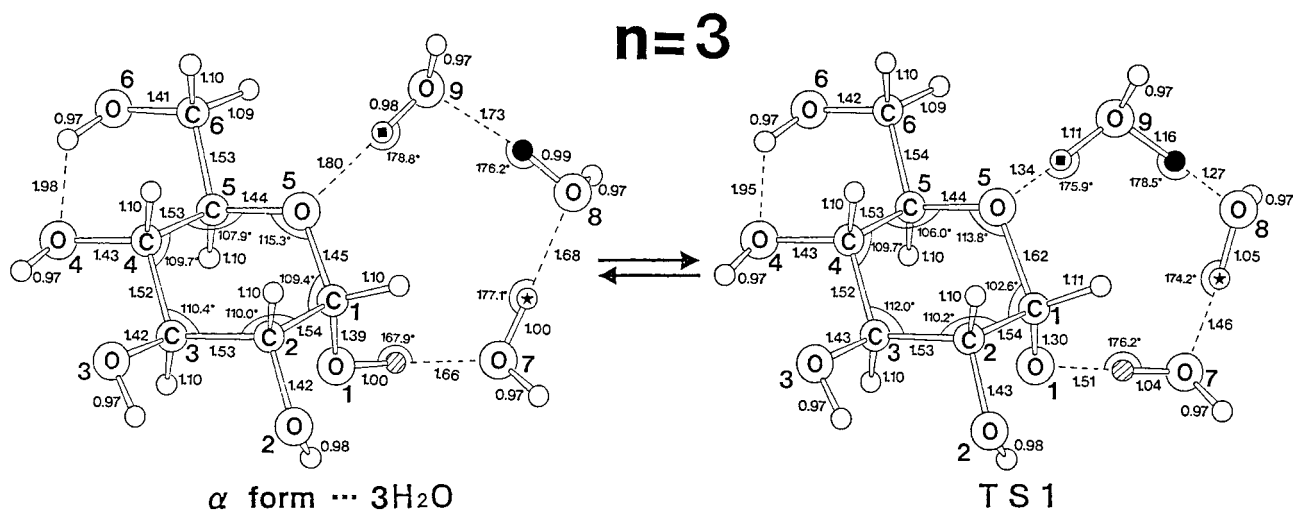
n=2

Figure 3. Isomerization including two water molecules ($n = 2$).

n=3

Figure 4. The geometry of a precursor and TS containing a water trimer.

After TS2, β form···$2H_2O$ is found, where the water dimer is sandwiched by two hydroxy groups $O(1)-H$ and $O(6)-H$ (rather than by one hydroxy proton and ether oxygen atom). Figure 3 demonstrates that the water dimer fits well the reaction moiety of the glucopyranose.

We have tested the possibility of water-trimer participation ($n = 3$). Geometries of the precurser and TS are shown in Figure 4. Three hydrogen bonds have good linearities, and proton relays would be as facile as those in $n = 2$. Although explicit determinations of $n = 3$

geometries other than the precursor and TS1 could not be made because of computer limitation, $n = 2$ and $n = 3$ mutarotations would likely be competitive judging from their precursor and TS1 geometries. The $n = 4$ geometry was also examined and was found to be unfavorable owing to the deformation of the hydrogen-bond network.[9]

Table 1 displays total energies (in hartree) and their differences (in kcal/mole). Figure 5 shows these difference energies. As expected from extent of the ring strain at TS, activation energies decrease as considerably $n = 0$

Table 1. B3-LYP(SCRF)/6-31G*//B3-LYP(SCRF)/6-31G* Total Energies and Relative Energies[a]

n	α form	α form···nH_2O	TS1	aldehyde···nH_2O	TS2	β form···nH_2O
0	−687.154 85 (0)	−687.154 85 (0)	−687.073 82 (+50.84)	−687.135 73 (+12.00)	−687.076 45 (+49.19)	−687.151 55 (+2.07)
1	−763.566 95 (0)	−763.580 01 (−8.20)	−763.530 90 (+22.62)	−763.561 21 (+3.60)	−763.533 53 (+20.97)	−763.579 60 (−7.94)
2	−839.993 32 (0)	−840.014 44 (−13.25)	−839.967 85 (+15.98)	−839.997 38 (−2.55)	−839.970 62 (+14.34)	−840.012 58 (−12.09)
3		−916.412 59[b] (0)	−916.447 15 (−21.69)	−916.407 51 (+3.19)		

[a] Total energies are in hartree, and relative energies (in parentheses) are in kcal/mol. Negative values mean more stable systems. [b] The water trimer is calculated to have a ring form. Although the ring form is meaningful in the gas phase, it is unlikely in the aqueous media. The overestimated stability due to three hydrogen bonds in the trimer is corrected by excluding one hydrogen-bond energy, 6.73 kcal/mole.
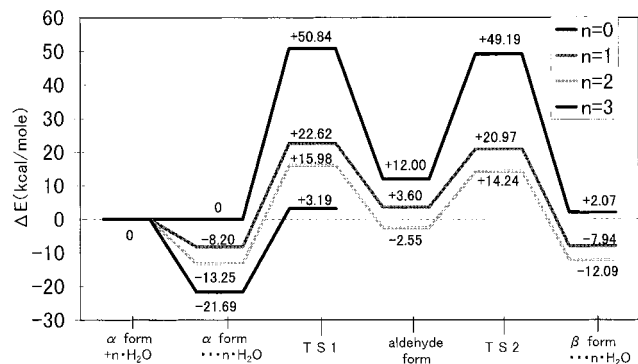

Figure 5. Energy diagrams of the mutarotation. Relative energies are shown in parentheses in Table 1. The corresponding geometries are exhibited in Figures 1 ($n = 0$), 2 ($n = 1$), 3 ($n = 2$), and 4 ($n = 3$).

→ 1→ 2 → 3. Although the α and β forms have similar stability, the aldehyde form is ca. 11−12 kcal/mol less stable. In Figure 5, the precursor, α form···nH_2O ($n = 1$−3), is stable relative to the reactant. The cyclic hydrogen-bond network in the precursor gives the stabilization. Activation energies of TS1 decrease considerably as $n = 0 → 1 → 2 → 3$. It is noteworthy that only the aldehyde form of $n = 2$ is more stable than the reactant (−2.55 kcal/mol). In the gas phase, the aldehyde form is found to be absent (+12.00 kcal/mol). Table 1 indicates that the mutarotation with the water trimer

participation proceeds most readily. As a ring-opening reaction between cyclic ethers and water molecules, the isomerization reaction between maleic anhydride and maleic acid is known well. The reaction was found to be caused by a water trimer ($n = 3$).[3u] In TSs of $n = 1$ and 2 isomerizations, hydrogen-bond angles are small (ca. 130°) and activation energies are large (47.68 kcal/mol for $n = 1$ and 45.37 kcal/mol relative to the energy of a precursor by MP3/6-31G*//RHF/6-31G*). However, in the $n = 3$ TS, hydrogen bonds are almost linear and the activation energy is small (30.64 kcal/mol)..[3u] This energy is interestingly similar to the present value, 29.23 (= 15.98 − (−13.25)) kcal/mole of $n = 2$ in Figure 5.

Figure 6 shows the reaction-coordinate vector of TS1. The vector indicates simultaneous proton transfers for $n = 0.1$ and 2.

In the hydrogen-bond network, the water dimer has been involved reasonably in Figure 3. At TS1, a hydronium-ion (H_3O^+)-like species is yielded, which would be subject to strong outer hydrogen bonds. The effect of outer H_2O molecules on the network needs to be examined. On account of the limit of computer resources, a model of (glucose···$2H_2O$)···$2H_2O$ is tested. The model is explained in Figure 7. One H_2O molecule is attached to the upper H_2O, because this becomes a hydronium-ion-like species at TS1. The other one is linked to the oxygen atom that becomes the carbonyl oxygen in the aldehyde form. At TS1, two outer H_2O molecules are found to change
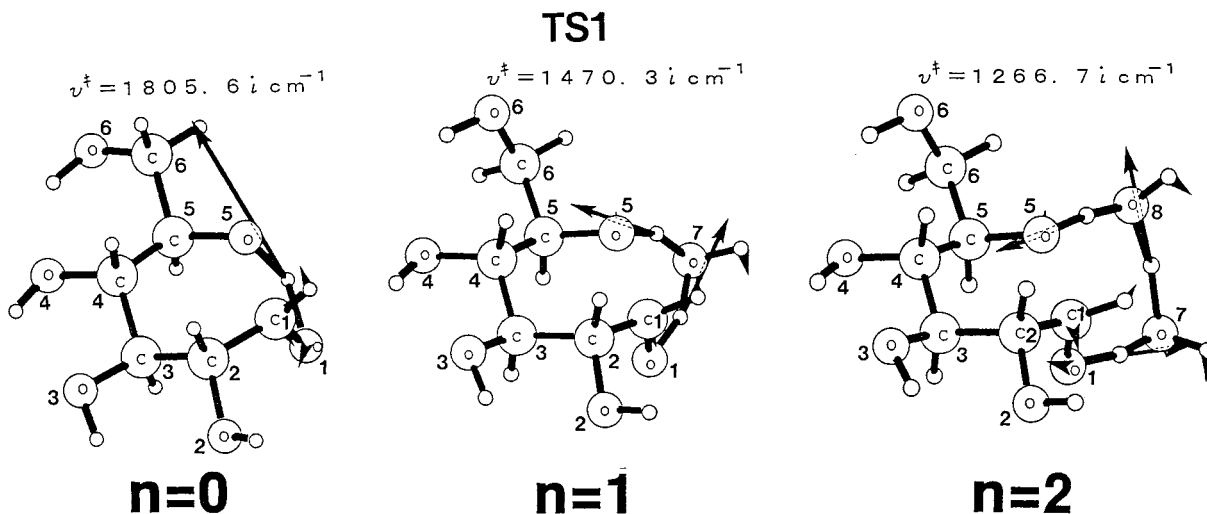

Figure 6. Reaction coordinates at TS1. For TS1, the reaction-coordinate vector corresponding to the sole imaginary frequency of B3-LYP(SCRF)/6-31G* is sketched.
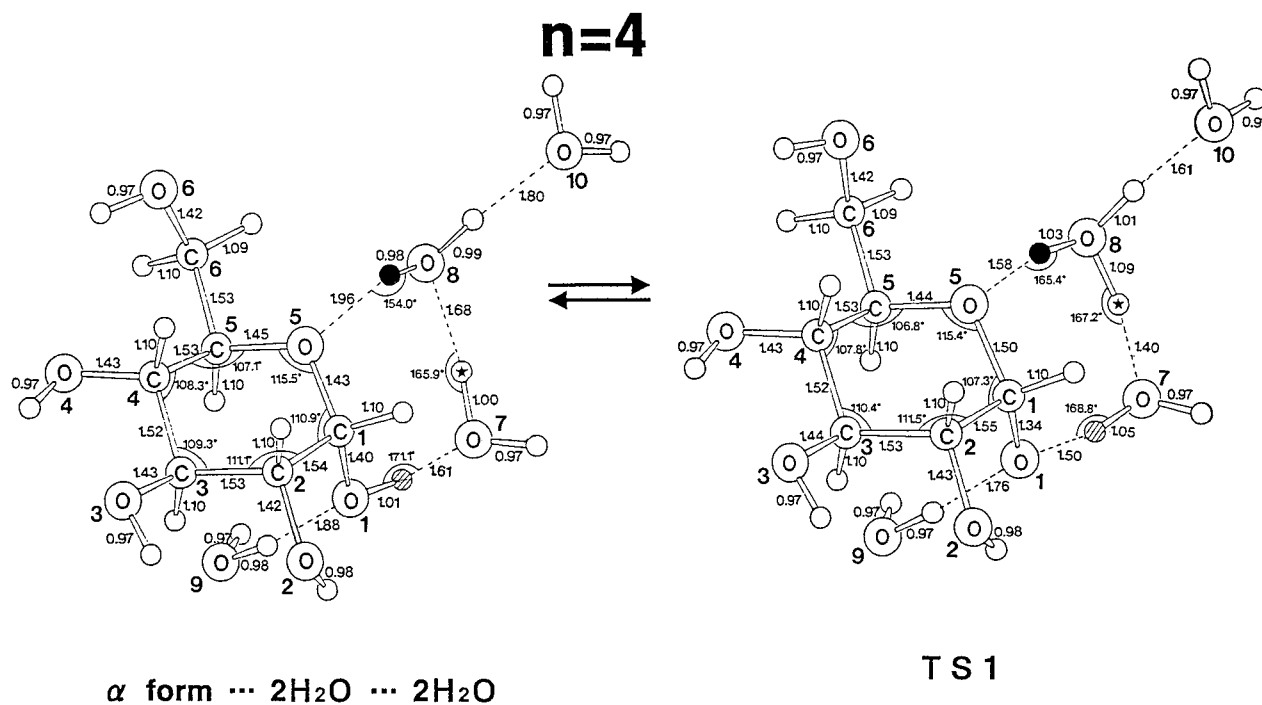
Figure 7. Geometries of the α form and TS1 including four water molecules ($n = 2$ and two outer H_2O). Total energies are -992.86478 hartree (α form) and -992.84195 hartree (TS1), with B3-LYP(SCRF)/6-31G*.

Scheme 2 Zwitterionic Intermediate Found to Be Absent
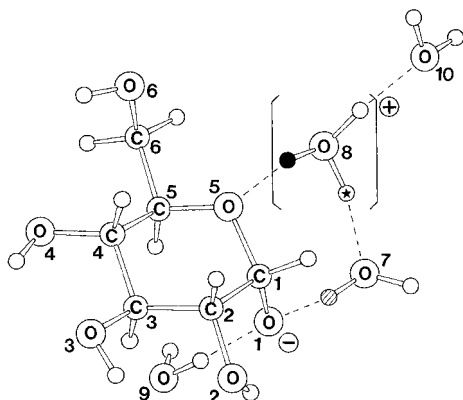
distances involved in the network appreciably, whereas the network shape itself is hardly distorted. The hydrogen bond of the outer H_2O molecule to the hydronium-ion species is strong (1.61 Å). At TS1, one ether C—O bond is not elongated so much (1.50 Å). A zwitterionic intermediate needs to be examined. After TS1, the intermediate has been sought but is, however, computed to be absent (Scheme 2).

After TS1, the geometry is distorted toward that of the aldehyde···4H₂O (not shown). Two outer H_2O molecules contribute to the energy changes as well. In Table 1, the

energy difference between TS1 and α form···2H₂O is $15.98 - (-13.25) = 29.23$ kcal/mol. The difference in n = 4 ($n = 2$ and two outer H_2O molecules) is 14.33 kcal/mol. Outer hydrogen bonds play a significant role structurally and energetically.

IV. Concluding Remarks

This work has dealt theoretically with the mutarotation of glucose assisted by a few water molecules. The water dimer and trimer are reasonably involved in the isomerization. In particular, the trimer can constitute a strain-free hydrogen-bond network for ready proton transfers. Outer solvent H_2O molecules change the extent of proton transfers in the network and energies. Despite this dependence, the $n = 2$ (and probably $n = 3$) network seems to be meaningful in the aqueous media. Table 1 shows the H_2O dimer and trimer are linked to the glucose molecule very strongly [-13.25 kcal/mol (-20.67 kcal/mol without SCRF) for α form···2H₂O and -21.69 kcal/mol for α form···3H₂O]. Aside from the mutarotation, the dimer and trimer participation needs to be considered for many glucose conformers in view of those remarkably large hydrogen-bond energies.