Pergamon

Tetrahedron 55 (1999) 2193–2204

TETRAHEDRON

Studies on the Unusual Stability of *cis*-2,5-Diethoxy-2,5-bis(hydroxymethyl)-1,4-dioxane

Hideya Yuasa[a,*], Hironobu Hashimoto[a], Yutaka Abe[a], Tetsuya Kajimoto[b], Chi-Huey Wong[b,c,*]

[a]*Department of Life Science, Faculty of Bioscience and Biotechnology, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 226-8501 Japan,* [b]*Laboratory for Glycotechnology, Frontier Research Program, The Institute of Physical and Chemical Research (RIKEN), 2-1 Hirosawa, Wako, 351-0106, Japan, and* [c]*Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, California 92037, USA*

Received 2 November 1998; accepted 21 December 1998

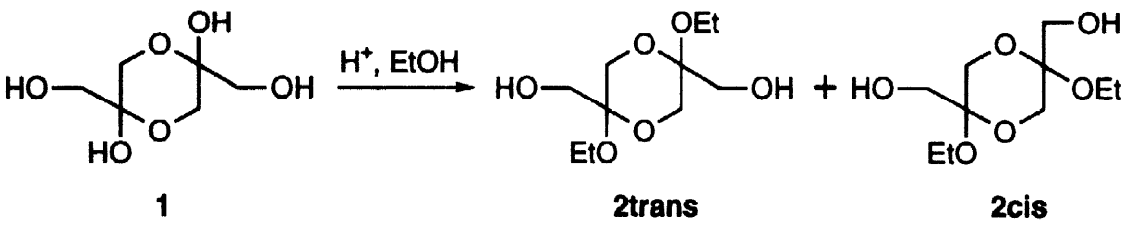
Abstract: Almost equal amounts of the trans and cis isomers of 2,5-diethoxy-2,5-bis(hydroxymethyl)-1,4-dioxane (**2trans** and **2cis**) are obtained by treating dihydroxyacetone with acidic ethanol. To explain the formation of an unusually large quantity of **2cis**, conformation analyses and equilibration experiments were performed for the related compounds. The results indicate that the stability of **2cis** derives not from the hydroxymethyl groups but from the unusually stable twist-boat conformation. The factors stabilizing the twist-boat conformation in **2cis** were discussed.

INTRODUCTION

Aldolases have been successfully used for the synthesis of unnatural sugars and related chiral compounds.[1] Among them, four known aldolases, i.e., D-fructose-1,6-diphosphate aldolase (EC 4.1.2.13), L-fuculose-1-phosphate aldolase (EC 4.1.2.17), L-rhamnulose-1-phosphate aldolase (EC 4.1.2.19), and D-tagatose-1,6-diphosphate aldolase, require dihydroxyacetone phosphate (DHAP) as a common donor substrate while accepting a broad spectrum of aldehyde substrates. In this context, the facile chemical synthesis of DHAP has been a subject of interest.[2,3]

One of the most efficient chemical syntheses of DHAP includes conversion of dihydroxyacetone dimer (**1**) into 2,5-diethoxy-2,5-bis(hydroxymethyl)-1,4-dioxane (**2**) in acidic ethanol, in which the trans and cis isomers were obtained in almost equal amounts (Scheme 1), followed by phosphorylation of the hydroxyl groups and hydrolysis to give DHAP in 61 % overall yield.[2] The formation of **2** is, however, very slow. We are also curious about the existence of equal amounts of the two isomers of **2** during the preparation, as **2trans** is considered to be more stable than **2cis**, due to the presence of the two bulky hydroxymethyl groups in the equatorial orientation and the stabilizing anomeric effect from the two axially oriented ethoxy groups. In this paper, we described an improved synthesis of **2** and studied the unusual stability of the cis isomer, starting with

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00003-4



Scheme 1

the structural investigation of related compounds (**3**-**6**) using NMR and X-ray analyses, and *ab initio* calculations.

The X-ray and NMR analyses of structures **2trans** and **2cis** have been reported[4] and have shown that the trans and cis isomers adopt chair and twist-boat conformations, respectively, in the crystalline state and presumably in solution. In order to investigate the contribution of stereoeffect, the hydroxymethyl group of **2** was replaced with CH_2OAc, CH_2OTs, CH_2OBn or H group. It was felt that the X-ray analysis of the diacetate **3trans** and the ditosylate **4cis** would provide useful information regarding their conformational preference; the large tosyl group may perturb the twist-boat conformation if it is unstable. We also determined the equilibrium constants of the acid catalyzed trans-cis isomerization of the dibenzyl ether **5** and 2,5-diethoxy-1,4-dioxane **6** to examine the energestic difference between the two respective isomers (Figure 1).

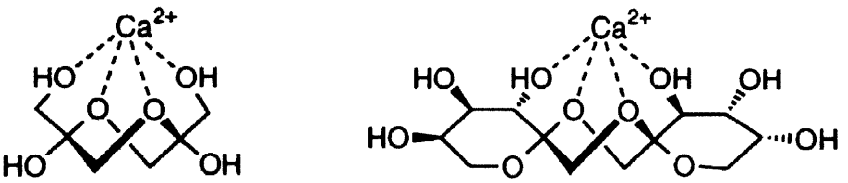
	X
2	CH_2OH
3	CH_2OAc
4	CH_2OTs
5	CH_2OBn
6	H

Figure 1. Proposed structures of 1,4-dioxane derivatives.

RESULTS AND DISCUSSION

The reported preparation of compound **2** requires stirring the reaction mixture for a week at 4 °C.[2] This sluggish reaction might be due to a poor solubility of dihydroxyacetone in ethanol. We found that pre-treatment of dihydroxyacetone with calcium chloride dihydrate in ethanol gave a clear solution after 30 min. By subsequent addition of ethylorthoformate and sulfuric acid to this solution, the reaction was completed in only 5 h at room temperature to give **2trans** (35 %) and **2cis** (40 %). The same reaction conditions without calcium

chloride led to multiproducts. These results are presumably due to a complex formation between calcium cation and the dihydroxyacetone dimer to improve the solubility in ethanol. Particularly, the cis isomer of dihydroxyacetone dimer (**1cis**), in its twist-boat form, has the four oxygen atoms suitably located for coordination to calcium ion (Figure 2). Indeed, it has been reported[5] that di-β-D-fructopyranose 1,2':1',2-dianhydride **7**, in which the central 1,4-dioxane ring is in a twist-boat form, complexes readily with $CaCl_2$ (Figure 2), whereas five isomeric D-fructose dianhydrides do not form complexes.



1cis **7**

Figure 2. Suggested complex formation between calcium ion and ketose dimers (**1cis** and **7**).

To examine if the hydroxymethyl group has relevance to the formation of **2cis**, acid catalyzed equilibration was performed for the dibenzyl derivative **5** and for 2,5-diethoxy-1,4-dioxane **6**, which was prepared by a modified method of the reported synthesis.[6] The HPLC analyses for the equilibration of **5** showed a trans/cis ratio of 1.03 in the presence of sulfuric acid in ethanol at 40°C (Figure 3). Most of **5** decomposed when other solvents were used. Though the trans/cis ratio for the dibenzyl derivative **5** is slightly larger than the product ratio in the syntheses of **2**, 0.88 in this paper and 0.81 in the literature,[2] the cis isomer **5cis** is still unusually stable. Increasing the temperature up to 70°C had little effect on the ratio (0.97), suggesting that the entropy as well as the enthalpy contribution to the free energy change, $\Delta G = \Delta H - T\Delta S$, is negligibly small. The GC analyses for the equilibration of **6** in toluene in the presence of boron trifluoride diethyl etherate gave the trans/cis ratio of 0.87 at 30 °C and 0.88 at 70 °C (Figure 4). These values correspond to the product ratio in the synthesis of **2**, the free energy difference between the trans and cis isomers being very small (ΔG = ca 8.5×10^{-2} kcal/mol). The hydroxymethyl groups of compound **2** and their derivatives are therefore not relevant to the unusual stability of the cis isomer.

As shown in the equilibration experiment for compounds **5**, addition of a large substituent to the hydroxyl groups appeared to have little effect on the relative stability of **5cis** compared to **5trans**. To investigate whether the stable cis conformation of **2** is maintained by weak crystal packing forces, **2trans** and **2cis** were derivatized to diacetate **3trans** and ditoluenesulfonate **4cis**, respectively, and the crystals were subjected to X-ray analyses. As a result, both **3trans** and **4cis** were found to have the same ring conformations as those of **2trans** and **2cis**, respectively (see Figure 5,6). Therefore, it is unlikely that crystal packing forces generate these conformations.

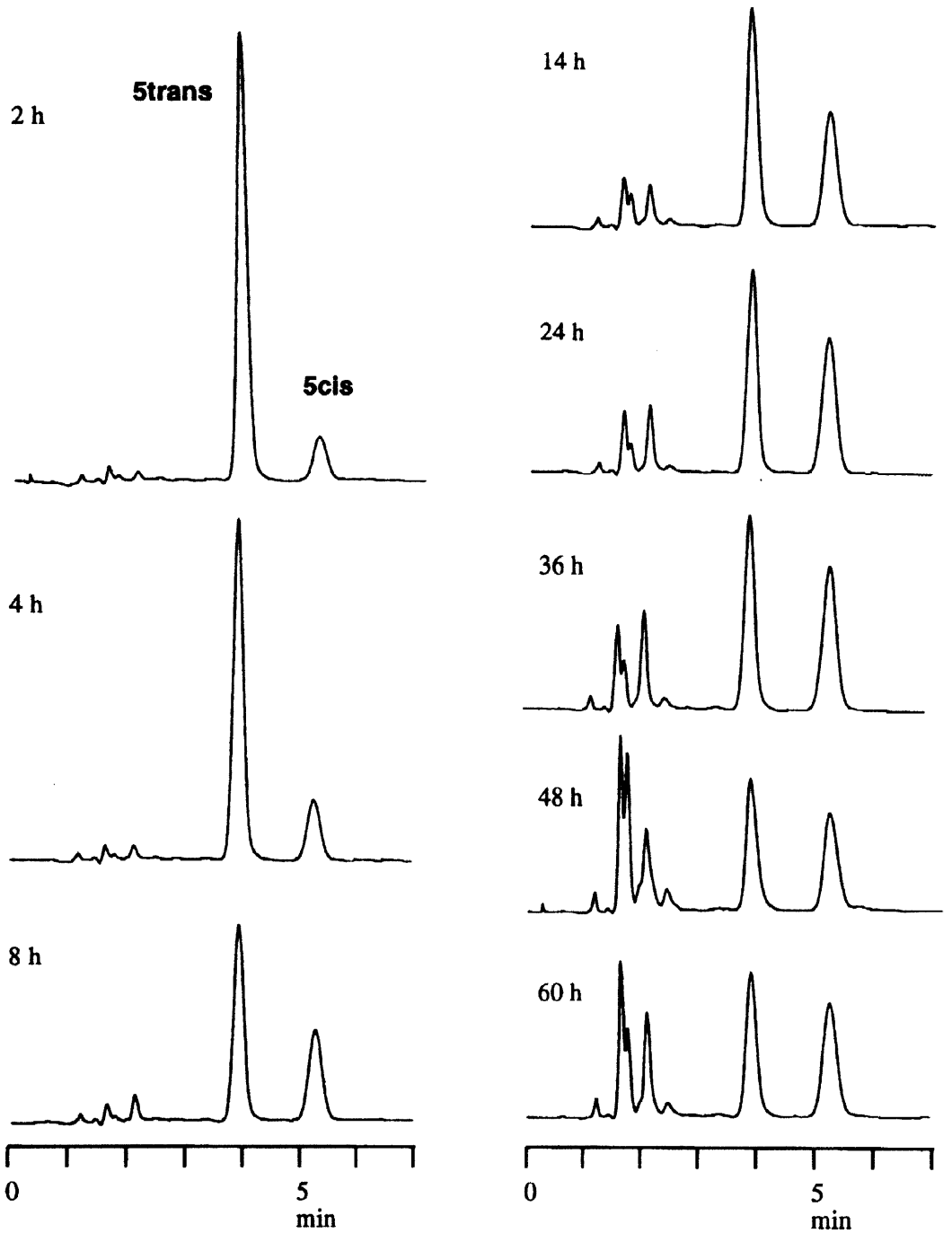


Figure 3. HPLC profiles for the equilibration between **5trans** and **5cis** at 40 °C. The number at the upper left of each chromatogram represents the equilibration time. See Experimental for details.

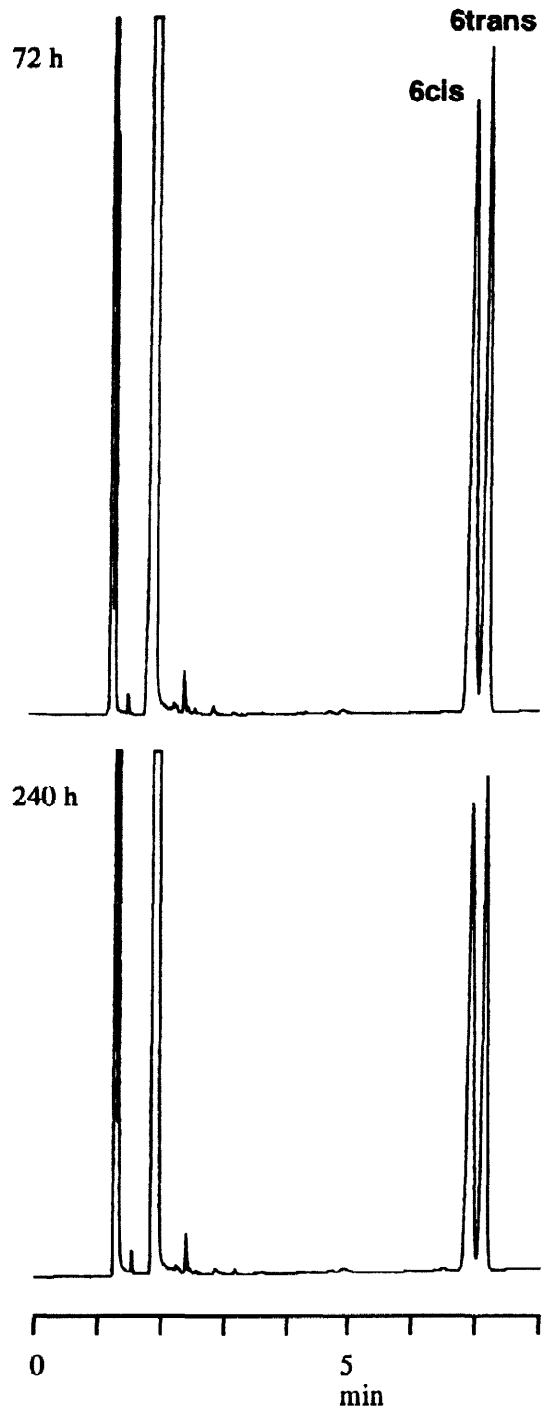


Figure 4. GC profiles for the equilibration between **6trans** and **6cis** at 30 °C. The number at the upper left of each chromatogram represents the equilibration time. See Experimental for details.

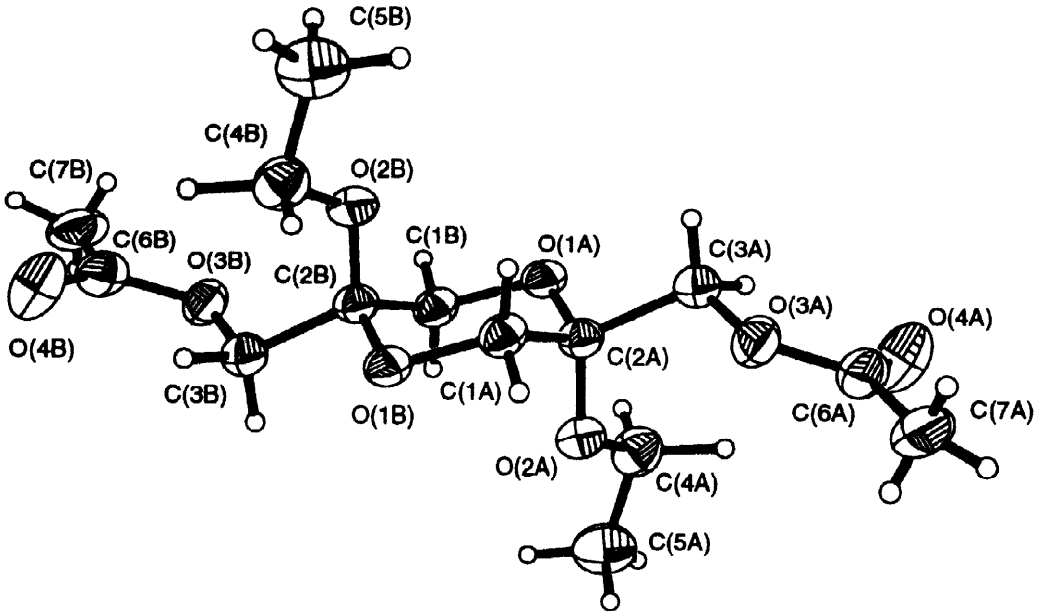


Figure 5. Molecular structure of **3trans**.

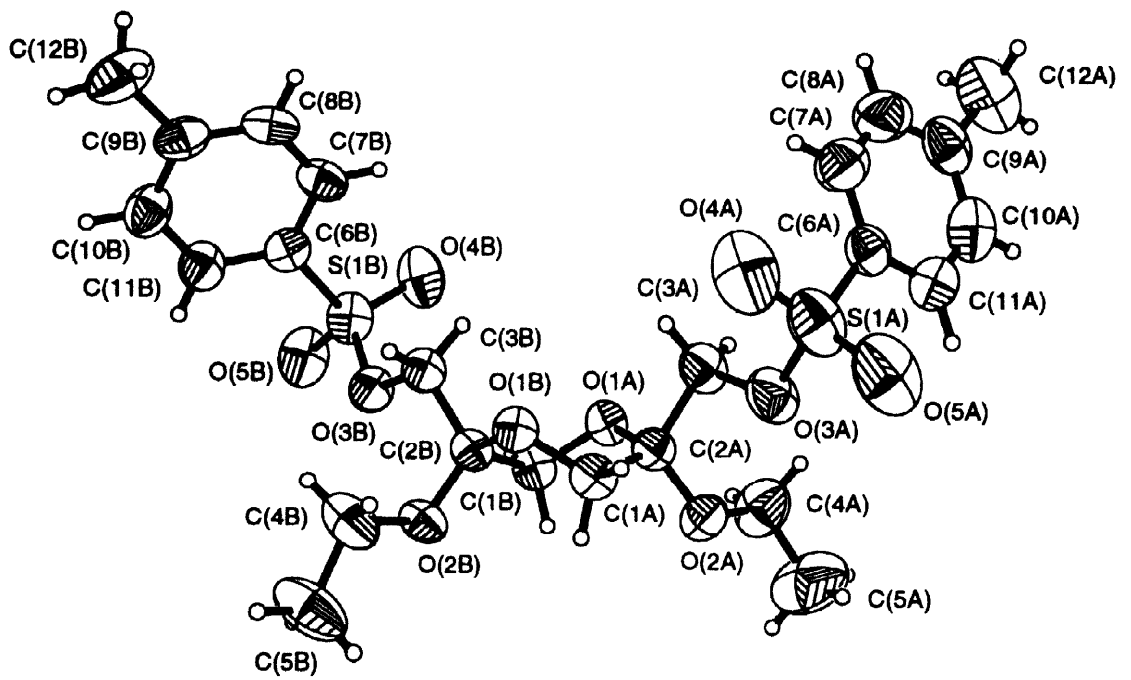


Figure 6. Molecular structure of **4cis**.

The ^{1}H NMR spectrum of **5cis** appeared to be unchanged on going from –90°C to 20°C in CS_2-CD_2Cl_2 4:1, and a small coupling of 1.7 Hz was observed between the pseudoaxial ring proton (3.50 ppm) and one of the methylene protons in the -CH_2OH group (3.58 ppm). These characteristics are similar to those reported for **2cis**,[4] suggesting that **5cis** adopts a twist-boat conformation in solution. Though the *J*-values of **6trans** ($J_{2,3a}$ = 2.0, $J_{2,3b}$ = 2.3 Hz) are consistent with a chair conformation, those of **6cis** ($J_{2,3a}$ = 5.3, $J_{2,3b}$ = 3.0 Hz) are difficult to interpret. Indeed, both the chair-chair interconversion and the twist-boat conformation have been assigned for some six-membered rings from similar *J*-values.[7,8] However, the chair-chair interconversion is unlikely with the *R* (J_{trans}/J_{cis}) value of 1.77.[7] Thus molecules with *R* values in the range of 1.9-2.2, such as that of **6cis**, adopt a twist-boat conformation or distortion from the normal shape of the ring. The twist-boat conformation is further supported by the *ab initio* calculations at the 3-21G* level for **6trans** and **6cis**, which indicate that **6cis** is most stable in its twist-boat conformation and less stable than **6trans** by only 0.36 kcal/mol.

Although the free energy difference between the chair and twist-boat conformations of 1,4-dioxane is unknown, the difference in 5-9 kcal/mol has been reported for cyclohexane (5.5 kcal/mol),[9] tetrahydropyran (5.5 kcal/mol),[10] and 1,3-dioxane (8.1 kcal/mol),[11] and the difference in 7.55 kcal/mol has been deduced from *ab initio* calculations at the 3-21G* level . That is, if **6trans** and **6cis** adopt chair and twist-boat conformations, respectively, as disccussed above, ca 7.5 kcal/mol difference in the conformation energy must be compensated by the difference in steric and/or stereoelectronic effects of the two ethoxy groups of each isomer.

A possible explanation for the above anomaly is that **6cis** experiences a stronger anomeric effect than does **6trans** due to its $CO_{endo}CO_{exo}$ orthogonal torsion angle in which the p-σ* interaction is maximized (Figure 7). There has been evidence that the ring oxygen atom of a pyranose has a p-lone pair and thus the anomeric effect is maximal at a torsion angle of 90° because of the p-σ* interaction.[12,13] Moereover, it has been pointed out from the MM3 calculation, in which the COCO torsional energy is parameterized to allow the minimum at 90°,[14] that addition of an anomeric hydroxyl group to tetrahydropyran causes a 2 kcal/mol stabilization of a twist-boat form.[10]

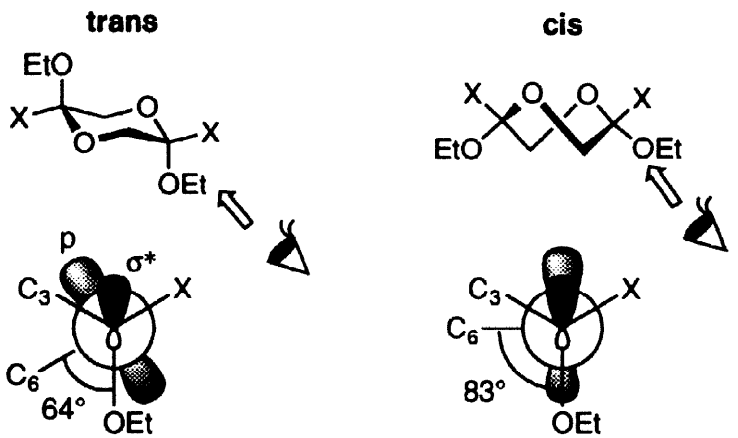


Figure 7. Conformation of 2,5-diethoxy-1,4-dioxane derivatives and the corresponding Newman projection for the $CO_{endo}CO_{exo}$ torsion angle.

In addition, the disadvantageous steric repulsion between the ethoxy groups and the axial hydrogen atoms in **6trans** may increase the relative stability of **6cis**, because the pseudoaxially oriented ethoxy groups of **6cis** in its twist-boat form are considered to be less subject to this steric repulsion. If the maximal anomeric effect in **6cis** and the steric repulsion in **6trans** are taken together, the 7.5 kcal/mol difference in the conformational energy as discussed above may be compensated.

EXPERIMENTAL

General Methods. Dihydroxyacetone dimer was purchased from Nacalai Tesque, Co. Ltd. Column chromatography was performed on Merck Kieselgel 60 (Art 7734) or Wako gel C-300 with the solvent systems specified. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL JNM-EX-270 spectrometer. Chemical shifts were recorded as δ values in parts per million (ppm) from tetramethylsilane as an internal standard in $CDCl_3$. The compounds **3trans** and **4cis** were recrystalized from ethyl acetate–hexane and acetone-water, respectively, for X-ray analyses. Crystal data and measurment procedures of the X-ray analyses are summarized in Table 1.

***ab initio* Molecular Orbital Calculations.** All *ab initio* molecular orbital calculations were carried out using the Gaussian 94 program (Revision B. 3)[15] on a Cray C-916/12256 supercomputer. The results were analyzed using UniChem (version 4.0, Oxford Molecular Ltd.) software on a Silicon Graphics Inc. Indigo2 IMPACT workstation. The geometry optimization was carried out at the HF/3-21G* level and the single point energy calculations were carried out at the MP2/3-21G* level. Geometry optimization of a skew conformation of 1,4-dioxane falls into the one with both ring oxygen atoms in the reference plane. Since our interest is in the proposed skew conformation of the 1,4-dioxane ring of the compound **6cis**, in which one of two ring oxygen atoms is in the reference plane and the other is out of the plane, the ethoxy groups of the geometrically optimized **6cis** were substituted with hydrogen atoms and the resulting 1,4-dioxane was used for the single-point energy calculation.

Equilibration Experiment for the Compound 5. The solutions of **5trans** (23.54 mM) and H_2SO_4 (3.52 mM) in ethanol in sealed ampoules were incubated on thermostated water bath. Each sample was analyzed by HPLC (Hitachi L-6000 HPLC system equipped with a YMC ODS column) at an appropriate time. The samples were eluted with CH_3CN-H_2O 85:15 at a flow rate of 1 mL/min and an absorbance at 254 nm was detected. The trans/cis ratio was determined simply from the the peak area ratio, since it was confirmed that the 1:1 mixture of **5trans** and **5cis** by weight produced a 1:1 peak area ratio in the HPLC spectrum.

Table 1 Crystal data and summary of data collection and refinement.

	3trans	**4cis**
formula	$C_{14}H_{24}O_8$	$C_{22}H_{32}O_{10}S_2$
formula weight	320.34	544.62
crystal system	monoclinic	triclinic
space group	$P2_1/n$	$P\bar{1}$
color of crystal	clear	clear
dimensions of crystal, mm	0.35 × 0.30 × 0.20	0.20 × 0.40 × 0.40
a, Å	9.535(2)	9.715(3)
b, Å	7.027(2)	16.696(5)
c, Å	12.574(2)	9.253(1)
α, deg	90	96.26(2)
β, deg	98.66(2)	108.67(2)
γ, deg	90	78.31(1)
value of Z	2	2
absorption coeff, mm^{-1}	0.893	0.242
range of transmission factors	0.7760-1.2093	0.266-1.000
temp, K	293	298
wavelength, Å	1.54178 (CuKα)	0.71073 (MoKα)
2θ range, deg	up to 120.0	up to 69
no. of data and cutt-off	1358; 329	4535; 1058
no. of parameters refined	100	325
goodness of fit	1.80	1.157
calculated density, g/cm^3	1.277	1.300
measurement method	Rigaku AFC7R	ccd area detection method with siemens SMART SYSTEM
final R indices[a]	R1; wR [I>3σ(F)]	R1; wR2 [I>2σ(I)]
	0.045; 0.065	0.0634; 0.1520
R indices (all data)[a]	—	R1; wR2
		0.0711; 0.1578

[a] $R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$. $wR2 = [\Sigma[w(F_o^2 - F_o^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

Equilibration Experiment for the Compound 6. The solutions of **6trans** (0.5 M) and $BF_3 \cdot OEt_2$ (10%mol) in toluene (0.86 mL) in sealed ampoules were incubated on thermostated water bath. Each sample was analyzed by GC (Hitachi G-5000 GC system equipped with a Shimadzu GV-101 column) at an appropriate time after the reaction was stopped by adding 20 μL of 1 M NaOMe. GC conditions were as follows: N_2, 3 kg/cm^2; H_2, 1.5 kg/cm^2; air, 6.0 kg/cm^2; injection at 200 °C; FID detection at 200 °C; column teperature, 90 °C–150 °C at 3 °C/min intervals. It was confirmed that the 1:1 micture of **6trans** and **6cis** by weight produced a

1:1 peak area ratio in the GC spectrum.

Preparation of 2,5-diethoxy-2',5'-dihydroxymethyl-1,4-dioxane (2). The mixture of dihydroxyacetone dimer (1.02 g, 5.66 mmol) and calcium chloride dihydrate (80 mg, 0.54 mmol) in ethanol (20 mL) was stirred at room temperature until it became clear solution (ca 1h). To this solution were added ethyl orthoformate (3 mL, 18.0 mmol) and conc H_2SO_4 (40 mg) and the solution was stirred for additional 5 h. The solution was neutralized with $NaHCO_3$, the insoluble material filtered off, and the filtrate evaporated in the presence of silica gel (4.0 g). The resulting silica gel powder was embedded on the top of a column of silica gel and eluted with hexane-ethyl acetate 1:2 to give **2cis** (0.545 g, 40 %) and **2trans** (0.474 g, 35 %). ^1H and ^{13}C NMR spectra of these compounds were in good accordance with those reported.[2,4]

***trans*-2,5-Diethoxy-1,4-dioxane-2,5-dimethanol O-2^1,O-5^1-Bis-acetate (3trans).** The compound **2trans** (0.475 g, 2.01 mmol) was dissolved in the mixture of pyridine (15 mL) and acetic anhydride (10 mL), and the solution was kept at room temperature for 15 h. After cold methanol (10 mL) was slowly added, the solution was evaporated and chromatographed on silica gel (hexane–ethyl acetate, 6:1–4:1) to give crystalline **3trans** (0.560 g, 87 %): mp 111-112 °C; R_f 0.29 (hexane–ethyl acetate, 4:1); ^1H NMR ($CDCl_3$) δ 4.25 (d, 2H, J = 12.2 Hz), 4.00 (d, 2H, J = 12.2 Hz), 3.82 (d, 2H, J = 11.6 Hz), 3.62–3.54 (m, 8H), 2.09 (s, 6H), 1.24 (t, 6H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 170.2, 93.9, 63.6, 62.7, 56.7, 20.7, 15.3. Anal. Calcd for $C_{14}H_{24}O_8$: C, 52.49; H, 7.55. Found: C, 52.32; H, 7.54.

***cis*-2,5-Diethoxy-1,4-dioxane-2,5-dimethanol O-2^1,O-5^1-Bis-p-toluenesulfonate (4cis).** The mixture of the compound **2cis** (40 mg, 0.169 mmol) and p-toluenesulfonyl choloride (97 mg, 0.509 mmol) in pyridine (1 mL) was stirred overnight. After the addition of methanol (1 mL), the reaction mixture was evaporated and chromatographed on silica gel (hexane–ethyl acetate, 4:1) to give crystalline **4cis** (59 mg, 64 %): mp 118–119 °C (decomp); R_f 0.20 (hexane–ethyl acetate, 4:1); ^1H NMR ($CDCl_3$) δ 7.79 (d, 4H, J = 8.3 Hz), 7.37 (d, 4H, J = 8.3 Hz), 3.96 (dd, 2H, J = 2.0, 10.6 Hz), 3.85 (d, 2H, J = 10.6 Hz), 3.65 (d, 2H, J = 12.5 Hz), 3.52 (m, 2H), 3.49 (dd, 2H, J = 2.0, 12.5 Hz), 3.27 (m, 2H), 2.46 (s, 6H), 1.10 (t, 6H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 145.2, 132.5, 130.0, 127.9, 96.5, 65.4, 61.0, 56.9, 21.7, 15.2. Anal. Calcd for $C_{24}H_{32}O_{10}S_2$: C, 52.93; H, 5.92; S, 11.78. Found: C, 52.85; H, 5.81; S, 11.96.

2,5-Diethoxy-1,4-dioxane-2,5-dimethanol O-2^1,O-5^1-Bis-benzyloxylate (5). To a stirred mixture of NaH (4 equiv) in DMF (1 mL for 0.4 mmol of **2**) was added a solution of **2trans** or **2cis** (1 equiv) in DMF (1 mL for 0.4 mmol of **2**). After 1 h, benzyl chloride (3 equiv) was slowly added and the mixture was stirred overnight. Ice-water was added and the mixture was extracted with Et_2O. The Et_2O layer was dried over $MgSO_4$, evporated, and chromatographed on silica gel (hexane–ethyl acetate, 10:1 for **5trans** or 15:1 for **5cis**) to give crystalline **5trans** (89 %) or **5cis** (64 %).

5trans: mp 113-114 °C; R_f 0.34 (hexane–ethyl acetate, 6:1); ^{1}H NMR ($CDCl_3$) δ 7.37–7.26 (m, 10H), 4.58 (d, 2H, J = 11.9 Hz), 4.52 (d, 2H, J = 11.9 Hz), 3.83 (d, 2H, J = 11.6 Hz), 3.65 (d, 2H, J = 11.6 Hz), 3.75 (d, 2H, J = 10.6 Hz), 3.53 (m, 4H), 3.37 (d, 2H, J = 10.6 Hz), 1.21 (t, 6H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 137.79, 128.36, 127.82, 127.76, 94.81, 73.44, 69.53, 63.94, 56.37, 15.46; ESI MS m/z 439.3 (M + Na). Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 68.92; H, 7.71.

5cis: mp 66-67 °C; R_f 0.51 (hexane–ethyl acetate, 6:1); ^{1}H NMR ($CDCl_3$) δ 7.41–7.26 (m, 10H), 4.60 (d, 2H, J = 12.2 Hz), 4.50 (d, 2H, J = 12.2 Hz), 3.81 (d, 2H, J = 11.9 Hz), 3.69–3.41 (m, 8H), 3.35 (d, 2H, J = 10.2 Hz), 1.18 (t, 6H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 137.75, 128.37, 127.84, 127.75, 97.92, 73.42, 67.98, 61.49, 56.57, 15.42; ESI MS m/z 439.3 (M + Na). Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 68.81; H, 7.52.

Preparation of 2,5-Diethoxy-1,4-dioxane (6). The solution of glycol aldehyde dimer (317 mg, 2.64 mmol), ethyl orthoformate (1.5 mL, 8.45 mmol), and H_2SO_4 (32 mg, 0.3 mmol) in ethanol (9 mL) was heated at 90 °C for 48 h. The mixture was cooled, neutralized with $NaHCO_3$, and concentrated. The residue was chromatographed on a silica gel (hexane–ethyl acetate, 20:1—5:2) to give syrupy **6cis** (92 mg, 20 %), amorphous **6trans** (90 mg, 19 %), and glycol aldehyde diethyl acetal (263 mg, 37 %). ^{1}H and ^{13}C NMR spectra of **6cis** and **6trans** are not given in the reference [6].

6trans: ^{1}H NMR ($CDCl_3$) δ 4.60 (t, 2H, J = 2.0 Hz), 4.04 (dd, 2H, J = 2.0, 11.5 Hz), 3.83 (m, 2H), 3.54 (m, 2H), 3.46 (dd, 2H, J = 2.0, 11.5 Hz), 1.26 (t, 6H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 94.57, 63.40, 62.21, 15.02.

6cis: ^{1}H NMR ($CDCl_3$) δ 4.62 (dd, 2H, J = 5.3, 3.0 Hz), 3.85 (m, 2H), 3.77 (dd, 2H, J = 5.3, 11.9 Hz), 3.63 (dd, 2H, J = 3.0, 11.9 Hz), 3.52 (m, 2H), 1.23 (t, 6H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 95.26, 63.54, 63.51, 15.04.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research (Grant No. 09780523) from the Japanese Ministry of Education, Science and Culture, and the Frontier Research Program on Glycotechnology at RIKEN directed by Professor Yoshitaka Nagai and coordinated by Professor Tomoya Ogawa. We thank Professor Nobuo Tanaka for the X-ray analysis of the compound **3trans**. We thank Dr Takeshi Wada for carrying out the *ab initio* calculations.

REFERENCES

[1] Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443-473.

[2] Jung, S.-H.; Jeong, J.-H.; Miller, P.; Wong, C.-H. *J. Org. Chem.* **1994**, *59*, 7182-7184.

[3] Gefflaut, T.; Lemaire, M.; Valentin, M.-L.; Bolte, J. *J. Org. Chem.* **1997**, *62*, 5920-5922.

[4] Waagen, V.; Barua, T. K.; Anthonsen, H. W.; Hansen, L. K.; Fossli, D.-J. *Tetrahedron* **1994**, *50*, 10055-10060.

[5] Angyal, S. J. *Adv. Carbohydr. Chem. Biochem.* **1989**, *47*, 1-43.

[6] Parham, W. E.; Reiff, H. E. *J. Am. Chem. Soc.* **1955**, *77*, 6391-6393.

[7] Lambert, J. B. *Acc. Chem. Res.* **1971**, *4*, 87-94.

[8] Augé, J.; David, S. *Tetrahedron* **1984**, *40*, 2101-2106.

[9] Squillacote, M.; Sheridan, R. S.; Chapman, O. L.; Anet, F. A. L. *J. Am. Chem. Soc.* **1975**, *97*, 3244-3246.

[10] Dowd, M. K.; French, A. D.; Reilly, P. J. *Carbohydr. Res.* **1994**, *264*, 1-19.

[11] Clay, R. M.; Kellie, G. M.; Riddell, F. G. *J. Am. Chem. Soc.* **1973**, *95*, 4632-4633. References are cited therein.

[12] Fuchs, B.; Schleifer, L.; Tartakovsky, E. *Nouv. J. Chim.* **1984**, *8*, 275-278.

[13] Cossé-Barbi, A.; Watson, D. G.; Dubois, J. E. *Tetrahedron Lett.* **1989**, *30*, 163-166.

[14] Allinger, N. L.; Rahman, M.; Lii, J.-H. *J. Am. Chem. Soc.* **1990**, *112*, 8293-8307.

[15] 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.; Zakrewski, V. G.; Ortiz, J. V.; Foresman, J. B.; 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.; Gonzales, C.; Pople, J. A. Gaussian, Inc., Pettsburgh, PA, 1995.