Computational Study of the Conformational Space of Methyl 2,4-Diacetyl-*β*-D-xylopyranoside: $^4C_1$ and $^1C_4$ Chairs, Skew-Boats (^2S_O, $^1S_3$), and $B_{3,O}$ Boat Forms

Sajjad Karamat and Walter M. F. Fabian*

Institut für Chemie, Karl-Franzens Universität Graz, Heinrichstr. 28, A-8010 Graz, Austria

Received: February 17, 2006; In Final Form: April 11, 2006

Ring and substituent rotamer conformations of methyl 2,4-diacetyl-*β*-D-xylopyranoside, for which experimental results are controversial, were studied in the gas phase and in solvents of different polarity (CCl_4, $CHCl_3$, DMSO, and H_2O) by B3LYP density functional theory. The $^1C_4$ chair is the most stable ring form in the gas phase, followed by $^4C_1$ and $^2S_0$. Solvents of increasing polarity shift the equilibrium toward the $^4C_1$ chair. Homodesmotic reaction energies show that the $^1C_4$ and ^2S_O forms are stabilized by hydrogen bonding and anomeric effects and that steric repulsion is smallest in the $^4C_1$ chair and largest in skew-boats.

Introduction

The structure and conformations of carbohydrates are of paramount importance for their biological functions and material properties.[1,2] Like cyclohexane, the six-membered pyranose rings generally exist in one of two isomeric chair conformations, $^4C_1$ and $^1C_4$, although other ring structures, for example, skew-boats, also have been observed. Frequently, one of the possible ring conformations strongly predominates; however, certain and quite subtle structural features can induce a ring flip,[3] for example, a strong anomeric effect (**1a** ↔ **1b**)[4] or the reverse anomeric effect (**2a** ↔ **2b**).[5]

Substituents on the pyranose ring are mostly oriented equatorially; strong 1,2-steric repulsion between very bulky substituents (**α-3** ↔ ***β*-3**)[6] or *π*-stacking of 1,3-diaryl (diaroyl) groups (**4a** ↔ **4b**)[7] also can induce a ring flip to attain a stable axial-rich conformation. Intermolecular interactions, for example, protein−carbohydrate binding[8] or metal ion complexation frequently also lead to interchanges between the various pyranose ring conformations (Scheme 1). This latter process, $^4C_1$ ↔ $^1C_4$ ring flip of a xylopyranose hinge sugar (**5a** ↔ **5b**), has been exploited for the construction of metal ion sensors.[7] Ideally, for a proper functioning of such devices, the uncomplexed carbohydrate should exist (almost) exclusively in a different ring conformation than the metal-bound form. Thus, for a rational design, a detailed knowledge of the conformational properties of candidate carbohydrates is an essential prerequisite. Interestingly, the effect of acylation on the preferred ring conformation of xylopyranosides, $^4C_1$ vs $^1C_4$, is still a matter of debate: earlier reports[9] that "the conformation of the pyranose ring is altered very little, if at all, by the introduction of an acyl group at any position" have not been substantiated by others, who found a dependence of the pyranoid ring conformation on both the nature and position of the acyl groups as well as the solvent.[10] Specifically, for methyl 2,4-diacetyl-*β*-D-xylopyranoside **6** (Figure 1), a $^4C_1$ conformer population of 0.56 as compared with 0.87 for methyl *β*-D-xylopyranoside in $CHCl_3$ was estimated from NMR coupling constants.[10a] An IR study in CCl_4 found an even more pronounced shift toward the $^1C_4$ chair conformation in this derivative (>80%).[11] Since **6** exhibits all the essential features except *π*-stacking interactions for a metal-ion induced conformational interchange (see **4** and **5** in Scheme 1), a better understanding of its conformational properties clearly is needed.

Despite substantial challenges,[12,13] computational methods have become increasingly important as a complement to experiment for the determination of carbohydrate structure and conformation.[14−20] Although several computational studies concerning xylopyranose conformations, including metal complexation,[14a,19,21] have been published, to the best of our knowledge, none of them has addressed the question of substituent effects on conformer stability.

The aim of the present paper is to present a comprehensive computational study by density functional theory calculations on the ring conformation ($^4C_1$, $^1C_4$, ^2S_O as well as some other boat and skew-boat structures) of methyl 2,4-diacetyl-*β*-D-xylopyranoside **6** in the gas phase and in solvents of different polarity (CCl_4, $CHCl_3$, DMSO, and H_2O). The particular orientation of the hydroxyl groups around the ring plays a significant role in determining the energy and stable conformation, especially of boat and skew-boat ring structures.[15a] Consequently, for each one of the above-mentioned main ring structures, a detailed conformational search with respect to the orientation of the substituents has been performed (see Figure 1 for the definition of the various torsional angles).

Computational Details

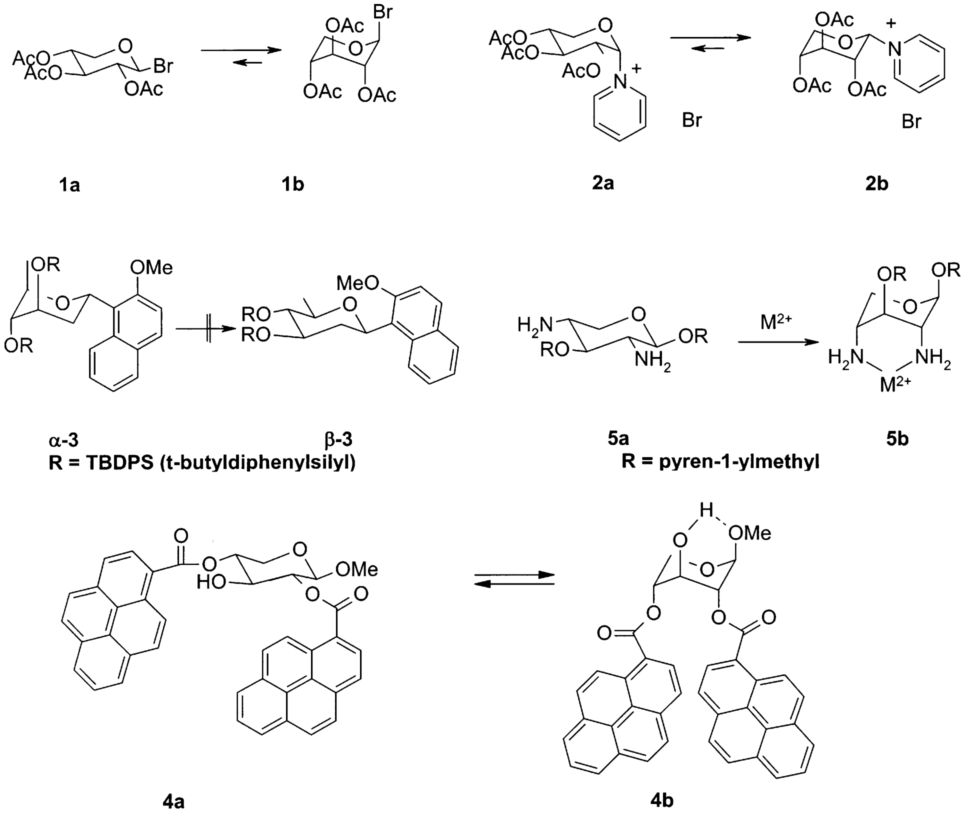
All computations have been performed with the Gaussian 03 suite of programs[22] using Becke's three-parameter hybrid Hartree−Fock density functional method[23] with the Lee−Yang−Parr correlation functional[24] (B3LYP) and the LANL2DZ basis set.[25] Initially, for both the $^4C_1$ and the $^1C_4$ chair as well as the ^2S_O skew-boat conformation, all 324 possible rotamers resulting from staggered orientations (τ ($C_{i+1}-C_i-O_i-R$ = ±60° and 180°, Figure 1) of the acetoxy (R=CH_3CO), hydroxy (R=H), and methoxy (R=CH_3) groups and syn or anti arrangement (τ ($C_i-O_i-C{=}O$) = 0° and 180°) of the carbonyl moiety were optimized (B3LYP/Lanl2DZ). All unique structures resulting

---

* To whom correspondence should be addressed. E-mail: walter.fabian@uni-graz.at. URL: http://www.uni-graz.at/walter.fabian.

10.1021/jp061024g CCC: $33.50

SCHEME 1: Typical Structural Features Responsible for $^4C_1 \rightarrow {}^1C_4$ Ring Flips in Pyranoses



thereby (~250) were then reoptimized with a polarization function (d for oxygen, α = 0.8; p for hydrogen, α = 1.1) and diffuse functions taken from the 6-311++G(d,p) standard basis set, added to oxygen (sp-type) and hydroxyl−hydrogen (s-type) atoms,[13,20] thereafter denoted as basis II. This basis set has proven as a reasonable compromise between computational efficiency and reliability, especially with respect to extension of the computational studies to sugar metal complexes.[21b] Besides $^4C_1$, $^1C_4$, and ^2S_O, several other higher energy ring conformations were obtained during the optimization procedure. All structures were characterized by frequency calculations as true minima. Zero-point energies (ZPE) and thermal corrections to Gibbs' free energies are obtained from the B3LYP/basis II calculations and are unscaled. In addition, for the lowest energy structures of each ring conformation, a composite model[13c] was used to assess correlation and basis size effects on conformational energies E(C)

$$E(\mathrm{C}) = E(\mathrm{MP2/cc\text{-}pVTZ//MP2/cc\text{-}pVDZ}) + [E(\mathrm{CCSD/6\text{-}31G(d)//MP2/6\text{-}31G(d)}) - E(\mathrm{MP2/6\text{-}31G(d)//MP2/6\text{-}31G(d)})] \quad (1)$$

Solvent effects (CCl_4, $CHCl_3$, DMSO, and H_2O) were estimated by single-point B3LYP/basis II IEF-PCM[26] and B3LYP/6-311++G(d,p) Poisson−Boltzmann SCRF (PB-SCRF)[27] calculations, as implemented in the Jaguar program.[28] Natural bond orbital (NBO) analysis[29] was done at the B3LYP/6-311++G(d,p) level of theory. Molecular structures were visualized and analyzed with MOLDEN;[30] Pople−Cremer ring puckering parameters[31] were determined with PLATON.[32]

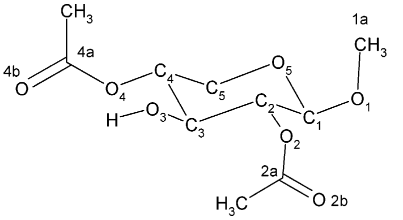


Figure 1. Structure and atom numbering of methyl 2,4-diacetyl-*β*-D-xylopyranoside ($^4C_1$ chair). The torsional angles describing substituent orientations are defined by $\tau_1 = \tau$(C2−C1−O1−C1a), $\tau_2 = \tau$(C3−C2−O2−C2a), $\tau_3 = \tau$(C4−C3−O3−H), $\tau_4 = \tau$(C5−C4−O4−C4a), $\tau_5 = \tau$(C2−O2−C2a−O2b), and $\tau_6 = \tau$(C4−O4−C4a−O4b). For $\tau_1 - \tau_4$, three values (±60°, 180°) and two (0°, 180°) for τ_5 and τ_6 are used, leading to a total of $3 \times 3 \times 3 \times 3 \times 2 \times 2 = 324$ conformations.

Results and Discussion

Relative energies of the 20 lowest energy conformations out of ~250 of methyl 2,4-diacetyl-*β*-D-xylopyranoside are summarized in Table 1. Results are given for the gas phase and four solvents of different polarity and hydrogen-bonding acceptor and/or donor abilities (CCl_4, $CHCl_3$, DMSO, and H_2O). Total energies, zero-point energy contributions, thermal corrections to enthalpy and Gibb's free energy, and solvation energies are given in Tables S1 and S2 of the Supporting Information. The various ring structures are characterized by the Pople−Cremer ring puckering parameters[31] as well as the three improper dihedrals $\alpha_1 = \alpha$(C4−O5−C2−C1), $\alpha_2 = \alpha$-(O5−C2−C4−C3), and $\alpha_3 = \alpha$(C2−C4−O5−C5) (Table S3).[1a,15a] Similar to calculations on glucopyranose,[15a] several of the initial $^1C_4$ and/or ^2S_O structures collapsed upon optimization to $^4C_1$, $^2S_O/^1C_4$, or other boat and skew-boat conformations. Each one of these main ring structures is characterized by the six substituent torsional angles (Table S4; for definition, see Figure 1), $\tau_1 = \tau$(C2−C1−O1−C1a), $\tau_2 = \tau$(C3−C2−O2−C2a), $\tau_3 = \tau$(C4−C3−O3−H), $\tau_4 = \tau$(C5−C4−O4−C4a), $\tau_5 = \tau$(C2−O2−C2a−O2b), and $\tau_6 = \tau$(C4−O4−C4a−O4b) as gauche$^+$ (g$^+$, $\tau_1 - \tau_4 = +60°$), gauche$^-$ (g$^-$, $\tau_1 - \tau_4 =$

TABLE 1: Calculated[a] Relative Energies Including Zero-Point Energy Corrections, Δ(E + ZPE), Enthalpies, ΔH, and Gibbs's Free Energies, ΔG, in the Gas Phase and in Solution (CCl_4, $CHCl_3$, DMSO, and H_2O) of Methyl 2,4-Diacetyl-β-D-xylopyranoside 6

		Δ(E+ZPE)	ΔH	ΔG	ΔG_{CCl4}		ΔG_{CHCl3}		ΔG_{DMSO}		ΔG_{H2O}	
		gas phase			PCM	PB-SCRF	PCM	PB-SCRF	PCM	PB-SCRF	PCM	PB-SCRF
$^1C_4$	ttg$^-$g$^-$ss	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$^1C_4$	tg$^-$g$^-$tss	1.21	1.31	0.03	−0.36	−0.49	−0.92	−1.23	−1.46	−2.11	−1.69	−9.76
$^1C_4$	ttg$^-$tss	0.31	0.31	0.24	0.24	0.04	0.02	−0.19	−0.13	−0.48	−0.36	−8.18
$^4C_1$	tg$^-$tg$^-$ss	0.54	0.56	0.44	0.04	0.46	−0.31	−0.01	−0.90	−0.30	−0.75	−7.85
^2S_O	ttg$^+$tss	0.72	0.69	0.48	0.00	0.62	−0.45	0.31	−1.09	−0.19	−1.06	−7.87
^2S_O	tg$^-$g$^-$g$^-$ss	0.81	0.91	0.48	−0.15	0.38	−0.47	0.20	−1.02	0.12	−0.90	−7.97
$^1C_4$	tg$^-$g$^-$g$^-$ss	0.31	0.26	0.56	0.23	0.39	−0.07	0.05	−0.35	0.02	−0.26	−8.08
$^4C_1$	ttg$^+$g$^-$ss	1.53	1.75	1.17	0.10	0.50	−1.21	−0.53	−2.95	−1.84	−3.46	−9.53
$^4C_1$	tttg$^-$ss	1.63	1.87	1.22	0.29	0.45	−1.04	−0.53	−2.80	−1.66	−3.40	−9.71
^2S_O	tg$^-$tg$^-$ss	1.85	1.79	1.40	1.07	1.54	1.00	1.48	0.71	1.35	0.99	−6.05
$^1S_3$	tg$^-$tg$^-$ss	1.56	1.58	1.41	0.96	1.36	0.76	1.53	0.33	1.15	0.39	−6.85
^2S_O	tttg$^-$ss	1.80	1.98	1.42	0.51	0.66	−0.58	−0.08	−1.93	−0.98	−2.09	−8.97
$^1C_4$	tg$^-$ttss	2.78	3.10	1.43	0.32	0.82	−0.82	0.13	−2.38	−0.74	−2.75	−9.36
^2S_O	tttg$^-$ss	1.81	1.98	1.43	0.53	0.61	−0.57	−0.17	−1.92	−1.00	−2.08	−8.96
$^1S_3$	ttg$^+$g$^-$ss	2.01	2.23	1.50	0.76	1.04	0.10	0.68	−0.83	0.03	−1.52	−7.94
$B_{3,O}$	tttg$^-$ss	3.10	3.38	1.66	0.55	0.96	−0.39	0.42	−1.59	−0.21	−2.29	−8.80
$^4C_1$	g$^-$ttg$^-$ss	2.24	2.41	1.98	0.61	1.64	−0.28	1.18	−1.67	0.44	−2.29	−7.65
$^1C_4$	tg$^-$ttss	2.83	3.10	2.12	1.01	1.42	−0.11	0.82	−1.68	0.08	−2.06	−8.68
$^4C_1$	g$^-$tg$^-$tss	2.34	2.42	2.15	1.28	2.06	0.61	1.91	−0.28	1.48	0.16	−6.20
$^1S_3$	ttg$^-$tss	2.45	2.57	2.24	2.04	2.16	1.80	2.06	1.37	1.76	0.69	−6.10

[a] B3LYP/basis II, in kcal mol^{-1}.

TABLE 2: Calculated[a] Populations of $^4C_1$, $^1C_4$ Chair, and ^2S_O Skew-boat Ring Conformations of Methyl 2,4-Diacetyl-β-D-xylopyranoside 6 in the Gas Phase and Solution (CCl_4, $CHCl_3$, DMSO, and H_2O)

		$^4C_1$	$^1C_4$	^2S_O
gas phase		0.16 (0.56)	0.57 (0.35)	0.27 (0.10)
CCl_4	IEF-PCM	0.27	0.40	0.33
	PB-SCRF	0.18 (0.65)	0.57 (0.26)	0.25 (0.09)
$CHCl_3$	IEF-PCM	0.42	0.30	0.28
	PB-SCRF	0.27 (0.71)	0.52 (0.16)	0.21 (0.13)
DMSO	IEF-PCM	0.62	0.21	0.17
	PB-SCRF	0.41 (0.88)	0.44 (0.09)	0.15 (0.03)
H_2O	IEF-PCM	0.70	0.17	0.13
	PB-SCRF	0.39 (0.81)	0.41 (0.08)	0.20 (0.11)

[a] On the basis of B3LYP/basis II relative Gibb's free energies. The values in parentheses refer to relative energies obtained by the composite energy approach, eq 1, with MP2/cc-pVDZ corrections to Gibb's free energies.

−60°), trans (t, $\tau_1 - \tau_4 = 180°$), syn (s, τ_5, $\tau_6 = 0°$), or anti (a, $\tau_5 - \tau_6 = 180°$). In the following, first the energies and structural features of the individual ring conformations and their respective rotamers are described. Then we discuss the factors responsible for the stability of the various ring forms.

Energies. From the data given in Table 1, some dependence of the energetic ordering on energy/enthalpy, Δ(E + ZPE) or ΔH, on one hand and Gibb's free energy ΔG on the other one, can be seen, for example, tg$^-$g$^-$tss − $^1C_4$ compared with ttg$^-$tss − $^1C_4$ or tg$^-$tg$^-$ss − $^4C_1$. For these, the relative enthalpies are $\Delta H_{rel} = 1.31$, 0.31, and 0.56 kcal mol^{-1}; in contrast, $\Delta G_{rel} = 0.03$, 0.24, and 0.44 kcal mol^{-1}; see Table 1. This dependence may be attributed to inaccuracies of calculated entropies for flexible compounds with several low-frequency vibrations.[33] However, irrespective of whether Δ(E + ZPE), ΔH, or ΔG is used, the relative gas-phase stability of the various ring conformations follows the ordering $^1C_4 > {}^4C_1 > {}^2S_O > {}^1S_3 > B_{3,O}$: $\Delta(E + ZPE)_{rel} = 0.00$, 0.54, 0.72, 1.56, 3.10; $\Delta H_{\,rel} = 0.00$, 0.56, 0.69, 1.58, 3.38; $\Delta G_{rel} = 0.00$, 0.44, 0.48, 1.41, 1.66 kcal mol^{-1}, respectively. Clearly, $^1S_3$ skew-boats and $B_{3,O}$ boats should play negligible roles in the gas-phase conformational equilibrium of methyl 2,4-diacetyl-β-D-xylopyranoside ring structures. Surprisingly, the calculated Gibb's free energies of $^4C_1$ chairs and ^2S_O skew-boats are quite similar, $\Delta G_{rel} = 0.44$ and 0.48 kcal mol^{-1} (Table 1). Calculated populations of the various ring forms ($^1C_4$, $^4C_1$, and ^2S_O) in the gas phase and solution are given in Table 2. According to both solvation models, IEF-PCM and PB-SCRF, solvents of increasing polarity and hydrogen-bond acceptor and/or donor capabilities (CCl_4, $CHCl_3$, DMSO, and H_2O) stabilize the $^4C_1$ chairs with a concomitant shift of the distribution between the various ring structures toward the $^4C_1$ chair forms.

There are, however, significant differences between these two models for solvent effects concerning the amount of this shift. Whereas with PB-SCRF the $^1C_4$ chair is obtained as the most stable ring structure of **6** in all solvents considered, with IEF-PCM the $^4C_1$ chair is calculated as the global minimum in all solvents but CCl_4. If only the electrostatic contribution to solvation is taken into account within the framework of the IEF-PCM procedure, then a somewhat increased stability of the $^1C_4$ chair forms results. $^1C_4$ populations derived thereby are higher by 0.05 to 0.1 than those given in Table 2.

Besides a solvent-induced shift in the ring conformation, different orientations (rotamers) of the substituents are differently stabilized by solvation. In view of the relatively low energies of the skew-boat ring structures, these should be significantly populated. This is in contrast to experimental investigations where ^2S_O conformations apparently have either not been considered[10a] or been estimated as negligible[11] contributors to the ring conformation equilibrium. To assess the feasibility of the presence of skew-boat ring structures, a CSD search[34] has been done. This gave ca. 15 structures for acylated β-D-xylopyranosides; however none of them contains a free hydroxyl group which, according to the IR study, is a necessary structural feature to induce a significant or almost complete $^4C_1 \rightarrow {}^1C_4$ ring flip.[11] Not surprisingly, then, only one $^1C_4$ structure was found in the crystal (1,2,3,4-tetrabenzoyl-β-D-xylopyranose, OBZXYP10). Noteworthy, the data set also includes one ^2S_O skew-boat conformation (MTBZXP10, methyl 2,3,4-tribenzoyl-β-D-xylopyranoside). Thus, the presence of nonnegligible amounts of skew-boats in the pyranose ring conformational equilibrium of **6** is not completely unreasonable. In addition, as a further check, for the respective lowest energy rotamer of

TABLE 3: Calculated[a] Relative Energies Including Zero-Point Energy Corrections, $\Delta(E + \mathrm{ZPE})$, Enthalpies, ΔH, and Gibbs's Free Energies, ΔG, in the Gas Phase and in Solution (CCl_4, $CHCl_3$, DMSO, and H_2O) of Methyl 2,4-Diacetyl-β-D-xylopyranoside 6

		ΔE	ΔH	ΔG	ΔG			
		gas phase			CCl_4	$CHCl_3$	DMSO	H_2O
$^1C_4$	ttg$^-$g$^-$ss	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$^1C_4$	tg$^-$g$^-$tss	1.08	1.06	1.05	0.53	0.03	−0.73	−0.83
$^4C_1$	tg$^-$tg$^-$ss	0.28	0.48	−0.18	−0.37	−0.57	−0.97	−1.05
^2S_O	ttg$^+$tss	1.54	1.53	1.20	1.30	1.23	0.77	1.10
^2S_O	tg$^-$g$^-$g$^-$ss	1.43	1.50	1.16	0.87	−0.05	0.74	−0.96
$^4C_1$	ttg$^+$g$^-$ss	1.25	1.54	0.37	−0.34	−1.08	−2.18	−2.25
^2S_O	tttg$^-$ss	2.84	3.10	1.98	1.20	0.63	0.02	−0.25
$B_{3,O}$	tttg$^-$ss	4.06	4.33	3.30	2.59	2.10	1.28	1.18

[a] Composite energy approach, eq 1, with MP2/cc-pVDZ corrections to zero-point energies and thermal corrections to enthalpies and Gibb's free energies. Solvation energies from B3LYP/6-311++G(d,p) PB-SCRF calculations.

the $^4C_1$ and $^1C_4$ chairs and the ^2S_O skew-boat, calculated in the gas phase and the four solvents, CCl_4, $CHCl_3$, DMSO, and H_2O, relative composite energies E(C)[13c] according to eq 1 are listed in Table 3 (for total energies, see Table S5).

Although with this level the $^1C_4$ chair also has a slightly greater stability than the $^4C_1$ chair [$\Delta(E + ZPE)_{\mathrm{rel}} = 0.3$ and $\Delta H_{\mathrm{rel}} = 0.5$ kcal mol^{-1}), the Gibb's free energies indicate the $^4C_1$ chair to be slightly favored, $\Delta G_{\mathrm{rel}} = -0.2$ kcal mol^{-1}. Also, ^2S_O skew-boats are calculated to be less stable, $\Delta G_{\mathrm{rel}} = 1.2$ kcal mol^{-1} (Table 3), than with the B3LYP/basis II model chemistry, $\Delta G_{\mathrm{rel}} = 0.5$ kcal mol^{-1} (Table 1). Their population in the equilibrium mixture, thus, is found to be considerably smaller with the composite energy approach, ca. 10% except in DMSO, but still nonnegligible.

Comparison with Experiment. Experimental populations for the $^4C_1$/$^1C_4$ ring conformation equilibria of methyl 2,4-diacetyl-β-D-xylopyranoside have been determined in CCl_4 and $CHCl_3$ solution by IR[11] and NMR[10a] spectroscopy, respectively. Depending on the respective ring conformation, O3−H can be involved in different types of intramolecular hydrogen bonds, resulting in characteristic shifts, $\Delta\nu$(OH), of the O3−H stretching vibration. On the basis of these shifts, IR spectra obtained in CCl_4 indicated the presence of <20% of the $^4C_1$ chair,[11] to be compared with 27% (IEF-PCM − B3LYP/basis II), 18% (PB-SCRF − B3LYP/basis II), and 65% [PB-SCRF − ΔG(C)]. When ΔH(C) is used instead of ΔG(C), this latter value is reduced to 35%. Possible reasons for the much larger calculated $^4C_1$ populations, especially with the composite energy approach, are discussed below in the paragraph about the effect of hydrogen bonding on conformer stability. In $CHCl_3$, an approximate equimolar $^1C_4$/$^4C_1$ composition ($^4C_1$ mol fraction = 0.56) was deduced from NMR coupling constants. It should be noted that the experimental population is based on the assumption of the presence of only $^4C_1$ and $^1C_4$ chairs as well as using values for $^3J_{\mathrm{HH}}$ from model compounds.[10a] Conversely, the calculated $^4C_1$, $^1C_4$, and ^2S_O structures (H−H dihedral angles), allow the estimation of NMR coupling constants via an extended Karplus-type equation[35] and, thus, conformer populations.[7] Together with the experimental $^3J_{\mathrm{HH}}$ of **6**,[10a] these can be used to derive an experimental population of 0.55 ($^1C_4$), 0.35 ($^4C_1$), and 0.10 (^2S_O). The corresponding calculated values are 0.52, 0.27, 0.21 (PB-SCRF − B3LYP/basis II) and 0.16, 0.71, 0.13 [PB-SCRF − ΔG(C)], respectively. Apparently, the B3LYP/basis II approach somewhat overestimates the ^2S_O stability. With the composite energy approach, using the MP2/cc-pVDZ correction to Gibb's free energies, a too great stability of the $^4C_1$ chair is obtained. Problems associated with ΔG for flexible molecules with low-frequency vibrations have already been stressed.[33] Indeed, if ΔH instead of ΔG is used, the calculated conformer population in $CHCl_3$ results as 0.44 ($^1C_4$), 0.39 ($^4C_1$), and 0.17 (^2S_O), in much closer agreement with experiment.

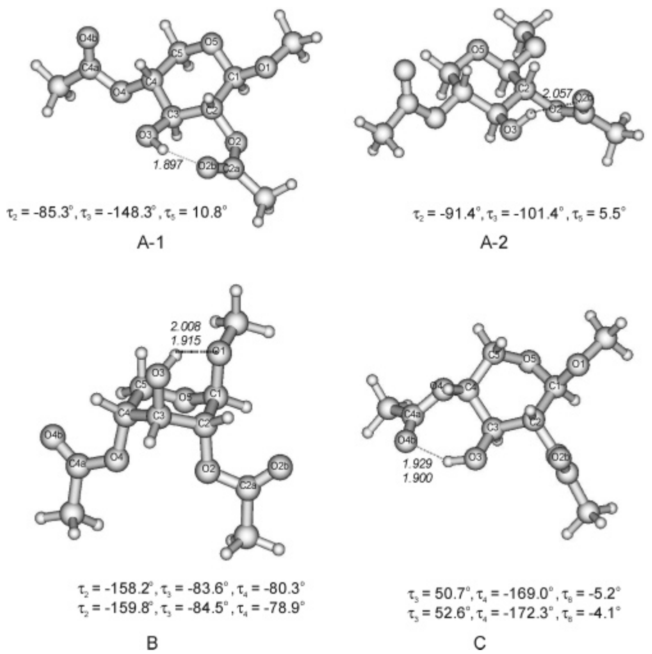


Figure 2. Calculated lowest energy conformations of $^4C_1$ (A-1, B3LYP/basis II; A-2, MP2/cc-pVDZ), $^1C_4$ ((B) upper values, B3LYP/basis II; lower values, MP2/cc-pVDZ), and ^2S_O ((C) upper values, B3LYP/basis II; lower values, MP2/cc-pVDZ) ring structures of methyl 2,4-diacetyl-β-D-xylopyranoside **6**.

Structures. The lowest energy structures (B3LYP/basis II) of the $^1C_4$, $^4C_1$, and ^2S_O ring conformations are depicted in Figure 2. All the low-energy conformations are characterized by syn orientations of the acetyl groups (ss rotamers in Table 1; $\tau_5 \sim \tau_6 \sim 0°$, Table S4). In fact, anti isomers are at least ~5 kcal mol^{-1} higher in energy and are not among the first 50 conformations. This result is completely in line with the experimental[36] and MP2/6-311+G(d,p) calculated[37] *E/Z* (anti − syn) difference for methyl acetate, $\Delta H = 8.5$ kcal mol^{-1} and $\Delta E = 8.6$ kcal mol^{-1}, respectively. The methoxy group preferentially adopts the trans orientation, $\tau_1 \sim 180°$; gauche$^-$ rotamers of the methoxy group, which also experience some stabilization by the *exo*-anomeric effect in β-pyranosides, are less stable by at least 2 kcal mol^{-1}. The first g$^+$ orientation of the methoxy group occurs in a skew-boat ring conformation, at approximately 4 kcal mol^{-1} above the lowest energy structure. Somewhat less stable are g$^+$ (MeO) rotamers of $^1C_4$ chairs, and none is found for $^4C_1$ chairs below ~35 kcal mol^{-1}. It should also be noted that the substituent torsions, especially the dihedral angles τ_2−τ_4, deviate quite strongly from the "standard" values ± 60° and 180° (Table S4), indicating some steric repulsion between the substituents. In the gas phase, the lowest energy rotamers for $^1C_4$, $^4C_1$, and ^2S_O ring conformations are characterized by the presence of an intramolecular hydrogen bond (Figure 2, note, however, the MP2/cc-pVDZ structure for the $^4C_1$ chair). In case of the $^1C_4$ chair, this intramolecularly hydrogen-bonded structure prevails in all solvents. In contrast, both $^4C_1$ and ^2S_O rings adopt this type of conformation only in the least polar solvent (CCl_4); already in $CHCl_3$ a shift toward conformers with little, if any, intramolecular hydrogen bonding occurs.

We now turn to a discussion of the factors responsible for the conformer, and especially ring structure stability. Several

TABLE 4: Calculated Geometrical Parameters[a] Describing Hydrogen Bonds and Vibrational Frequencies

			r_1	α_4	r_2	τ_7	τ_8	τ_9	ν(O−H)	ν(C2b=O2b)	ν(C4b=O4b)
$^1C_4$	ttg$^-$g$^-$ss	O3−H3···O1	2.008	140.9	2.837	−170.5	162.1	−158.9	3733	1773	1766
			1.915	144.2	2.763	−171.4	165.7	−164.7	3741	1827	1823
$^4C_1$	tg$^-$tg$^-$ss	O3−H3···O2b	1.897	157.8	2.824	−70.5	81.5	−72.4	3683	1747	1776
			2.057	138.8	2.860	−63.1	64.0	−64.3	3774	1815	1830
^2S_O	ttg$^+$tss	O3−H3···O4b	1.929	148.2	2.804	−94.4	63.1	−97.9	3713	1794	1745
			1.900	147.4	2.770	−90.1	60.2	−100.7	3740	1847	1807
^2S_O	tg$^-$g$^-$g$^-$ss	O3−H3···O2b	2.154	134.9	2.921	−93.4	55.8	−77.6	3773	1759	1767
			2.129	131.0	2.862	−91.2	51.9	−75.3	3787	1818	1824
$^4C_1$	ttg$^+$g$^-$ss	O3−H3···O4	2.569	100.8	2.911	−68.2	70.2	−69.2	3835	1795	1783
			2.442	105.2	2.853	−66.4	68.5	−66.8	3825	1847	1834
^2S_O	tttg$^-$ss	O3−H3···O2	2.542	100.1	2.875	−95.7	61.6	−84.2	3837	1798	1769
			2.384	105.7	2.806	−91.8	57.3	−82.8	3824	1847	1825

[a] $r_1 = r$(H3···Ox), $\alpha_4 = \alpha$(O3−H3···Ox), $\tau_7 = \tau$(O1−C1−C2−O2), $\tau_8 = \tau$(O2−C2−C3−O3), and $\tau_9 = \tau$(O3−C3−C4−O4); for each structure, the upper line corresponds to B3LYP/basis II and the lower line corresponds to the MP2/cc-pVDZ results. Vibrational frequencies are in cm^{-1}.

weak interactions determine the relative stability of carbohydrate conformers, mainly (in order of their importance) hydrogen bonding, anomeric effect, steric effects (ratio of equatorial vs axial substituents), and the Δ2 effect.[19] This latter effect does not apply to xylopyranosides.

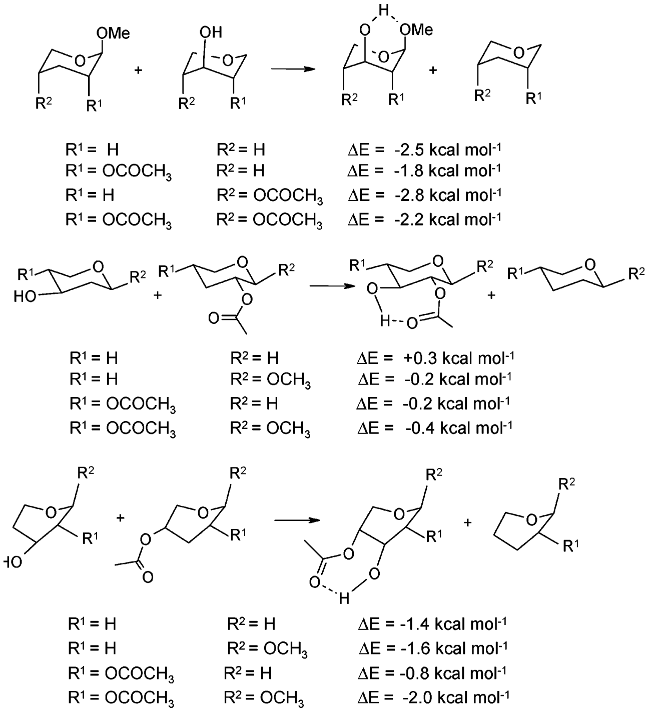
Hydrogen Bonding. The number of hydrogen bonds has been found to be the most important factor contributing to carbohydrate conformational energies.[19] Pertinent structural data describing hydrogen-bonding interactions [O3−H3···Ox distance r_1, O3···Ox distance r_2, O3−H3···Ox angle α_4, and torsional angles O1−C1−C2−O2 (τ_7), O2−C2−C3−O3 (τ_8), and O3−C3−C4−O4 (τ_9)] are summarized in Table 4 and Table S6 of the Supporting Information. In **6**, only conformations with at most one hydrogen bond are possible. As mentioned above, in the gas phase, the lowest energy rotamers of both the $^4C_1$ and $^1C_4$ chairs as well as the ^2S_O skew-boats are characterized by the presence of an intramolecular hydrogen bond. However, for the various ring structures, different types of hydrogen bonding exist, namely, the seven-membered rings formed in the $^4C_1$ chairs or ^2S_O skew-boats by O3−H3···O2b or O3−H3···O4b interactions between the C3 hydroxyl group and the carbonyl oxygen atom of the acetyl group at either C2 or C4 or the six-membered ring resulting from the O3−H3···O1 interaction in the $^1C_4$ chair (Figure 2). In principle, similar to the parent monosaccharide, hydrogen bonds leading to five-membered rings involving O3−H3 and the ester oxygen atoms O2 or O4 are also possible. For this latter type, hydrogen−oxygen distances are in the range $r_1 = 2.43-2.65$ Å, comparable with those found between the hydroxyl groups in nonfunctionalized sugars,[19] including methyl β-D-xylopyranoside itself.[21b] The O3−H3···O1 distance characteristic for the intramolecularly hydrogen bonded $^1C_4$ chair is significantly shorter (2.01−2.02 Å) but slightly longer than in the unsubstituted parent molecule (1.97 Å)[21b] and substantially longer than that in two methanol molecules [1.88 Å (B3LYP/basis II), 1.90 Å (B3LYP/6-311++G(d,p),[19] and 1.89 Å (MP2/cc-pVDZ)]. In contrast, hydrogen bonds involving the seven-membered rings with the carboxyl oxygens O2b or O4b are characterized by much shorter distances (1.87−1.93 Å), comparable with or even shorter than the calculated hydrogen bond between methanol and methyl acetate [1.93 Å (B3LYP/basis II), 1.94 Å (MP2/cc-pVDZ)]. Note that this H-bond length is larger than that calculated for two methanol molecules. Cambridge Structural Database (CSD) searches[34] for intermolecular O−H···O contacts in the range 0−2.5 Å gave ~2100 hits (~3800 entries) and ~600 hits (~700 entries) for those between two secondary alcohols and a secondary alcohol and the carbonyl oxygen of esters, respectively. About 60% of the intermolecular O−H···O contacts determined by X-ray crystallography are in the ranges 1.82−2.06 Å for hydrogen bonding between secondary alcohols and 1.91−2.15 Å for the analogous interaction between a secondary alcohol and the carbonyl oxygen of esters. Unconstrained alcohol−ester hydrogen bonds are, thus, indeed longer than those between two alcohols. The calculated interaction energies are not too different and slightly stronger for the methanol−methyl acetate complex, $\Delta H = -4.4$ (B3LYP/basis II) and −6.9 kcal mol^{-1} (MP2/cc-pVDZ), than for the methanol dimer, $\Delta H = -4.6$ (B3LYP/basis II) and −7.3 kcal mol^{-1} (MP2/cc-pVDZ).

A comparison of the relative energies of the lowest energy conformations of $^4C_1$, $^1C_4$, and ^2S_O (Table 1) and their respective hydrogen-bonding distances (Table 4) shows that a shorter O−H···O distance does not necessarily correspond to a greater stability. A similar result had been previously found for H-bond lengths in furanoses vs pyranoses,[19] attributed to an unfavorable local dipole interaction as the O−C−C−O torsion becomes smaller. For 2-hydroxyethyl acetate as a model for the seven-membered ring structure in O3−H3···O2b (O4b) intramolecular hydrogen bonds, without the constraints imposed by the pyranose ring, the calculated (B3LYP/basis II) H-bond length is 1.95 Å. This elongation is caused by a larger O−C−C−O torsional angle (95°) to be compared with a value of $\tau_8 \sim 82°$ in the pyranose. For O−C−C−O fragments not involved in this type of hydrogen bonding, the respective torsional angles are ~70°, for example, τ_7 and τ_9 (Table 4) of the lowest energy $^4C_1$ conformer. This deviation from the preferred dihedrals (~70° and 95° in the cyclic and acyclic structures, respectively) likely adds some strain to the seven-membered cyclic H-bonding in the $^4C_1$ chair. In contrast, for the ^2S_O structures, this dihedral angle (B3LYP/basis II, −98°; MP2/cc-pVDZ, −101°) closely matches that of the acyclic model compound, suggesting greater H-bond strength. For skew-boat forms, both O3−H3···O2b and O3−H3···O4b H-bonding is found; no O3−H3···O4b seven-membered ring structure is among the lowest five $^4C_1$ chairs.

There exists another type of O3−H3···O2b and O3−H3···O4b interaction, where both the hydroxyl and carboxyl groups are twisted out of the plane of the seven-membered ring with a concomitant increase in the hydrogen−oxygen distance (2.15−2.16 Å, Table 4). It is interesting to note that, with MP2/cc-pVDZ optimizations, the structure of the "original" O3−H3···O2b hydrogen-bonding motif changes to this latter type in the case of the $^4C_1$ chair but not for the ^2S_O skew-boat (Table 4). Noteworthy, for the methyl acetate−methanol hydrogen-bonded complex, a planar structure results with the B3LYP/basis II calculation, whereas in contrast, MP2/cc-pVDZ yields a substantial out-of-plane movement of the MeOH molecule. As mentioned above, the shifts of the O−H stretching frequency resulting from hydrogen bonding have been used to determine the ring conformation populations of acylated xylopyranoses by IR spectroscopy.[11] Calculated (B3LYP/basis II and MP2/cc-pVDZ) wavenumbers for O−H and C=O stretching vibrations are also given in Table 4. By comparison with experimental data for secondary alcohols (ν(OH) = 3626 cm^{-1})[11] and methyl acetate (ν(C=O) = 1761 cm^{-1})[38] with calculated ones [2-propanol, 3832 (B3LYP/basis II), 3838 (MP2/cc-pVDZ); methyl acetate, 1775 (B3LYP/basis II), 1835 cm^{-1} (MP2/cc-pVDZ)], scaling factors for ν(OH) = 0.95 and for ν(C=O) = 0.96 (MP2/cc-pVDZ) or 0.99 (B3LYP/basis II) can be derived. With these scaling factors, $\Delta\nu$(OH) = 84−95 cm^{-1} for $^1C_4$ chairs with the six-membered O3−H3···O1 hydrogen bond, well within the experimental range ($\Delta\nu$ = 71−106 cm^{-1}).[11] For the tg$^-$ttss conformation of the $^1C_4$ chair, which does not contain this H-bond, ν(OH) differs only marginally from the value for a free hydroxyl group in secondary alcohols ($\Delta\nu \sim -5$ cm^{-1}). Five-membered rings with O3−H3···O2 or O3−H3···O4 interactions (ester oxygens) in $^4C_1$ chairs or skew-boats also lead to quite small values of $\Delta\nu \sim -5$ to +11 cm^{-1}, comparable with the experimental shifts[11] of $\Delta\nu \sim 7$ to 43 cm^{-1}. The calculated shift $\Delta\nu$(OH) for the seven-membered rings in O3−H3···O2b or O3−H3···O4b hydrogen bonds depends on the above-mentioned type: H-bonds with H3···O2b/O4b distances $r_2 \sim 2.15$ Å as in tg$^-$g$^-$g$^-$ss − ^2S_O (Table 4) or g$^-$tg$^-$tss − $^4C_1$ (Table S6) have $\Delta\nu$ = 57 (47 with MP2/cc-pVDZ) and 51 cm^{-1}, respectively, intermediate between the experimental values for five-membered and six-membered rings in $^4C_1$ and $^1C_4$ chairs. For H-bonds with H3···O2b/O4b distances $r_2 \sim 1.90$ Å as in tg$^-$tg$^-$ss − $^4C_1$ or ttg$^+$tss − ^2S_O (Table 4), $\Delta\nu$ = 142 cm^{-1} (experiment[11] ∼ 135−150 cm^{-1}) and 114 cm^{-1} (92 cm^{-1} with MP2/cc-pVDZ). This latter shift for the ^2S_O form more closely corresponds to the experimental $\Delta\nu$ of the six-membered O3−H3···O1 hydrogen-bond characteristic of the $^1C_4$ chair! If indeed present in the equilibrium composition, thus, this ring conformation could add to the apparent $^1C_4$ population as determined by IR spectroscopy. The calculated shift for tg$^-$tg$^-$ss − $^4C_1$ clearly should be characteristic and, if observed, be useful to estimate the amount of this ring structure. Note, however, that upon optimization with MP2/cc-pVDZ this conformation collapses to a structure with a much weaker hydrogen bond, $\Delta\nu$(OH) = 60 cm^{-1} (Table 4), a value more closely matching the experimental shift for the six-membered O3−H3···O1 hydrogen-bond characteristic of the $^1C_4$ chair! Thus, $^4C_1$ chairs with this weak hydrogen bond also would add to an apparent $^1C_4$ population.

Besides the X−H···Y distances, the strength of hydrogen bonds can be estimated by a number of other criteria.[39] Here, we use homodesmotic reactions[40] to assess the strengths of the different types of hydrogen bonds possible in methyl 2,4-diacetyl-β-D-xylopyranoside (Scheme 2). According to the calculated (B3LYP/basis II, ZPE included, last lines in Scheme 2) reaction energies, the hydrogen-bond strength in **6** decreases in the following order: $^1C_4$ (−2.2 kcal mol^{-1}) > ^2S_O (−2.0 kcal mol^{-1}) ≫ $^4C_1$ (−0.4 kcal mol^{-1}). The above-mentioned relatively weak nature of the O3−H3···O2b hydrogen bond in $^4C_1$ chairs is thereby quantified. Obviously, since the skew-boat is less stable than the $^4C_1$ chair (Table 1), besides hydrogen bonding other factors also must contribute to conformer stability.

SCHEME 2: Homodesmotic Reactions to Estimate the Energies (B3LYP/basis II, ZPE included) of the Different Types of Hydrogen Bonds in 6



R^1 = H	R^2 = H	ΔE = -2.5 kcal mol^{-1}
R^1 = OCOCH$_3$	R^2 = H	ΔE = -1.8 kcal mol^{-1}
R^1 = H	R^2 = OCOCH$_3$	ΔE = -2.8 kcal mol^{-1}
R^1 = OCOCH$_3$	R^2 = OCOCH$_3$	ΔE = -2.2 kcal mol^{-1}

R^1 = H	R^2 = H	ΔE = +0.3 kcal mol^{-1}
R^1 = H	R^2 = OCH$_3$	ΔE = -0.2 kcal mol^{-1}
R^1 = OCOCH$_3$	R^2 = H	ΔE = -0.2 kcal mol^{-1}
R^1 = OCOCH$_3$	R^2 = OCH$_3$	ΔE = -0.4 kcal mol^{-1}

R^1 = H	R^2 = H	ΔE = -1.4 kcal mol^{-1}
R^1 = H	R^2 = OCH$_3$	ΔE = -1.6 kcal mol^{-1}
R^1 = OCOCH$_3$	R^2 = H	ΔE = -0.8 kcal mol^{-1}
R^1 = OCOCH$_3$	R^2 = OCH$_3$	ΔE = -2.0 kcal mol^{-1}

Anomeric Effect. To estimate the anomeric effect, that is, the greater stability of an axial C1−O1 orientation in pyranoses,[41] two different homodesmotic reactions, shown in Scheme 3, were used. The first one yields reaction energies (B3LYP/basis II, ZPE contributions included) of −7.4 ($^1C_4$), −8.5 (^2S_O), and −6.0 kcal mol^{-1} ($^4C_1$); thus, a stabilization by the anomeric effect of the lowest energy rotamers of the $^1C_4$ chair and ^2S_O skew-boat relative to the $^4C_1$ chair of −1.4 and −2.5 kcal mol^{-1}, respectively, can be estimated.

The second type of homodesmotic reaction, with $\Delta E(^4C_1)$ = 0.0 kcal mol^{-1} by definition, results in −1.7 kcal mol^{-1} ($^1C_4$) and −3.2 kcal mol^{-1} (^2S_O), also indicating a substantial stabilization of this latter ring structure. The anomeric effect can be interpreted in terms of the $n_{O5} \rightarrow \sigma^*$(C1−O1) orbital interaction (charge transfer),[42] which is especially favorable for an axial C1−O1 orientation. A measure of the stabilization provided thereby is the second-order perturbation energy for the various orbital interactions,[20] available from a natural bond orbital (NBO) analysis:[29] $\Delta E^{(2)}$ = 12 ($^1C_4$), 13 (^2S_O), and 3 ($^4C_1$) kcal mol^{-1}. For the *exo*-anomeric effect, $n_{O1} \rightarrow \sigma^*$(C1−O5) charge transfer, largely responsible for the conformational properties of the glycosidic linkage, $\Delta E^{(2)}$ values are 12 ($^1C_4$) and 14 ($^4C_1$, ^2S_O) kcal mol^{-1}, in line with the preferred trans conformation of the methoxy group. To put these numbers in context, $\Delta E^{(2)}$ = 40−50 kcal mol^{-1} for the resonance of the ester oxygen lone pairs with the carbonyl group of the acetoxy moieties. Nevertheless, NBO analysis also shows that the anomeric effect adds stability not only to the $^1C_4$ chairs but also to the ^2S_O skew-boat ring structures.

Steric Effect. Generally, all of the lowest energy pyranose chair conformations have a greater or equal number of equatorial than axial substituents.[19] Only in some special cases, most prominently π-stacking between aryl groups in the 1,3 position[7a] or steric repulsion of very bulky equatorial 1,2-substituents,[6] a shift toward axial-rich ring conformations is observed. Neither one of these two effects should play any significant role in determining the stability of methyl 2,4-diacetyl-β-D-xylopyranoside ring conformations. To estimate the influence of the acetoxy group orientation, the model systems (X = O, CH$_2$) shown in Chart 1 were used. Clearly, for 1,3-diacetoxy substitution, the eq−eq ($^4C_1$) is favored over the ax−ax ($^1C_4$) arrangement (ΔE = 2.1 and 2.6 kcal mol^{-1} for X = O and X = CH$_2$, respectively, B3LYP/basis II, ZPE correction included).

SCHEME 3: Homodesmotic Reactions Shown for the $^4C_1$ and $^1C_4$ Chairs, Respectively, Used to Estimate the Anomeric Effect (B3LYP/basis II, ZPE included)

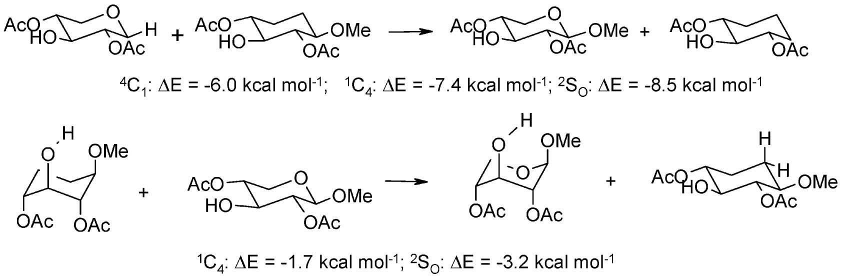
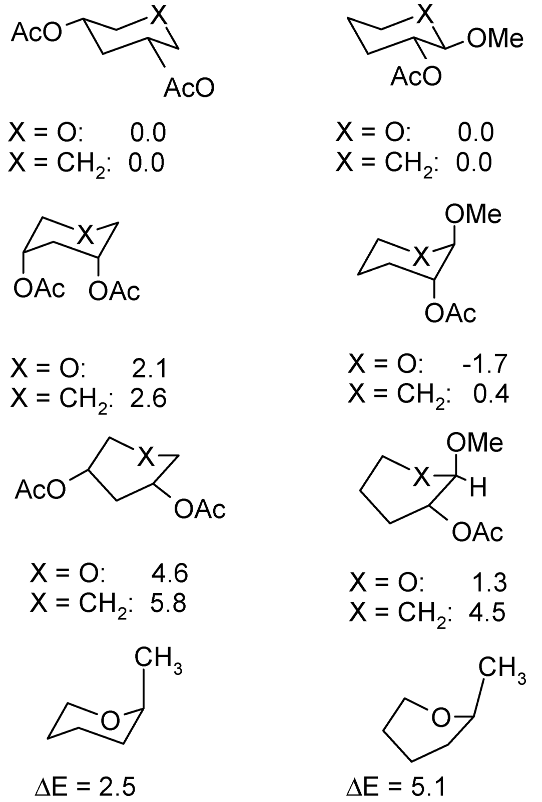


CHART 1: Model Compounds Used to Estimate the Steric Effect in $^4C_1$, $^1C_4$, and ^2S_O Ring Conformations of Methyl 2,4-Diacetyl-β-D-xylopyranoside[a]



[a] Energies (B3LYP/basis II, ZPE included) are given relative to the $^4C_1$ chairs.

Still higher in energy is the ^2S_O structure of both model compounds ($\Delta E = 4.6$ and 5.8 kcal mol^{-1} for X = O and X = CH$_2$, respectively). In contrast to the $^1C_4$ chair, evidently, this significantly larger energy difference cannot be overcome by the anomeric effect and hydrogen bonding. Similarly, in the vicinal methoxy−acetoxy derivatives of cyclohexane (X = CH$_2$), steric effects favor the eq−eq orientation, especially in the skew-boat ($\Delta E = 0.4$ and 4.5 kcal mol^{-1} for $^1C_4$ and ^2S_O, respectively, Chart 1). Generally, it is difficult to separate steric effects from torsional energies. To estimate the difference between the steric energy of the ring vs the substituents, 2-methyl tetrahydropyran was used as a model system (Chart 1). Relative energies of the $^1C_4$ and ^2S_O rings with respect to the $^4C_1$ chair, $\Delta E = 2.6$ and 5.1 kcal mol^{-1}, indicate that ring torsion significantly accounts for the respective energy differences. In contrast, for the tetrahydropyran system, the anomeric effect apparently is large enough to overcome the unfavorable ax−ax arrangement ($\Delta E = -1.7$ kcal mol^{-1}) in the $^1C_4$ chair but not in the case of the skew-boat ring conformation ($\Delta E = +1.3$ kcal mol^{-1}). Thus, steric effects are quite important as destabilizing factors for skew-boat conformations in methyl 2,4-diacetyl-β-D-xylopyranoside.

Conclusions

A comprehensive conformational analysis by density functional calculations (B3LYP) with extended basis sets of methyl 2,4-diacetyl-β-D-xylopyranoside yields the $^1C_4$ chair as the energetically favored ring structure in the gas phase, followed by $^4C_1$ and, nearly isoenergetic, ^2S_O. Solvents of increasing polarity (CCl_4, $CHCl_3$, DMSO, and H_2O) preferentially stabilize the $^4C_1$ chair. However, the two models for bulk solvent effects, IEF-PCM[26] and PB-SCRF,[27] show substantial differences in the amount of this stabilizing effect: whereas with PB-SCRF the $^1C_4$ chair remains the most stable ring form, with IEF-PCM in all solvents but CCl_4 the $^4C_1$ chair is predicted to be more stable. Compared with experiments, IR in tetrachloromethane,[11] a smaller $^1C_4$ population, especially with IEF-PCM, at the expense of skew-boat structures, is obtained. The computed frequency shift, $\Delta\nu$(OH), of the O3−H hydroxy group involved in a seven-membered intramolecular hydrogen bond in the ^2S_O skew-boat is similar to that of the six-membered ring characteristic for the $^1C_4$ chair and, thus, might add to an apparent $^1C_4$ population. Calculations for the chloroform solution more closely match NMR results,[10a] although here too, a quite large ^2S_O population is predicted. Possible factors responsible for ring conformation stability, namely, hydrogen bonding, anomeric and steric effects, are analyzed using homodesmotic reactions and/or appropriate model compounds. Despite a rather short O3−H···O2b distance in the seven-membered intramolecular hydrogen bonds of $^4C_1$ chairs, this type of H-bonding strength is quite weak; homodesmotic reaction energies indicate a decrease of hydrogen bonding in the order $^1C_4 > {}^2S_O \gg {}^4C_1$. The anomeric effect not only stabilizes the $^1C_4$ chair but also the skew-boat conformation, ^2S_O. In contrast, unfavorable steric interactions are largest in this latter ring structure.

Acknowledgment. S.K. thanks the Higher Education Commission of Pakistan for a scholarship.

Supporting Information Available: Tables for total energies (Table S1), PB-SCRF solvation energies (Table S2), ring puckering parameters and torsional angles (Tables S3 and S4), composite energies (Table S5), and parameters describing H-bonding (Table S6). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Rao, V. S. R.; Qasba, P. K.; Balaji, P. V.; Chandrasekaran, R. *Conformation of Carbohydrates*; Harwood Academic Publishers: Amsterdam, The Netherlands, 1998. (b) Ramesh, H. P.; Tharanathan, R. N. *Crit.*

Rev. Biotechnol. **2003**, *23*, 149−173. (c) Rinaudo, M. *Biomacromolecules* **2004**, *5*, 1155−1165. (d) Hricovini, M. *Curr. Med. Chem.* **2004**, *11*, 2565−2583.

(2) (a) Imberty, A.; Perez, S. *Chem. Rev.* **2000**, *100*, 4567−4588. (b) Duus, J. O.; Gotfredsen, C. H.; Bock, K. *Chem. Rev.* **2000**, *100*, 4589−4614. (c) Wormald, M. R.; Petrescu, A. J.; Pao, Y.-L.; Glithero, A.; Elliott, T.; Dwek, R. A. *Chem. Rev.* **2002**, *102*, 371−386.

(3) Lindhorst, Th. K. *Essentials of Carbohydrate Chemistry and Biochemistry*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2003; p 16.

(4) (a) Durette, P. L.; Horton, D. *Carbohydr. Res.* **1971**, *18*, 57−80. (b) Horton, D.; Durette, P. L. *J. Org. Chem.* **1971**, *36*, 2658−2669.

(5) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2205−2213.

(6) (a) Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 663−666. (b) Yamada, H.; Nakatani, M.; Ikeda, T.; Marumoto, Y. *Tetrahedron Lett.* **1999**, *40*, 5573−5576.

(7) (a) Yuasa, H.; Miyagawa, N.; Nakatani, M.; Izumi, M.; Hashimoto, H. *Org. Biomol. Chem.* **2004**, *2*, 3548−3556. (b) Izumi, T.; Hashimoto, H.; Yuasa, H. *Chem. Commun.* **2004**, 94−95. (c) Yuasa, H.; Miyagawa, N.; Izumi, T.; Nakatani, M.; Izumi, M.; Hashimoto, H. *Org. Lett.* **2004**, *6*, 1489−1492. (d) Yuasa, H.; Izumi, T.; Mitsuhashi, N.; Kajihara, Y.; Hashimoto, H. *Chem.−Eur. J.* **2005**, *11*, 6478−6490.

(8) Kogelberg, H.; Solis, D.; Jimenez-Barbero, J. *Curr. Opin. Struct. Biol.* **2003**, *13*, 646−653.

(9) (a) Yoshimoto, K.; Itatani, Y.; Shibata, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1980**, *28*, 208−219. (b) McEwan, T.; McInnes, A. G.; Smith, D. G. *Carbohydr. Res.* **1982**, *104*, 161−168.

(10) (a) Petrakova, E.; Schraml, J. *Carbohydr. Res.* **1983**, *117*, 285−290. (b) Petrakova, E.; Schraml, J. *Collect. Czech. Chem. Commun.* **1983**, *48*, 877−888. (c) De Bruyn, A.; Anteunis, M.; Van Rijsbergen, R.; Claeyssens, M.; Kovac, P. *J. Carbohydr. Chem.* **1983**, *1*, 301−309.

(11) Kacurakova, M.; Petrakova, E.; Hirsch, J.; Ebringerova, A. *Vib. Spectrosc.* **1994**, *7*, 31−36.

(12) (a) Perez, S.; Imberty, A.; Engelsen, S. B.; Gruza, J.; Mazeau, K.; Jimenez-Barbero, J.; Poveda, A.; Espinosa, J.-F.; van Eyck, B. P.; Johnson, G.; French, A. D.; Kouwijzer, M. L. C. E.; Grootenuis, P. D. J.; Bernardi, A.; Raimondi, L.; Senderowitz, H.; Durier, V.; Vergoten, G.; Rasmussen, K. *Carbohydr. Res.* **1998**, *314*, 141−155. (b) Perez, S.; Kouwijzer, M.; Mazeau, K.; Engelsen, S. B. *J. Mol. Graphics* **1996**, *14*, 307−321.

(13) (a) Lii, J.-H.; Ma, B.; Allinger, N. L. *J. Comput. Chem.* **1999**, *20*, 1593−1603. (b) Csonka, G. I. *J. Mol. Struct. (THEOCHEM)* **2002**, *584*, 1−4. (c) Barrows, S. E.; Storer, J. W.; Cramer, C. J.; French, A. D.; Truhlar, D. G. *J. Comput. Chem.* **1998**, *19*, 1111−1129.

(14) (a) Dowd, M. K.; Rockey, W. M.; French, A. D.; Reilly, P. J. *J. Carbohydr. Chem.* **2002**, *21*, 11−25. (b) French, A. D.; Johnson, G. P. *Cellulose* **2004**, *11*, 5−22. (c) French, A. D.; Johnson, G. P. *Cellulose* **2004**, *11*, 449−462. (d) Ford, Z. M.; Stevens, E. D.; Johnson, G. P.; French, A. D. *Carbohydr. Res.* **2005**, *340*, 827−833. (e) Lii, J.-H.; Chen, K.-H.; Johnson, G. P.; French, A. D.; Allinger, N. L. *Carbohydr. Res.* **2005**, *340*, 853−862.

(15) (a) Appell, M.; Strati, G.; Willett, J. L.; Momany, F. A. *Carbohydr. Res.* **2004**, *339*, 537−551. (b) Momany, F. A.; Appell, M.; Strati, G.; Willett, J. L. *Carbohydr. Res.* **2004**, *339*, 553−567. (c) Appell, M.; Willett, J. L.; Momany, F. A. *Carbohydr. Res.* **2005**, *340*, 459−468. (d) Momany, F. A.; Appell, M.; Willett, J. L.; Bosma, W. B. *Carbohydr. Res.* **2005**, *340*, 1638−1655.

(16) (a) Woods, R. J. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; John Wiley: New York 1996; Vol. 9, pp 129−165. (b) Woods, R. J. *Glycoconjugate J.* **1998**, *15*, 209−216. (c) Case, D. A.; Cheatham, T. E., III; Darden, T.; Gohlke, H.; Luo, R.; Merz, K. M., Jr.; Onufriev, A.; Simmerling, C.; Wang, B.; Woods, R. J. *J. Comput. Chem.* **2005**, *26*, 1668−1688. (d) Glennon, T. M.; Merz, K. M., Jr. *J. Mol. Struct. (THEOCHEM)* **1997**, *395−396*, 157−171.

(17) (a) Mackerell, A. D., Jr. *J. Comput. Chem.* **2004**, *25*, 1584−1604. (b) Lins, R. D.; Hünenberger, P. H. *J. Comput. Chem.* **2005**, *26*, 1400−1412. (c) McNamara, J. P.; Muslim, A.-M.; Abdel-Aal, H.; Wang, H.; Mohr, M.; Hillier, I. H.; Bryce, R. A. *Chem. Phys. Lett.* **2004**, *394*, 429−436. (d) Rasmussen, K. *J. Mol. Struct. (THEOCHEM)* **1997**, *395−396*, 91−106.

(18) (a) Tvaroska, I. *Trends Glycosci. Glycotechnol.* **2005**, *17*, 177−190. (b) Taravel F. R.; Mazeau, K.; Tvaroska, I. In *Polysaccharides*, 2nd ed.; Dumitriu, S., Ed.; Marcel Dekker: New York, 2005; pp 281−304. (c) Raab, M.; Kozmon, S.; Tvaroska, I. *Carbohydr. Res.* **2005**, *340*, 1051−1057. (d) Tvaroska, I. *Carbohydr. Res.* **2004**, *339*, 1007−1014. (e) Tvaroska, I.; Andre, I.; Carver, J. P. *Glycobiology* **2003**, *13*, 559−566. (f) Andre, I.; Tvaroska, I.; Carver, J. P. *Carbohydr. Res.* **2003**, *338*, 865−877. (g) Tvaroska, I.; Andre, I.; Carver, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 8762−8776.

(19) Guler, L. P.; Yu, Y.-Q.; Kenttämaa, H. I. *J. Phys. Chem. A* **2002**, *106*, 6754−6764.

(20) Nyerges, B.; Kovács, A. *J. Phys. Chem. A* **2005**, *109*, 892−897.

(21) (a) Hünig, I.; Painter, A. J.; Jockusch, R. A.; Çarçabal, P.; Marzluff, E. M.; Snoek, L. C.; Gamblin, D. P.; Davis, B. G.; Simons, J. P. *Phys. Chem. Chem. Phys.* **2005**, *7*, 2474−2480. (b) Fabian, W. M. F. *Theor. Chem. Acc.*, in press.

(22) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision B.04; Gaussian, Inc.: Wallingford, CT, 2004.

(23) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.

(24) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

(25) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284−298.

(26) Tomasi, J.; Mennucci, B.; Cances, E. *J. Mol. Struct. (THEOCHEM)* **1999**, *464*, 211−226.

(27) (a) Tannor, D. J.; Marten, B.; Murphy, R.; Friesner, R. A.; Sitkoff, D.; Nicholls, A.; Honig, B.; Ringnalda, M.; Goddard, W. A., III. *J. Am. Chem. Soc.* **1994**, *116*, 11875−11882. (b) Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. *J. Phys. Chem.* **1996**, *100*, 11775−11788.

(28) *Jaguar 4.1*; Schrödinger, Inc.: Portland, OR, 2000.

(29) (a) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899−926. (b) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO*, Version 3.1; University of Wisconsin: Madison, WI, 1988.

(30) Schaftenaar, G.; Noordik, J. H. *J. Comput.-Aided Mol. Des.* **2000**, *14*, 123−134.

(31) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354−1358.

(32) Spek, A. L. *PLATON, A Multipurpose Crystallographic Tool*; Utrecht University: Utrecht, The Netherlands, 2005.

(33) Cramer, C. J. *Essentials of Computational Chemistry*; J. Wiley & Sons: Chichester, U.K., 2002; p 340.

(34) (a) Allen, F. H.; Davies, J. E.; Galloy, J. J.; Johnson, O.; Kennard, O.; Macrae, C. F.; Mitchell, E. M.; Mitchell, G. F.; Smith, J. M.; Watson, D. G. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 187−204. (b) Allen, F. H.; Motherwell, W. D. S. *Acta Crystallogr., Sect. B: Struct. Sci.* **2002**, *58*, 407−422.

(35) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792.

(36) Blom, C. E.; Günthard, H. H. *Chem. Phys. Lett.* **1981**, *84*, 267−271.

(37) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935−5943.

(38) Wong, M. W.; Wiberg, K. B.; Frisch, M. *J. Chem. Phys.* **1991**, *95*, 8991−8998.

(39) Grabowski, S. J. *J. Phys. Org. Chem.* **2004**, *17*, 18−31.

(40) Sanz, P.; Mo, O.; Yanez, M. *Phys. Chem. Chem. Phys.* **2003**, *5*, 2942−2947.

(41) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527−548.

(42) David, S.; Eisenstein, O.; Hehre, W. J.; Salem, L.; Hoffmann, R. *J. Am. Chem. Soc.* **1973**, *95*, 3806−3807.