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Theoretical Studies of the Potential Energy Surfaces and Compositions of the D-Aldo- and D-Ketohexoses

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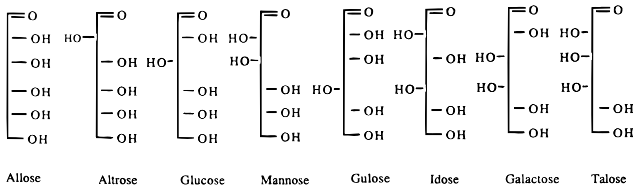
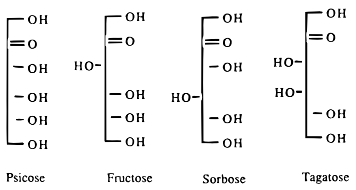
Abstract: The potential energy surfaces of all eight D-aldohexoses and four D-ketohexoses have been extensively studied, employing quantum mechanical and molecular mechanical calculations. Anomeric preferences for the axial OH positions were observed for all of the hexoses studied. Several stability factors determining the potential energy surface were examined, and we found that the Hassel−Ottar effect, the delta-two effect and the cis−trans effect are not discernible on the gas-phase potential energy surfaces of the cyclic hexoses. Instead, the anomeric effect and intramolecular hydrogen bonding effects dominate. The most important finding in this study is that in the gas phase, furanose forms are more stable than pyranose forms for all of the hexoses except galactose, idose, psicose, and sorbose, in contrast to the generally greater stability of pyranose forms observed in solution. The decrease of intramolecular hydrogen bonding stabilization in solution was found to be primarily responsible for the composition differences between the gas and solution phases.

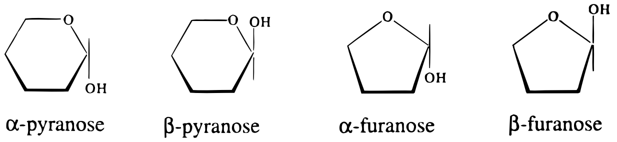
Introduction

Although the primary significance of carbohydrates rests on their major importance in biology, they also represent a unique family of polyfunctional compounds. An understanding of their interrelationships was of profound importance in the development of sterochemistry, and hence of the whole subject of organic chemistry. Basic to the family are the monosaccharides, which may be polyhydroxy aldehydes or ketones, i.e., aldoses or ketoses. There are eight D-aldohexoses and four D-ketohexoses, whose acyclic forms are listed as Fischer projections below. (the twelve L-forms are the corresponding mirror images, and they have potential surfaces that are mirror images of those of the D-forms and will not be specifically discussed here.)





However, in solution these compounds all cyclize to produce five- and/or six- membered rings (furanoses and pyranoses, respectively), which are much more stable than their open chain forms. For the purpose of classification, the structure and sterochemistry of the cyclic sugar is conveniently represented by a planer Haworth structure, even though the real structure is puckered, of course.



The achiral C1 carbon atom of an aldose (written at the top in the acyclic structure) becomes chiral in the cyclic form. Depending on the position of the OH group generated at the C1 atom upon cyclization, there are two sterochemical species (anomers) for a pyranose or for a furanose. The anomers are termed α or *β* when the OH group at C1 is below or above the ring plane of the Haworth formula, respectively. Thus, for each aldo- or ketohexose, there are four possible forms (α, *β* pyranose and α, *β* furanose), which are experimentally distinguishable. The compositions in terms of these four forms have been extensively studied and well documented[1,2] for the componds in aqueous solution. However, even a hundred years after Fisher established the configuration of D-glucose, part of the behavior of these monosaccharides still seems surprising, and is not readily explained.[1] A central question here concerns the relative stabilities of the four forms of a sugar. For a given sugar, is the α anomer or *β* anomer preferred? Is the furanose or pyranose preferred? Why? Generally speaking, the pyranose form dominates (for example, the concentrations of furanose forms are negligible for equilibrium mixtures of glucose or mannose in water solution). However, the concentrations of furanose forms are substantial for many monosaccharides. The preference for an α anomer or *β* anomer seems to be unpredictable a priori as well.

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Our present knowledge concerning the relative stabilities of the monosaccharides focuses on three factors, namely, electronic effects, intramolecular hydrogen bonding, and solvation effects. It was observed that for most C1-substituted pyranoses, the α anomer is more stable than the β. Since in simple cyclohexane derivatives the equatorial hydroxyl is more stable, the reversal of the usual order here is called the anomeric effect.[3] There was originally considerable discussion as to the cause of the anomeric effect.[3] It is now clear that the effect can be explained completely and quantitatively only as being due to a major contribution from hyperconjugation, plus a minor contribution from dipole−dipole interaction.[4] Intramolecular hydrogen bonding is also important in determining the energetic interrelationships in these molecules, as demonstrated by theoretical studies of isolated molecules,[4−9] and by experimental studies in solution.[1,10] Solvation has profound effects. Angyal has shown that the compositions of reducing sugars in DMSO are much different from those in aqueous solution, and that the solvation effect varies from case to case.[1] Clearly, a study of the interplay of these three factors would be crucial for our understanding of the relative stabilities of the structures of reducing sugars. Such a study should examine the reducing sugars in a systematic manner, rather than focus on one particular compound. Theoretical calculations have provided thermodynamic differences for the isomers in the gas phase, and recently, in solution. Many studies have been carried out in that direction.[4−9] However, most previous work has been restricted to glucopyranose.

We have carried out quantum and molecular mechanical computations for all eight D-aldohexoses and four D-ketohexoses, in both the gas phase and solution, in an effort to understand their relative stabilities. Our present work is also the first theoretical endeavor to compare the relative stabilities and the heats of formation of both the pyranose and furanose forms and the aldohexose and ketohexose structures.

Theoretical Method

Quantum mechanical calculations were carried out by employing the Gaussian 94 program.[11] Five d-type functions were used for carbon and oxygen atoms. Starting from MM3 optimized structures, the geometries of the hexose conformers were all optimized at the SCF/6-31G** level, and at the density functional theory (DFT) B3LYP/6-31G** level. The solvation effects on the energies of the ab initio structures were examined by using the isodensity surface continuum model[11] (IPCM) at the STO-3G level with SCF/6-31G** optimized geometries. The IPCM calculations with larger basis sets are not presently practical.

The molecular mechanics computations were carried out with the MM3 (96) program.[12]

Results and Discussion

(A) Nomenclature. (1) Aldohexose. The numbering scheme for the atoms of an aldohexose, with glucose as an example, in the pyranose and furanose forms, is indicated in Figure 1. The convention of symbols for the chair forms of pyranoid sugars uses superscripts, subscripts, and a letter C. The superscripts and subscripts are the locants of the ring atoms that lie “above” or “below” a reference plane, which is defined by two parallel ring sides.[13] The two possible aldopyranose chair forms are $^4C_1$ (Figure 1a) and $^1C_4$. In the $^1C_4$ conformation the hydroxymethyl group is in an axial position, and the conformation is unfavored. For all of the aldopyranoses studied here, the $^4C_1$ ring conformations are used unless otherwise stated. The conformers are named according to the orientations of the extracyclic C6−O6 bond (some authors, for example, in ref 9, used the term exocyclic, we think that the term extracyclic in ref 13 is more appropriate) relative to the C5−O5 and C4−C5 bonds in the ring: gauche gauche (GG), gauche trans (GT), and trans gauche (TG).

The two extreme conformations for the furanoid ring are the envelope (E) and twist (T) forms. However, the barrier to the interconversion is very low,[13] and we do not specify the ring conformation. There are two extracyclic C−O bonds in an aldofuranose (C5−O5 and C6−O6, Figure 1). We may use four letters to describe the aldofuranose conformers, for example, GGGG, in the order of the torsional position of O6−C6−C5−O5, O6−C6−C5−C4, O5−C5−C4−O4, and O5−C5−C4−C3.

(2) Ketohexose. The numbering scheme for the atoms of a ketohexose, with fructose as an example, in the pyranose and furanose forms is illustrated in Figure 2. The ketopyranose ring may have $^2C_5$ and $^5C_2$ conformations. The orientation of the extracyclic CH_2OH group, similar to that of an aldopyranose, may be specified by the torsional angle of O1C1C2O6 and O1C1C2C3 as GG, GT, and TG.

The conformations of a ketofuranose are simpler than those of an aldofuranose, due to the fact that the two extracyclic C−OH bonds are not coupled. We also use four letters to indicate the conformations of a ketofuranose, for example, GGGG, in the order of O6C6C5O5, O6C5C5C4, O1C1C2O5, and O1C1C2C3 torsional positions.

(B) General Description of the Potential Energy Surface. The conformational energy surfaces of hexoses are extremely complex. Given the rotational freedom of the hydroxyl groups, there are thousands of possible conformers. However, the complexity can be greatly reduced when intramolecular hydrogen bonding is considered in preliminary conformation search, i.e., the low lying conformation should maximize intramolecular hydrogen bonding. Therefore in this work the search for possible low-lying conformations was restricted to those with cooperative arrangements of intramolecular hydrogen bonding which we believe to be a reasonable approximation.

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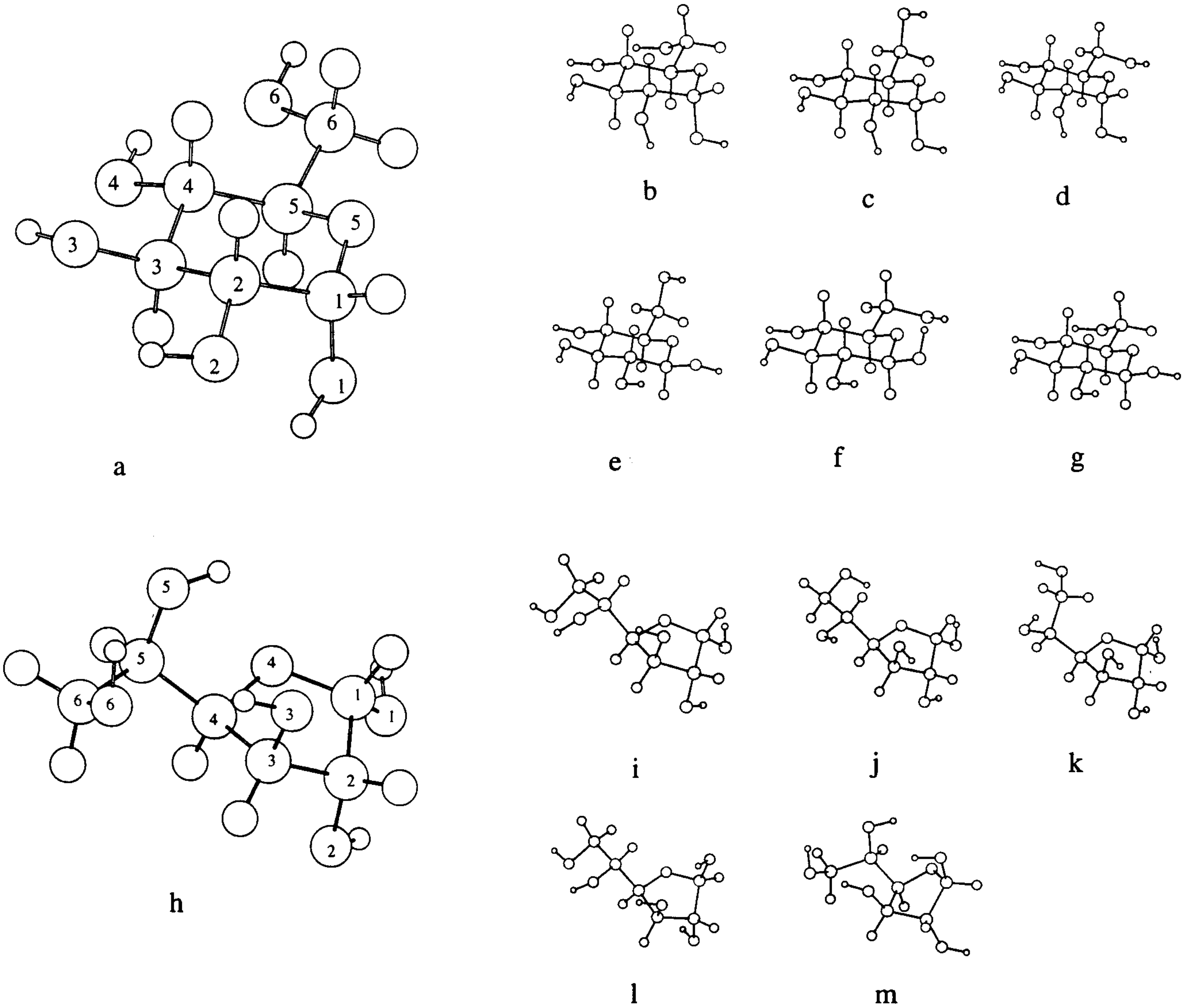

Figure 1. Conformers of glucose: (a) α pyranose, TG conformation, clockwise hydrogen bonding orientation; (b) α pyranose, TG conformation, counterclockwise hydrogen bonding orientation; (c) α pyranose, GG conformation; (d) α pyranose, GT conformation; (e) *β* pyranose, GG conformation; (f) *β* pyranose, GT conformation; (g) *β* pyranose, TG conformation; (h) α furanose, GGGG conformation; (i) α furanose, GGTG conformation; (j) α furanose, TGTG conformation; (k) α furanose, GGGT conformation; (l) *β* furanose, GGTG conformation; and (m) *β* furanose, GGGG conformation.

Parts of potential energy surfaces of glucopyranose have been previously studied by quantum mechanical calculations.[4−9] No study of glucofuranose has been reported. The relative energies of the various conformers of glucopyranose vary with the change of basis functions and correlation levels. Barrows[7a] et al. studied the GT and TG conformers of *β*-glucopyranose at the MP2/6-31G*, CCSD/6-31G*//MP2/6-31G*, and MP2/cc-pVTZ//MP2/cc-pVDZ levels, and found that their relative energies all agreed to within ±0.5 kcal/mol by all of these methods. As may be seen from Table 1, the relative energies of these glucopyranoses at the B3LYP/6-31G** level also agree almost this well with those at the MP2/6-31G* level, indicating that the B3LYP/6-31G** level is good enough for evaluating the potential energy surfaces of the cyclic hexoses to this level of accuracy. Recently, Csonka et al. also reported that the DFT and MP2 methods provide similar energetic differences for the glucose conformers.[7b] Because of the size of the molecules (12 heavy atoms) and the number of conformations possible, the computational speed of the DFT method was important, as a practical matter.

For the isolated molecule, the hydroxyls prefer to orient in such a way as to yield a cooperative hydrogen bonding that is as efficient as possible. For glucopyranose, the OH groups may take clockwise (Figure 1a) or counterclockwise (Figure 1b) orientations. Previously, it was found that the counterclockwise orientation is preferred,[8] and that preference was confirmed in this work. For a TG glucopyranose, the counterclockwise conformation was found to be 0.87 kcal/mol more stable than the corresponding clockwise conformation at the SCF/6-31G** level. The HO1C1O5 segment is in the gauche and trans positions for the counterclockwise and clockwise conformations, respectively. The reason for the preference is presumably due to the anomeric effect favoring the HO1C1O5 segment in the gauche position. However, it is not a golden rule for counterclockwise conformation preference. Recently, Damm et al. found that the clockwise conformation is preferred for galactose.[25]

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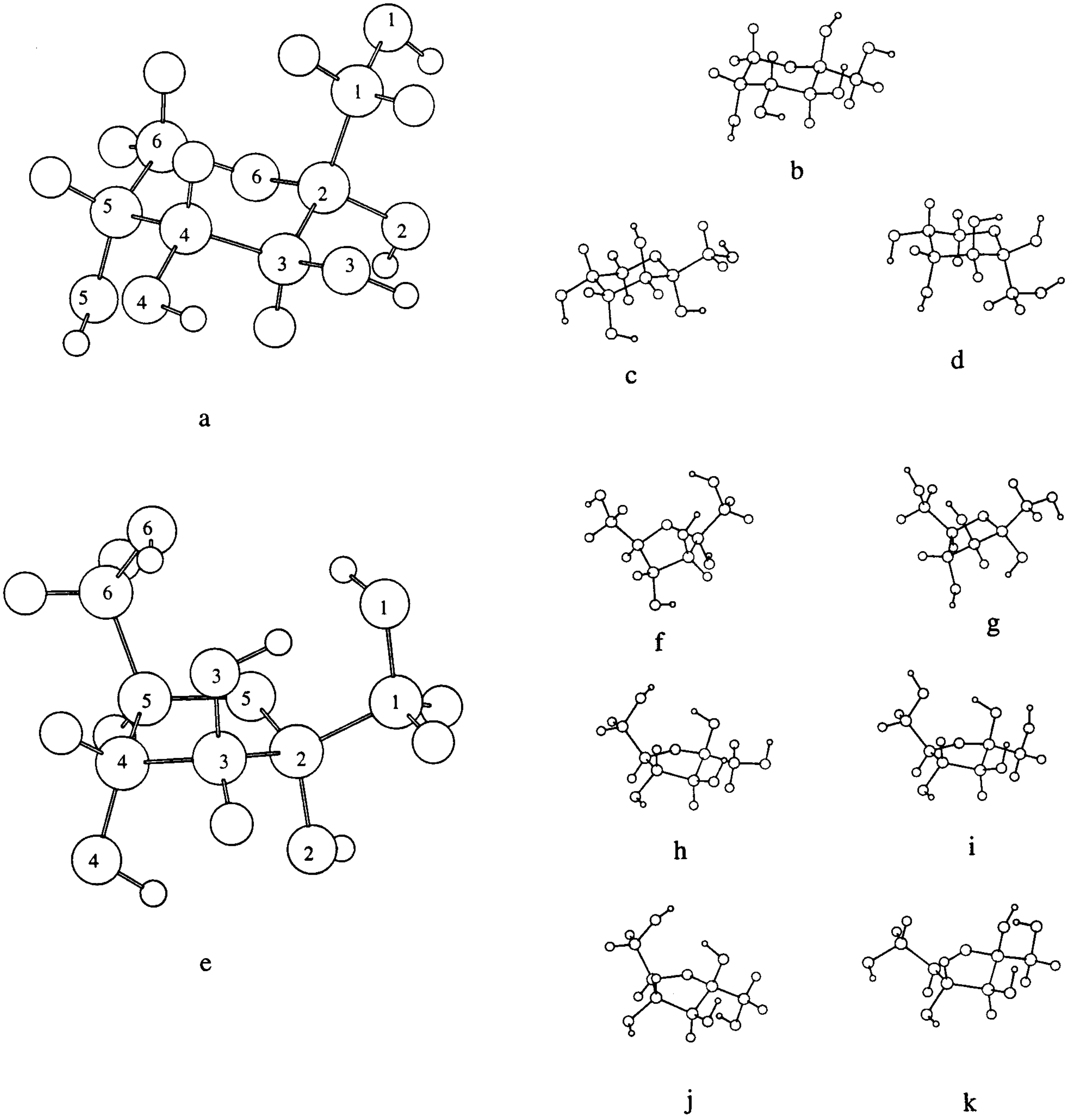

Figure 2. Conformers of fructose: (a) α pyranose, $^2C_5$ GT conformation; (b) *β* pyranose, $^2C_5$ GT conformation; (c) α pyranose, $^5C_2$ GT conformation; (d) *β* pyranose, $^5C_2$ GT conformation; (e) α furanose, GGGG conformation; (f) α furanose, GTGG conformation; (g) α furanose, GGGT conformation; (h) *β* furanose, GGTG conformation; (i) *β* furanose, GGGT conformation; (j) *β* furanose, GGGG conformation; and (k) *β* furanose, TGGT conformation.

Table 1. Conformational Energies of Glucopyranoses at Several Theoretical Levels (kcal/mol)

	6-31G* SCF[a,b]		6-31G** SCF[d]		6-311G(2d,1p) SCF[b]		6-31G* MP2[b,c]		6-31G** B3LYP[d]		MM3[d] ($D = 1.5$)	
conformer	α	*β*	α	*β*	α	*β*	α	*β*	α	*β*	α	*β*
pyranose GG (Figures 1c, 1e)	0.12		0.08	0.92	−0.16		0.02		0.55	2.3	0.66	−0.01
Pyranose GT (Figures 1d, 1f)	0.20	1.3	0.15	1.93	−0.04		0.56	3.02	0.81	2.8	−0.09	−0.65
Pyranose TG (Figures 1b, 1g)	0.0	1.2	0.0	1.01	0.0		0.0	2.57	0.0	1.9	0.0	−0.61

[a] Reference 4. [b] Reference 6. [c] Reference 7a. [d] This work. In the present study, we found that MM3(96) calculates the anomeric preferences systematically backward relative to correlated quantum mechanical calculations. See text.

The possible conformations of glucofuranose were searched for by the MM3 method first, and the several low-lying conformations found were then studied quantum mechanically. For D-glucofuranose, D-allofuranose, D-altrofuranose, and D-mannofuranose, both molecular mechanical and quantum mechanical results agree that the GGGG conformation is the global

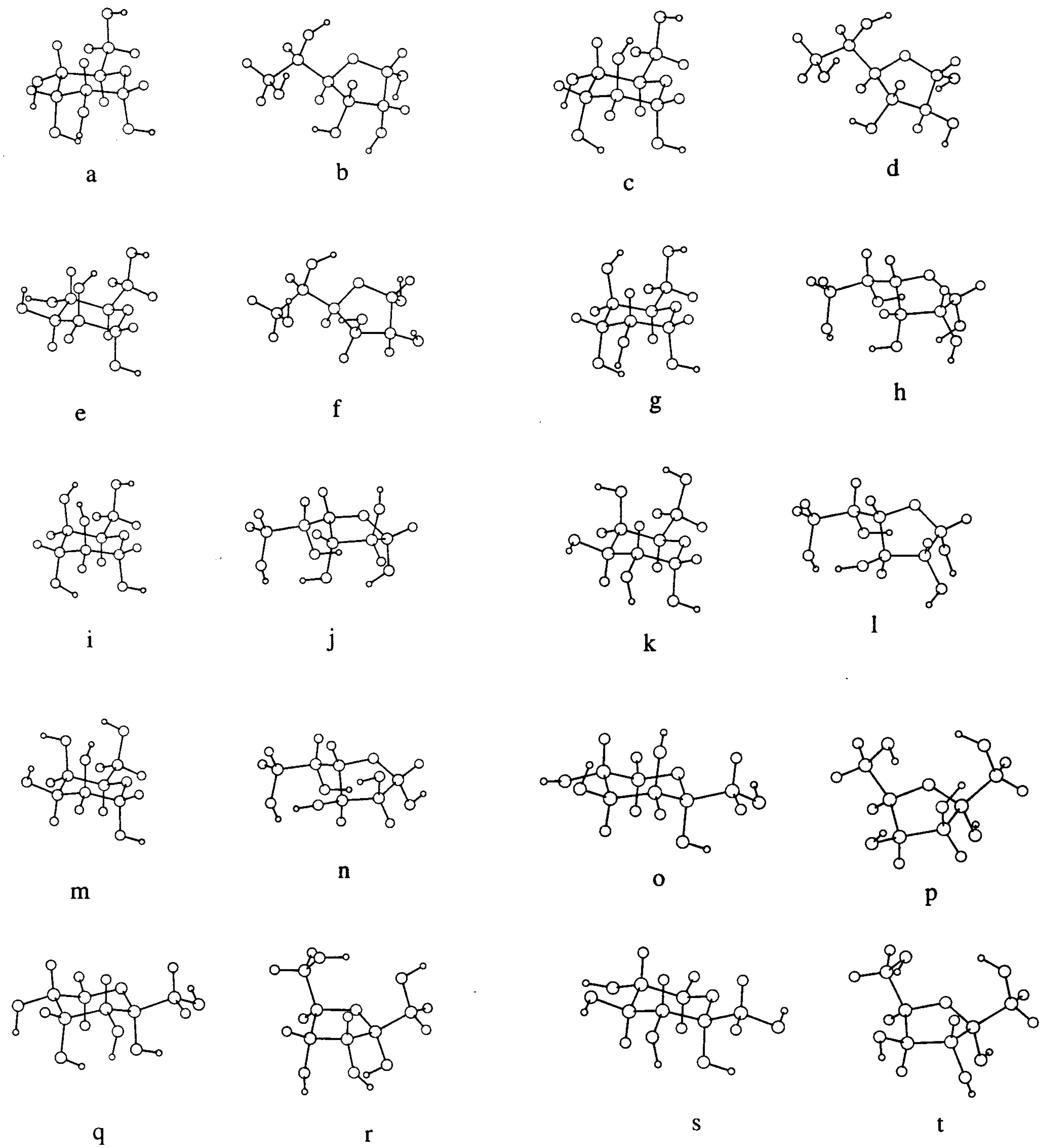

Figure 3. Conformations of D-aldohexose and D-ketohexose. Illustrated are GG conformers of aldopyranose, GGGG conformers of aldofuranose, $^5C_2$ GT conformers of ketopyranose, and GGGG conformers of ketofuranose: (a) allopyranose, (b) allofuranose, (c) altropyranose, (d) altrofuranose, (e) mannopyranose, (f) mannofuranose, (g) gulopyranose, (h) gulofuranose, (i) idopyranose, (j) idofuranose, (k) galactopyranose, (l) galactofuranose, (m) talopyranose, (n) talofuranose, (o) tagatopyranose, (p) tagatofuranose, (q) psicopyranose, (r) psicofuranose, (s) sorbopyranose, and (t) sorbofuranose. Other conformations are included in Support Information.

minimum structure. For the other aldofuranoses, only the GGGG conformer was studied.

The conformations and energies of the aldohexoses are reported in Figure 3 and Table 2, respectively. It may be seen from Table 2 that the energies of the most stable pyranose form of each aldohexose are all within a range of less than 4 kcal/mol at the B3LYP 6-31G** level. Our systematic study clearly showed the anomeric effect for aldopyranose. The axial α anomers are always more stable than the corresponding *β* anomers at the B3LYP 6-31G** level. Note that (from Table 2) the α anomeric preference is not clear at the SCF level,

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Table 2. Total Energies (kcal/mol) of Hexoses[a]

		SCF		B3LYP	
species	conformer	α	β	α	β
glucose	GG	0.08	0.92	0.55	2.25
pyranose	GT	0.15	1.93	0.81	2.77
	TG	**0.0**	1.01	**0.0**	1.82
furanose	GGGG	4.52	3.73	2.57	−0.23
	GGTG	4.73	4.95	5.52	2.67
	TGTG	7.49	8.43	8.00	8.00
	GGGT	12.81	11.52	11.97	9.28
allose	GG	0.93	−1.08	−0.93	0.50
pyranose	GT	0.97	0.11	−0.63	0.94
	TG	0.82	−0.06	−1.56	0.01
furanose	GGGG	−0.03	−0.16	−3.33	−1.03
	GGTG	7.67	3.80		
altrose	GG	2.59	1.29	0.72	2.89
pyranose	GT	2.54	2.50	0.80	3.64
	TG	2.25	2.36	−0.29	2.57
furanose	GGGG	4.74	0.68	3.10	−1.42
	GGTG	6.60	5.09		
mannose	GG	1.78	1.36	1.19	1.81
pyranose	GT	1.92	1.45	1.35	2.00
	TG	1.76	1.04	0.55	0.87
furanose	GGGG	5.20	4.27	2.32	−2.37
	GGTG	5.82	3.54		1.23
gulose	GG	1.47	0.01	−0.64	−0.04
pyranose	GT	4.79	3.94		
	TG	4.37	3.80		
furanose	GGGG	2.97	6.79	−2.17	3.46
idose	GG	0.15	3.12	−2.93	
pyranose	GT	4.12	2.77		2.86
	TG	4.29	2.61		2.79
furanose	GGGG	4.64	4.52	−0.89	2.59
galactose	GG	1.26	2.97	0.23	
pyranose	GT	0.24	1.94	0.28	2.35
	TG	0.34	2.11	0.38	2.44
	Clock-GG	−1.04		−1.75	
furanose	GGGG	0.68	3.15	−1.42	1.97
talose	GG	1.92	3.57	−0.75	
pyranose	GT	0.48	1.64	−1.09	
	TG	0.90	1.37	−0.78	0.2
furanose	GGGG	0.16	0.03	−1.03	−3.33
fructose	$^{2}C_{5}$ GG	6.00	−1.41	5.21	−2.24
pyranose	$^{2}C_{5}$ GT	4.12	−0.32	3.46	−1.06
	$^{2}C_{5}$ TG	5.56	−0.67		−2.25
	$^{5}C_{2}$ GG	0.26	6.47	2.01	7.15
	$^{5}C_{2}$ GT	−0.43	3.48	−3.23	5.82
	$^{5}C_{2}$ TG	3.02	6.62	0.93	6.48
furanose	GGGG	1.91	3.04	−3.66	1.45
	GTGG	3.33			
	GGGT	5.92	3.94		
	TGGT		2.95		2.19
	GGTG		3.37		
tagatose	$^{2}C_{5}$ GG		3.33		1.95
pyranose	$^{2}C_{5}$ GT	4.96	6.94		
	$^{2}C_{5}$ TG		3.85		
	$^{5}C_{2}$ GT	−0.58	5.1	−2.47	4.26
furanose	GGGG	2.63	−0.84	−2.65	−7.08
	GGTG		0.38		
psicose	$^{2}C_{5}$ GG		−0.47		−3.75
pyranose	$^{2}C_{5}$ GT	5.24	0.06		
	$^{2}C_{5}$ TG		0.20		
	$^{5}C_{2}$ GT	−2.96	4.03	−5.60	3.46
furanose	GGGG	0.65	2.19	−2.06	−1.76
	GGTG	−0.04	1.92	−1.95	1.49
sorbose	$^{2}C_{5}$ GG		0.86		−2.67
pyranose	$^{2}C_{5}$ GT	6.66	0.03		−1.87
	$^{2}C_{5}$ TG		2.11		
	$^{5}C_{2}$ GT	−3.45	4.51	−4.06	
furanose	GGGG	1.69	1.95	0.33	−2.42
	TGGG	2.74			
	GGTG		5.35		4.71

a. The total energies presented are relative to a TG glucose, whose total energies are −683.37438 hartrees at the SCF/6-31G** level and −687.17880 hartree at the B3LYP/6-31G** level. These values are equilibrium energies.

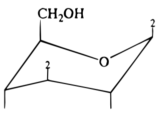
indicating the importance of including electron correlation in evaluating the conformational stabilities of the monosaccharides. We found that α-idopyranose is the most stable of the aldopyranoses at the B3LYP 6-31G** level. It might have been expected that glucose would have the lowest energy, but it does not. Five of the other aldohexoses are lower than glucose in energy with only mannose and galactose being slightly higher. At this level α-allofuranose and *β*-talofuranose have comparable stabilities, and those two structures are the most stable species of the aldohexoses.

The conformations and energies of the ketohexoses are also reported in Figure 3 and Table 2, respectively. The extracyclic hydroxymethyl group occupies the axial position, and the anomeric hydroxyl group an equatorial position, in the $^{2}C_{5}$ α- and $^{5}C_{2}$ *β*-ketopyranose. As expected, we found that the conformational energies of these structures are very high. The GG conformations are generally preferred for all four $^{2}C_{5}$ *β*-ketopyranoses. For $^{5}C_{2}$ α-fructopyranose, we found that the stabilities are in the order of GT > GG > TG at the B3LYP level. Subsequently, only the GT conformers are studied for other $^{5}C_{2}$ α-ketopyranoses. Generally, $^{5}C_{2}$ α-fructopyranoses are more stable than the $^{2}C_{5}$ *β*-fructopyranoses. We found that $^{5}C_{2}$ α-psicopyranose is the most stable species among the ketopyranoses at the B3LYP 6-31G** level.

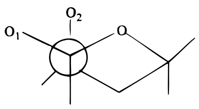
The GGGG conformations are preferred for ketofuranose at the B3LYP 6-31G** level. *β*-Tagatofuranose was found to be surprisingly stable at the B3LYP 6-31G** level, and it was the most stable species of all the hexose structures studied in this work.

It was generally believed that pyranose structures are more stable than the corresponding furanose structures, because experimentally pyranoses have been found to predominate at equilibrium in solution.[1] However, in the gas phase, at the B3LYP 6-31G** level, we found that the furanose forms are more stable for all of the hexoses except galactose, idose, psicose, and sorbose (Table 2).

(C) Stability Factors Determining Favored Conformations. There have been many previous empirical explanations of the stabilities of pyranose structures. Several of them are frequently discussed in the literature, especially the Hassel−Ottar effect,[13,14] the delta-two effect,[13,15] the anomeric effect, and intramolecular hydrogen bonding.



The Hassel-Ottar effect



The delta-two effect

The Hassel−Ottar effect states that conformation that places the CH_2OH group of aldohexapyranoses and an additional hydroxyl group in a synaxial position (on the same side of the ring of either positions "2" in the structure shown) was a very undesirable configuration. Having two bulky groups synaxial

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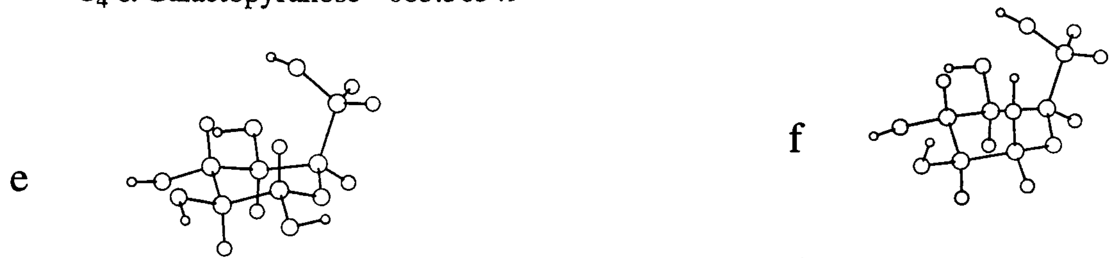
(25) Damm, W.; Frontera, A.; Tirado-Rives, J.; Jorgensen, W. L. *J. Compt. Chem.* **1997**, *18*, 1955.

$^1C_4$ α Altropyranose -683.36271

$^1C_4$ β Altropyranose -683.36784

$^1C_4$ α Galactopyranose -683.36349

$^1C_4$ β Galactopyranose -683.36924



$^1C_4$ α Idopyranose -683.36735

$^1C_4$ β Idopyranose -683.37003

$^1C_4$ α Talopyranose -683.36716

$^1C_4$ β Talopyranose -683.36753

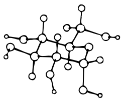
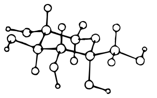
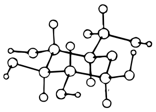
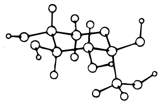
Figure 4. Several $^1C_4$ conformations of aldopyranose and their total energies (au) at the SCF/6-31G** level.

leads to a higher energy than additivity would predict. Thus one axial methyl has an interaction energy of 1.75 kcal/mol (with two axial hydrogens), so the CH_3/H interaction energy is 0.87 kcal/mol.[21] The corresponding Me/Me synaxial interaction energy is 3.70 kcal/mol. Similarly, the methyl/hydroxyl synaxial interaction is 1.9 kcal/mol.[22]

A careful examination of Figure 4 reveals that the Hassel–Ottar effect is not always obeyed. For example, the *β* anomers in Figure 4, whose hydroxyl groups are in synaxial positions, are systematically lower in energy than the corresponding α anomers, which situation is contrary to the Hassel–Ottar effect. The conformational energies of $^1C_4$ idopyranoses (Figure 4, parts e and f) are lower than those of $^1C_4$ talopyranoses (Figure 4, parts g and h), which situation may be explained in terms of the Hassel–Ottar effect. However, we also see that $^1C_4$ α-altropyranose (Figure 4a), which has no synaxial hydroxyl group, has the highest conformational energy among the conformers in Figure 4, which is also contrary to the Hassel–Ottar effect. The Hassel–Ottar effect is partially right, since the CH_2OH group itself introduces instability if it is in an axial position. However, an additional hydroxyl group in an axial position does not necessarily introduce further instability. The steric energy of the synaxial hydroxyl group could be lowered by better hydrogen bonding or by the anomeric effect.

Reeves stated[13,15] that any axial substituent, other than hydrogen, on a pyranose ring introduces an element of instability to the ring conformation, and this generalization is based on steric effects. Most notable among these is the Δ2 effect, which arises when the oxygen atom O2 bisects the angle formed by the ring oxygen atom and the oxygen atom O1 (see structure). This occurs in mannose and altrose, as is shown. The large circle here represents C-1 obscuring C-2. However, a comparison of the energies of mannose and altrose with the energies of other aldopyranoses does not support the existence of the

Table 3. Relative Energies of Aldohexose and Ketohexose

conformers	conformers	Relative energy (E_{ketose} - E_{aldose}) kcal/mol		
		SCF	DFT	MM3[a]
$^4C_1$ α GT Glucopyranose 	$^5C_2$ α GT Sorbopyranose 	-3.60	-4.87	-2.1
$^4C_1$ β GT Glucopyranose 	$^5C_2$ β GT Sorbopyranose 	2.58	1.91	3.29
$^4C_1$ α GT Allopyranose	$^5C_2$ α GT Psicopyranose	-3.93	-4.97	-2.36
$^4C_1$ β GT Allopyranose	$^5C_2$ β GT Psicopyranose	3.92	2.52	3.58
$^4C_1$ α GT Altropyranose	$^5C_2$ α GT Fructopyranose	-2.97	-4.03	-1.73
$^4C_1$ β GT Altropyranose	$^5C_2$ β GT Fructopyranose	0.98	2.18	4.96
$^4C_1$ α GT Mannopyranose	$^5C_2$ α GT Tagatopyranose	-2.60	-3.82	-1.56
$^4C_1$ β GT Mannopyranose	$^5C_2$ β GT Tagatopyranose	3.65	2.26	3.26

[a] Heats of formation are used for comparison.

unfavorable Δ2 effect. As may be seen in Table 2, the conformational energies of mannose and altrose are comparable to those of other hexoses. Rather, we found that the intramolecular hydrogen bonding and the anomeric effect dominate the potential energy surfaces of aldopyranoses. In many cases, we see that an axial OH group leads to better intramolecular hydrogen bonding, and thus lowers, rather than raises, the conformational energies.

Cis and trans factors[1,13] have been used to explain the relatively high stability of the furanose ring. Angyal stated that cis subsituents on a five-membered ring lead to instability whereas trans substituents are favored. This is certainly the case in hydrocarbons,[23] where steric effects dominate the situation. However, in the gas phase we found that there is no evidence of such a cis/trans effect in the structures being discussed here. Instead, the furanose conformational energies are largely determined by intramolecular hydrogen bonding (see section F), and in general, two cis hydroxyls will form a stronger hydrogen bond to one another than will the corresponding trans structure.[23]

(D) Relative Energies of Aldo- and Ketohexoses. There are four isomeric pairs of aldo- and ketopyranoses, for which the only differences are the position of the extracyclic methyloxyl group (sorbose and glucose, psicose and allose, fructose and altrose, tagatose and mannose). For example, the structural differences between $^4C_1$ glucopyranose and $^5C_2$ sorbopyranose are illustrated in Table 3. The relative energies of these four pairs provide an excellent opportunity to compare the relative stabilities of aldo- and ketohexoses. In Table 3 we see that α-ketopyranoses are more stable than α-aldopyranoses, while β-ketopyranose are less stable than β-aldopyranoses. It is easily understandable that β-ketopyranoses are less stable than β-aldopyranoses, because the methyloxyl group is in an equatorial position in the aldopyranose, and in an axial position in the ketopyranose, and we know that an axial methloxyl group is unfavorable. The MM3 results (heats of formation were used, so that they were comparable) agree with the quantum mechanical energy differences between β-ketopyranose and β-aldopyranose, indicating that the energy differences between β-ketopyranose and β-aldopyranose can be represented by classical behavior. However, the reason for the stability of α-ketopyranose deserves attention. The MM3 energy differences (heats of formation are used, so that they are comparable) between the α-ketopyranose and α-aldopyranose are only half of those from the quantum mechanical computations. The energy differences from the MM3 calculation account, we think pretty well, for the van der Waals forces and dipole interaction contributions. The discrepancy suggests that the additional stabilization of the α-ketopyranose found by the quantum mechanical calculations may result from a previously unrecognized electronic effect, or it may be that either the anomeric or the hydrogen bonding description is less accurate than previously recognized.

(E) Comparison with Experimental Composition: an Insight into Solvation Effects. Experimentally, the equilibrium compositions of the four cyclic forms of the hexoses in aqueous solution have been known for a long time. Recently, there has been interest in applying theoretical methods to trying to understand the anomeric ratios for sugars.[8,9,16−20] Most of those theoretical studies previously reported were concerned with the anomeric ratios of glucose, although xylose[19] and psicose[20] have also been studied. The solvation effect can be considered as having two contributions, one is the polarization effect on the intrinsic stability of the solute molecule, and the other is the direct solvent−solute hydrogen bonding. Cramer and Truhlar[8] studied the aqueous solvation effect on the anomeric ratios of glucose using a semiempirical continuum solvation method, and concluded that the solvation effect on this ratio is very small. Brady et al. carried out molecular dynamics free energy simulations of the anomeric equilibrium of glucose[18] and xylose.[19] In the study of the average number of solute−solvent hydrogen bonds, they found that β-xylose has only 0.26 more hydrogen bond than α-xylose. If those studies can be generalized, we would expect that the theoretical gas-phase compositions should be close to those in solution. However, we found that that is not the case. The most noticeable problem is that furanose structures dominate in the gas phase, while experimentally, pyranose structures dominate in solution.

Traditionally, it was simply thought that a pyranose structure is more stable than a furanose structure, because cyclohexane is more stable than cyclopentane. However, intramolecular hydrogen bonding favors the furanose structure over the pyranose structure. Experimentally,[28] *cis*-1,2-cyclopentanediol forms a strong intramolecular hydrogen bond, while *cis*-1,2-cyclohexanediol forms a weaker intramolecular hydrogen bond. Therefore, it is reasonable that furanose structures dominate in the gas phase. However, the decrease of the intramolecular hydrogen bonding energy in solution makes the pyranose structures more stable than the furanose structures in polar solvents.

Conventional wisdom has it that pyranose forms are stabilized in aqueous solution by better accommodation into the water structure, stabilization being greater for equatorial than for axial hydroxyl groups.[1] However, recent experiments have shown that the water structure is not fully responsible for the changes occurring when another solvent replaces water.[1]

To understand the composition difference in the gas phase and in the solution, we tried two approaches. First we used an ab initio continuum solvation model (IPCM). However, this approach was found to be unreliable at the theoretical level used. For example, the solvation energies of the glucose anomers differ by 10 kcal/mol. No conclusions regarding the anomeric preferences can be made from our IPCM study. The calculation with larger basis sets might be helpful, but it is not presently practical. In another approach with the MM3 program, we calculated the total energies and free energies of all the species using three different values for the dielectric constant ($\epsilon = 1.5$, 4.0, and 78.5). Usually, we use a dielectric constant of 1.5 to represent the gas phase, and 4.0 for a polar molecule such as a carbohydrate in a crystal. To simulate an aqueous solution we used a dielectric constant of 78.5. (These numbers were chosen as simple approximations to something complicated.) French et al.[20] studied the composition of psicose using the MM3 force field with a dielectric constant of 4.0, and a good agreement with experiment was obtained. Similar to the studies of French, our results from the MM3 calculations with those three dielectric constants reveal a clear trend. Namely the equilibrium furanose concentration decreases, and β the pyranose concentration increases, with increasing dielectric constant. As a result, a general qualitative agreement between experiments and computations regarding the furanose−pyranose ratio was obtained.

To compare the calculation with the experimental composition, all possible conformations should be included in a Boltzmann distribution. To circumvent this formidable calculation, we chose a particular conformation for each anomer and studied the composition, supposing that the other conformations have approximately proportional contributions, and thus may be neglected as a reasonable approximation. We found that the GT conformation of pyranose and the GGGG conformation of furanose are generally preferred on MM3 potential energy surfaces. Therefore, those two particular conformations were chosen to compute the anomeric compositions. Evidently, this approach is only approximate. Nevertheless, it has shown us a clear trend, as indicated in Table 4.

The MM3 results indicate a novel mechanism in the solvational differentiation of the structural composition of a sugar. We have noted that the intramolecular hydrogen bonding dominates the gas-phase potential energy surfaces of sugars, and the conformational energies are generally lowered considerably by better arrangements of intramolecular hydrogen bonding. However, the intramolecular hydrogen bonding contribution to the stability of a structure decreases substantially from the gas-phase to the solution phase, due to the increase of the dielectric constant. This is easy to understand for two reasons. First, hydrogen bonding involves a large contribution from electrostatic interactions, and electrostatic energies decrease with increasing dielectric constant. And second, in solution intramolecular hydrogen bonding is largely replaced by intermolecular hydrogen bonding of the solute to the solvent, which can greatly alter relative conformational stabilities. Note that our mechanism is not equivalent to the previous explanation that intramolecular hydrogen bonding vanished in solution due to competition of intermolecular (solvent−solute) hydrogen bonding. Experimentally, intramolecular hydrogen bonding still exists and contributes to the conformational energy,[10] but it is less important in high dielectric media.

It should be noted that solvation effects are very complex. At present, there is no definite conclusion about the mechanism of solvational preference of sugar anomers. We do not expect that our simplistic model of solvation using a uniformly high dielectric constant will accurately represent the complex solvation effect. Molecular mechanics calculations themselves are also inherently a simple representation of quantum mechanical complexities. However, within our present MM3 model, the decrease of intramolecular hydrogen bonding stabilization in solution appears to be primarily responsible for the composition difference between the gas and solution phases.

(F) The Contribution of Hydrogen Bonding Energies to Potential Energy Surfaces. We have said that hydrogen bonding contributes greatly to the potential energy surfaces of hexoses. In this section we will examine this contribution quantitatively. The MM3 method can calculate hydrogen bonding energy (including the contribution from the dipole−dipole interaction) between alcohols fairly well.[24] In Table 5 are reported the hydrogen bonding energies for hexoses. Three sets of results are included, i.e., the hydrogen bonding energies in B3LYP/6-31G** optimized geometries, and the hydrogen bonding energies in MM3 optimized geometries with $\epsilon = 1.5$ and 4.0. Several points may be made from those results: (1) furanose forms always have larger hydrogen bonding energies than do the corresponding pyranose forms; (2) hydrogen bonding energies have fair correlations with the conformational energies as indicated in Figure 5 (the correlation coefficient in Figure 5

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(26) Thomas, H. D.; Chen, K.; Allinger, N. L. *J. Am. Chem. Soc.* **1994**, 116, 5887.

(27) Dosen-Micovic, L.; Jeremic, D.; Allinger, N. L. *J. Am. Chem. Soc.* **1983**, *105*, 1716, 1723.

(28) Reference 21, p 18.

Table 4. MM3 Relative Free Energies ($\Delta G°$, kcal/mol) and Concentration[a,b]

		free energy $\Delta G°_{298}$				concentration, %			
species	ϵ	α P	β P	α F	β F	α P	β P	α F	β F
glucose	1.5	0.00	−1.35	1.55	0.96	9.1	88.5	0.7	1.8
	4.0	0.00	−1.60	2.77	2.75	6.3	93.6	0.1	0.1
	78.51	0.00	−1.78	3.09	3.97	4.7	95.3	0.03	0.01
	Exp					**38**	**62**	**0.0**	**0.14**
allose	1.5	0.00	−2.82	−1.47	−3.51	0.2	23.2	2.4	78.3
	4.0	0.00	−3.25	−0.64	−2.12	0.4	85.9	1.1	12.7
	78.51	0.00	−3.68	−0.59	−1.05	0.2	98.1	0.5	1.2
	Exp					**14**	**77.5**	**3.5**	**5**
altrose	1.5	0.00	−3.77	−3.42	−5.56	0.01	4.6	0.00	95.4
	4.0	0.00	−4.27	−2.44	−3.85	0.05	65.0	3.0	32.0
	78.51	0.00	−4.85	−2.57	−3.33	0.03	91.1	1.9	7.0
	Exp					**27**	**43**	**17**	**13**
mannose	1.5	0.00	−3.05	−0.05	−0.74	0.6	96.9	0.6	2.0
	4.0	0.00	−2.55	0.98	1.95	1.3	98.4	0.3	0.1
	78.51	0.00	−2.49	1.32	1.49	1.5	98.3	0.2	0.1
	Exp					**64.9**	**34.2**	**0.6**	**0.3**
gulose	1.5	0.00	−2.59	−2.07	−2.29	0.6	49.3	20.5	29.7
	4.0	0.00	−3.04	−0.41	0.03	0.6	97.7	1.2	0.6
	78.51	0.00	−3.64	1.3	0.21	0.2	99.6	0.02	0.2
	Exp					**16**	**81**	**0.00**	**3**
1.5	0.00	−2.39	0.38	−2.04	1.1	63.3	0.6	35.0	
idose	4.0	0.00	−2.50	−0.02	−1.80	1.1	74.8	1.1	22.9
	78.51	0.00	−2.71	−0.10	−2.19	0.7	69.6	0.9	28.9
	Exp					**38.5**	**36**	**11.5**	**14**
galactose	1.5	0.00	−1.19	−1.35	1.27	5.5	40.7	53.3	0.6
	4.0	0.00	−0.63	1.27	1.80	24.6	71.3	2.9	1.2
	78.51	0.00	−0.75	2.32	2.03	21.7	77.1	0.4	0.7
	Exp					**30**	**64**	**2.5**	**3.5**
talose	1.5	0.00	−1.04	−1.26	0.78	6.5	37.5	54.3	1.7
	4.0	0.00	−1.10	−0.15	1.65	11.4	73.2	14.7	0.7
	78.51	0.00	−1.18	0.15	1.83	10.9	80.1	8.5	0.5
	Exp					**42**	**29**	**16**	**13**
fructose	1.5	0.00	−4.46	−0.15	−1.04	0.1	99.6	0.1	0.3
	4.0	0.00	−5.97	0.06	−2.53	0.00	99.7	0.00	0.3
	78.51	0.00	−6.22	−0.77	−3.37	0.00	99.2	0.1	0.8
	Exp					**2.5**	**65**	**6.5**	**25**
tagatose	1.5	0.00	2.14	3.65	2.54	95.9	2.6	0.2	1.3
	4.0	0.00	0.98	3.92	2.10	81.9	15.6	0.1	0.4
	78.51	0.00	0.34	3.51	2.24	63.0	35.5	0.2	1.4
	Exp					**71**	**18**	**2.5**	**7.5**
psicose	1.5	0.00	−1.58	1.29	3.13	6.4	92.8	0.73	0.03
	4.0	0.00	−2.25	0.77	1.53	2.2	97.1	0.59	0.2
	78.51	0.00	−2.81	0.27	−0.01	0.9	97.8	0.54	0.9
	Exp					**22**	**24**	**39**	**15**
sorbose	1.5	0.00	3.59	7.21	5.36	99.76	0.2	0.00	0.01
	4.0	0.00	4.58	6.93	5.74	99.95	0.04	0.00	0.01
	78.51	0.00	5.25	5.54	5.53	99.97	0.01	0.01	0.01
	Exp					**93**	**2**	**4**	**1**

[a] Experimental concentrations are cited from ref 2, the experimental temperatures are between 22 and 44 °C. [b] α P: α pyranose form. β P: β pyranose form. α F: α furanose form. β F: β furanose form.

is 0.54. When only the data for α hexopyranoses were used, the correlation coefficient increased to 0.77); and (3) the furanose forms lost more hydrogen bonding energy (stabilization) than did the pyranose forms when the dielectric constant used was increased from 1.5 to 4.0. Thus, our previous conclusions about the contributions of hydrogen bonding have been confirmed quantitatively.

(G) Comparisons of Quantum Mechanical and Molecular Mechanical Calculations. We were rather surprised when we first looked at comparisons of these two types of calculations, for example, in Table 1, comparing B3LYP and MM3. The average discrepancies here are of the order of 1.5 kcal/mol. The question immediately comes to mind, Why?

First we need to consider the probable errors in the B3LYP calculations. When these are compared with the MP2 calculations, we see average errors of the order of about 0.5 kcal/mol. Note that the electron correlation makes a significant difference, relative to the several sets of Hartree−Fock calculations. On the basis of previous experience, and these studies, we might have expected that the MM3 results would be accurate to within 0.5 kcal/mol or so. Apparently this is not the case. Even allowing for the likely errors in the B3LYP numbers, the MM3 numbers still seem to be pretty far away from what is expected.

We do not know with certainty why these large errors are present. This problem is under investigation. However, we do know a few reasons for the discrepancies.

Earlier studies have shown that the idea of transferable numerical values for parameters between molecules, while usually a good approximation, is only an approximation.[26] The parameters previously studied, when looked at in detail, have proven to be functions, and not constants. The same is likely to occur here in polyhydroxy-substituted molecules, relative to the simple derivatives on which the force field was based. Another way to put it is a lack of transferability, or a

Table 5. MM3 Hydrogen Bonding Energies (−kcal/mol) of Hexoses

		B3LYP geometry $\epsilon = 1.5$		MM3 geometry $\epsilon = 1.5$		MM3 geometry $\epsilon = 4.0$		decrease of H bonding energy (from $\epsilon = 1.5$ to $\epsilon = 4.0$)	
species	conformer	α	β	α	β	α	β	α	β
Glucose									
Pyranose	GT	9.30	8.01	9.59	8.99	3.03	2.79	6.53	6.20
Furanose	GGGG	13.53	13.74	12.44	13.26	3.72	4.22	8.72	9.04
Allose									
Pyranose	GT	10.59	10.14	10.61	10.35	3.63	3.28	6.98	7.07
Furanose	GGGG	13.66	13.68	13.35	14.28	4.46	4.44	8.89	9.84
Altrose									
Pyranose	GT	10.02	9.19	10.05	8.90	3.40	2.76	6.65	6.14
Furanose	GGGG	9.99	15.8	10.38	15.34	3.49	5.02	6.89	10.32
Mannose									
Pyranose	GT	7.54	10.10	8.69	9.83	2.75	3.01	5.94	6.82
Furanose	GGGG	12.39	11.65	11.14	16.86	3.31	3.85	7.83	13.01
Gulose									
Pyranose	GT			8.63	8.24	3.00	2.49	5.63	5.75
Furanose	GGGG	15.82	11.18	14.18	11.13	4.60	3.32	9.58	7.81
Idose									
Pyranose	GT		10.55	10.92	10.53	3.82	3.42	7.10	7.11
Furanose	GGGG	15.52	13.54	14.09	12.50	4.10	3.73	9.99	8.77
Galctose									
Pyranose	GT	9.90	9.13	9.63	9.11	3.04	2.88	6.59	6.23
Furanose	GGGG	15.80	11.01	15.34	10.43	5.02	3.43	10.32	7.0
Talose									
Pyranose	GT	12.01	12.95	11.10	10.76	3.62	3.60	7.48	7.16
Furanose	GGGG	13.67	13.67	14.29	13.36	4.44	4.46	9.85	8.90
Fructose									
Pyranose	$^5C_2$ GT			11.45	7.60	3.69	2.40	7.76	5.20
Furanose	GGGG	14.06	9.43	13.94	9.92	4.19	3.15	9.75	6.77
Tagatose									
Pyranose	$^5C_2$ GT			9.68			3.11		6.57
Furanose	GGGG	13.98	13.52	13.98	15.04	3.37	4.18	10.15	10.86
Psicose									
Pyranose	$^5C_2$ GT			12.07	9.40	4.11	3.07	7.96	6.33
Furanose	GGGG	13.02	12.48	12.45	10.75	3.92	3.03	8.53	7.72
Sorbose									
Pyranose	$^5C_2$ GT			10.49	8.49	3.43	2.61	7.06	5.88
Furanose	GGGG	11.03	15.36	10.48	13.83	1.98	3.88	8.50	9.95

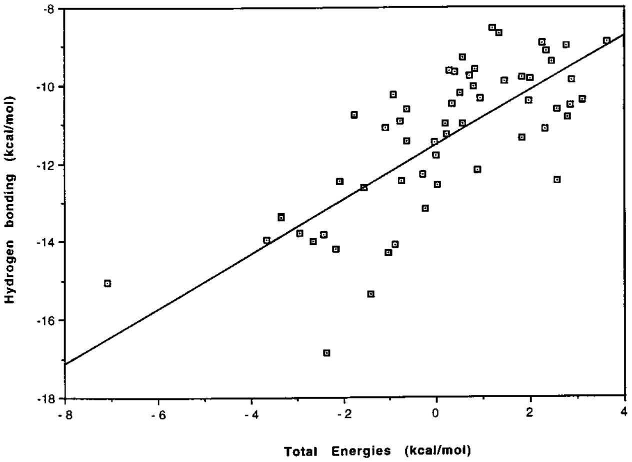

Figure 5. The correlation of hydrogen bonding energies and conformational energies of hexoses. The total energies are at the B3LYP/6-31** level, and the hydrogen bonding energies are calculated by the MM3 method with use of B3LYP/6-31G** optimized geometries. The correlation coefficient is 0.54. When only the data for α hexopyranoses were used, the correlation coefficient increased to 0.77.

nonadditivity, of some of the parameters involved in constructing the force field. They fit fine for small molecules, but much less well for the systems here.

If indeed there is a nontransferability of parameters between simple alcohols and the hexoses herein described, it is a serious matter. One practical solution to the problem would be simply to construct a hexose force field,[25] independent of what we know about simple alcohols. But this is unsatisfactory on two levels. First, on the practical level, there are a whole spectrum of structures between simple alcohols and hexoses, and presumably one would need a whole spectrum of force fields to deal with such structures. More importantly, there is a matter of understanding what is happening.

The philosophy of MM3 force field development is that we start from fitting simple compounds, like simple hydrcarbons and simple alcohols, then we apply the force fields developed from simple molecules to large systems. When discrepancies for large systems appear, we try to understand the *physical* reasons and add necessary correction terms. In the case of simple alcohols and polyhydroxy aldehydes and ketones, one such term has to do with induced dipoles. While previous studies showed[27] that these were not very significant in relatively simple systems (containing one or two polar bonds), the number of dipoles in a hexose molecule is considerably larger, and the number of polarizable bonds is substantial, and the results of neglecting polarization might be considerable. Indeed, preliminary studies show that while the relative energies for anomeric pairs calculated with MM3 and B3LYP given in Table 1 have uniformly opposite signs, inclusion of the induced dipoles turns around all of the MM3 numbers, so that they qualitatively come into agreement with the B3LYP values. But the quantitative agreement is still poor. So while induced dipoles are important here, there is more to it than that.

MM3 was fit only to experimental data, mostly in solution for the anomeric effect, and to experimental gas-phase data for studies on alcohols, apart from hydrogen bonding which was studied at the MP2 level. In this sense, we would expect that MM3 would agree better with experimental results in solution than with the gas-phase quantum mechanical data. Indeed, as we noted in section E and Table 4, MM3 satisfactorily calculated the equilibrium compositions of the four cyclic forms of the hexoses in aqueous solution.

Conclusions

The potential energy surfaces of all eight D-aldohexoses and four D-ketohexoses have been extensively studied, employing quantum mechanical and molecular mechanical calculations. Anomeric preferences of the hydroxyls for axial positions were observed for all hexoses studied. Several stability factors determining the potential energy surface were examined and we found that the previously discussed Hassel−Ottar effect, the delta-two effect, and the cis−trans effect are not very important in determining the gas-phase potential energy surfaces of the cyclic hexoses. Instead, the anomeric effect and intramolecular hydrogen bonding effects dominate the potential energy surfaces. The most important finding in this study is that in the gas phase, furanose rings are the most stable forms for all of the hexoses except galactose, idose, psicose, and sorbose, in contrast to the general preference of pyranose rings in solution. The decrease of intramolecular hydrogen bonding stabilization in solution was found to be primarily responsible for the composition difference between the gas and solution phases.

It appears that the MM3 force field for carbohydrates, derived largely from data in condensed phases, gives good results in condensed phases.[29] It gives results that agree poorly with the quantum mechanical calculations, which are for the gas phase. A major source of error here would appear to be the extrapolation from the condensed to the gas phase. This should serve as a warning that quantum mechanically derived (gas phase) force fields may face a similar difficulty when extrapolated to condensed phases.

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Supporting Information Available: Twenty four tables containing the Cartesian coordinates and total energies from quantum mechanical calculations are available (80 pages, print/PDF). See any current masthead page for ordering and Web access instructions.

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