

An Investigation of the Relationship between Sweetness and Intramolecular Hydrogen-Bonding Networks in Hexuloses Using the Semiempirical Molecular Orbital Method, AM1

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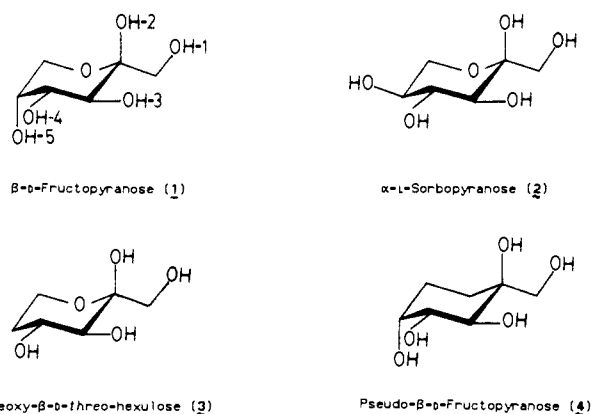
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Abstract: The AM1 optimized geometries and energies of the pyranoid forms of two naturally occurring sugars, D-fructose and L-sorbose, and of the synthetic derivatives, 5-deoxy-D-threo-hexulose (5-deoxyfructose) and the carbocyclic analogue of D-fructose (pseudo-D-fructose), provide an explanation for the relative sweetness of these compounds. A novel approach to predicting the global energy minima of monosaccharides is presented.

D-Fructose is the sweetest of the naturally occurring sugars¹ and crystallizes as the β -D-pyranose form in the ${}^2C_5(D)$ conformation.² Similarly, in aqueous solution β -D-fructopyranose (1) is the preponderant species and also exists in this conformation.³ Closely related to D-fructose is its C-5 epimer, namely L-sorbose, which adopts the α -L-pyranose form and the ${}^2C_5(L)$ conformation in the solid state⁴ and exists in aqueous solution³ almost exclusively as α -L-sorbopyranose (2). Despite the clear similarities of these two sugars, L-sorbose is markedly less sweet than D-fructose.⁵ It is generally accepted that O-5 in 1 or 2 is not involved in binding to the sweet taste receptor,^{5c,6,7} and early theories^{5c,6} to explain the lower sweetness of L-sorbose proposed that a hydrogen bond between HO-5 and O-6 could exist in D-fructose and could not exist in L-sorbose. The presence of the intramolecular hydrogen bond then might be responsible for releasing HO-2 and allowing it to interact with the sweet receptor in the case of D-fructose, whereas, in the case of L-sorbose, HO-2 would be inhibited by an intramolecular hydrogen bond to O-6.

In order to test this hypothesis the hydroxyl group at C-5 was removed to generate the synthetic derivative 5-deoxy-D-threo-hexulose (5-deoxyfructose) (3), which exists as the β -D-pyranose form in the ${}^2C_5(D)$ conformation in aqueous solution.⁸ This compound was found to be much sweeter than L-sorbose and nearly as sweet as D-fructose.⁸ Although the form shown (see chart I) is the preponderant one for D-fructose in aqueous solution, other isomers are also present, although to a lesser extent.^{3,9} The fructofuranoses are considered to be nearly void of sweet taste, and Shallenberger⁹ has rationalized this property as resulting from a lack of the required steric relation between the proton donor, proton acceptor, and hydrophobic bonding sites, which were believed to comprise the saporous unit in D-fructose. Of relevance is the recent observation¹⁰ that the carbocyclic analogue of β -D-fructopyranose (pseudo- β -D-fructopyranose, 4) was found to be nearly as sweet as D-fructose;¹¹ in contrast to D-fructose, 4 cannot mutarotenate and exists only in the conformation shown.

Chart I



We have reported^{12,13} earlier the results of ab initio calculations on 1 and 2 that were aimed at providing information about the electronic properties of these sugars, as part of a study concerned with a theory of sweetness. For each of these compounds, the anomeric hydroxyl group (HO-2) and O-1 had been identified as possible proton-donating (AH) and proton-accepting (B) groups, respectively; however, our results¹³ suggest that the assignment of groups to the AH,B system in the case of β -D-fructopyranose (1) should be reversed. Moreover, Birch et al.¹⁴ have suggested that the anomeric center of D-fructose may play no direct role in the sweet response; instead, the primary glycochore of D-fructopyranose may be the 3,4- α -glycol system. Until now no thorough study of the intramolecular interactions and their effects on the conformational preferences of hexuloses has been reported. In this paper we describe the results of such an investigation, which was undertaken in an effort to rationalize the different degrees of sweetness observed for compounds 1-4.

Any calculational method used in such a study has to meet several criteria, some of which are particularly unique to carbohydrates. Not only must the method reproduce the molecular geometries to a high degree of accuracy but also it must give reasonable values for the conformational, relative energies. Furthermore, the sugar ring conformation must be reproduced, and, most importantly, the intramolecular hydrogen bonds between adjacent hydroxyl groups must be predicted accurately, both geometrically and energetically.

While ab initio methods are in principle capable of meeting these requirements, it has been shown that hydrogen bonds are not well reproduced at the Hartree-Fock level unless a relatively

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large basis set is used in the calculation.¹⁵ Unfortunately, since we wished to perform, and indeed found it necessary to perform, full geometry optimizations on these molecules, the amount of computing time and memory required for ab initio calculations made them impractical. However, semiempirical methodologies offer a computationally accessible approach to the evaluation of the conformational preferences of sugars.

Methodology

Semiempirical methods have been criticized for their poor reproductions of ring geometries; MINDO/3¹⁶ and MNDO¹⁷ both underestimate the extent of the puckering in cyclohexane and related cyclic structures.^{18,19} It is also accepted that each of these methodologies fails to reproduce hydrogen bond geometries and energies.^{20,21} However, several methods which have been claimed to perform well on hydrogen-bonded systems have been published, including MINDO/3H,²² MNDO/H,²³ Goldblum's MNDO/H,²⁴ MNDO/M,²⁵ and AM1.²⁶ We have recently examined two of these, namely, MNDO/M and AM1, and the results of that study will be published separately.²⁷ While both MNDO/M and AM1 adequately predicted intermolecular hydrogen bonds in the complexations of the *N*-acetyl amides of L-asparagine and L-serine with water, only AM1 performed well in the case of the intramolecular hydrogen bonds present in β -D-fructopyranose. The primary reason for the poor performance of MNDO/M in regards to intramolecular hydrogen bonds in this case lies in the observation that MNDO/M, like its predecessor MNDO, significantly distorts the sugar ring toward planarity and creates unrealistically long hydrogen bond distances. On the basis of that preliminary work, we have performed all of the calculations in this paper by using AM1 at the restricted Hartree-Fock (RHF) level, employing the keywords PRECISE and PULAY (see ref 26b), in all calculations.

Geometry Selection

Carbohydrates present a unique problem to the choice of initial geometry for any calculation. The adjacent hydroxyl groups are sufficiently close to one another that each may be involved in intramolecular hydrogen bonding with its neighbor and/or possibly with the ring-oxygen atom. Furthermore, each hydroxyl group may act as a proton donor or a proton acceptor or both. Thus, in the case of hexuloses in the pyranoid form, not only do choices about the conformation of the ring have to be made but also the orientations of the hydroxymethyl and hydroxyl groups must be considered. In the case of pyranoses in the solid state, it is well-known that as many hydroxyl protons and oxygen atoms as possible are included in the hydrogen-bonding scheme;²⁸ however, even when this aspect is taken into account, the number of possible permutations of hydroxyl-group orientations is significant. Serrianni and Chipman,²⁹ in a recent ab initio study of furanose ring conformations, assumed that the orientation of the anomeric hydroxyl groups (HO-2 in 1-3) (see Chart I) would be controlled by the exo-anomeric effect.³⁰ We believe that this may not always

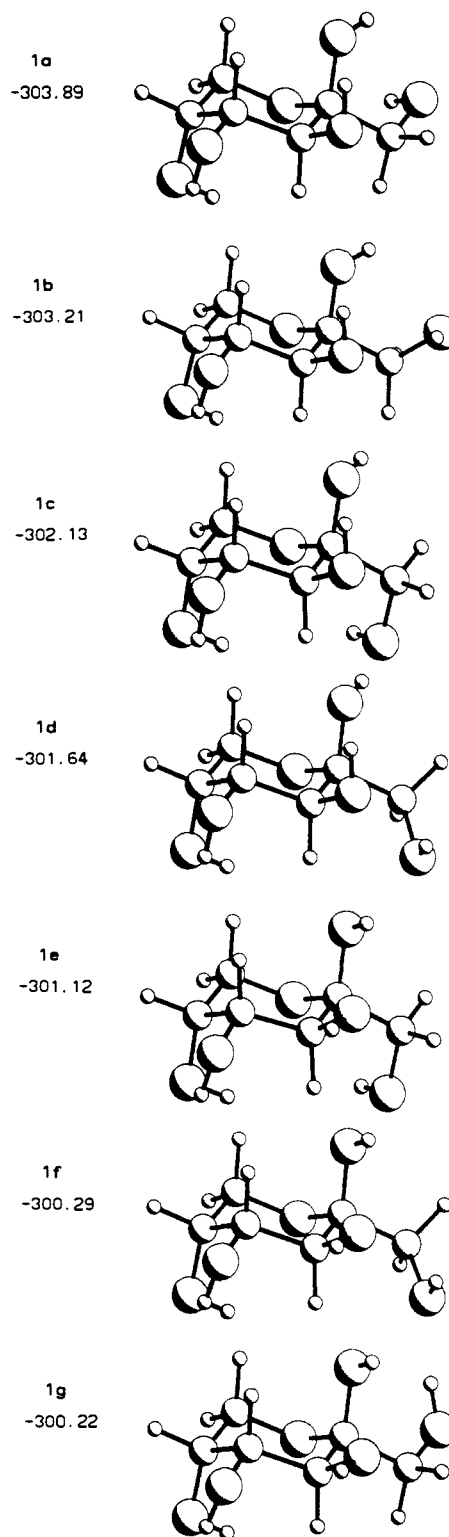


Figure 1. AM1 optimized geometries and heats of formation of β -D-fructopyranose (1). Structures are listed in order of increasing energy.

be the case, especially when the anomeric hydroxyl group participates in intramolecular hydrogen bonding.

In order to obtain an objective and independent starting point for these calculations, we chose to define the C-O-H bond angles, through the use of dummy atoms, as being linear. Also, standard bond lengths and angles³¹ and ideal torsion angles³² were employed

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(32) "Ideal torsion angles" refers to multiples of 60°.

to define the ring geometry. For each starting geometry the three staggered rotamers of the hydroxymethyl group (+gauche, G+; -gauche, G-; and antiperiplanar, AP; O-1 to O-2) were included. Optimization of these idealized starting geometries consistently led to low-energy conformations exhibiting high degrees of hydrogen bonding. In fact, manipulation of the hydroxyl groups in these optimized conformations followed by reoptimization, in attempts to examine other hydrogen bond patterns, led to higher energy conformations in all but one case.

This approach appears to generate global energy minima and allows for the examination of higher energy local minima.

Results

A. Global Energy Minima. In our preliminary report²⁷ of a comparison of the semiempirical methods MNDO/M and AM1, we indicated that optimization of the three idealized, starting geometries of **1** gave rise to structures **1a**, **1b**, and **1c** (see Figure 1). A more detailed discussion of the hydrogen bonds present in these conformations is now presented.

Rotamers **1a-c** differ noticeably only in the orientations of the hydroxymethyl group and, consequently, in the orientations of hydroxyl group HO-1. In each rotamer the secondary hydroxyl groups were predicted to form similar hydrogen bonds, namely, between HO-5 and O-6, HO-4 and O-5, and HO-3 and O-2. The anomeric hydroxyl group preferred to adopt the exo-anomeric orientation for all three of the rotamers. The hydrogen bond data are presented in Table I. The G+ conformation **1a** was calculated to be the most stable structure and, in addition to hydrogen bonds between the secondary hydroxyl groups, contained hydrogen bonds between HO-1 and O-6 and HO-2 and O-1. The energy of the G- conformation **1b** was found to be approximately 0.7 kcal/mol above that of **1a**. In **1b**, the hydroxymethyl group adopted an orientation such that HO-1 was hydrogen bonded to O-3, while HO-2 was hydrogen bonded to O-1, as in **1a**. In the third rotamer **1c** the hydroxymethyl group was oriented such that O-1 was AP to O-2, and, consequently, HO-2 could no longer form a hydrogen bond to O-1; HO-1 now formed a hydrogen bond to the ring oxygen atom, O-6. Conformation **1c** was the highest in energy, which was approximately 1.7 kcal/mol above that of **1a**. Conformations **1a** and **1b** were predicted to have the same number of hydrogen bonds, and the energy difference between them may be attributed to the fact that the G+ rotamer **1a** contains two stabilizing gauche effects³³ (between O-1 and O-2, and between O-1 and O-6), whereas the G- rotamer **1b** contains only one such interaction (between O-1 and O-2). Similarly, **1c** contains one gauche effect (between O-1 and O-6); however, **1c** also contains one fewer hydrogen bond than does either **1a** or **1b**.

Optimization of the idealized starting geometries of **2** gave rise to a G+ conformation **2a**, a G- conformation **2b**, and an AP conformation **2c**. Three hydrogen bonds were found to be common to all three rotamers of **2**: between HO-5 and O-4, HO-4 and O-3, and HO-3 and O-2. This pattern indicated a reversal of the hydrogen bonding involving O-4 and O-5, as compared to that in **1**. The hydrogen bond data for **2** are listed in Table II. The hydroxymethyl group and hydroxyl group HO-1, in **2**, adopted orientations completely analogous to those found for **1**. The lowest energy rotamer was calculated to be again the G+ conformation **2a**, while the G- rotamer **2b** was approximately 1.2 kcal/mol higher in energy. The AP rotamer **2c** was the highest energy structure, being approximately 1.7 kcal/mol higher in energy than **2a** (see Figure 2). As in **1**, hydroxyl group HO-2, in **2**, was found to prefer the exo-anomeric orientation in each of the three low-energy structures.

In **3**, the 5-deoxy analogue of **1** and **2**, the possibility of hydrogen bonding involving O-4 and O-5 does not exist, and optimization of the idealized rotamers of **3** gave rise to the low-energy conformers **3a**, **3b**, and **3c**. The hydrogen bond data for **3** are given in Table III. These conformers were found to exhibit hydrogen bonding between HO-4 and O-3 and between HO-3 and O-2,

Table I. Hydrogen Bond Distances (Å) and Angles (deg) for the AM1 Optimized Geometries of β -D-Fructopyranose (**1**)

conformation (heat of formation) ^a	D-H...A	D-H	D...A	H...A	\angle DHA
1a (-303.89)					
O-1-HO-1...O-6	0.967	2.820	2.491	99.73	
O-2-HO-2...O-1	0.969	2.784	2.275	111.78	
O-3-HO-3...O-2	0.967	2.786	2.472	98.63	
O-4-HO-4...O-5	0.968	2.805	2.354	107.76	
O-5-HO-5...O-6	0.967	2.939	2.490	108.22	
mean values	0.967	2.827	2.416	105.23	
1b (-303.21)					
O-1-HO-1...O-3	0.969	3.056	2.357	128.56	
O-2-HO-2...O-1	0.967	2.614	2.360	94.14	
O-3-HO-3...O-2	0.968	2.746	2.473	95.87	
O-4-HO-4...O-5	0.968	2.805	2.343	108.47	
O-5-HO-5...O-6	0.967	2.940	2.486	108.59	
mean values	0.968	2.832	2.404	107.13	
1c (-302.13)					
O-1-HO-1...O-6	0.967	2.699	2.331	101.72	
O-3-HO-3...O-2	0.967	2.747	2.425	98.96	
O-4-HO-4...O-5	0.968	2.816	2.377	106.98	
O-5-HO-5...O-6	0.967	2.930	2.488	107.64	
mean values	0.967	2.798	2.405	103.82	
1d (-301.64)					
O-1-HO-1...O-3	0.969	2.860	2.229	121.75	
O-3-HO-3...O-2	0.967	2.773	2.481	97.18	
O-4-HO-4...O-5	0.968	2.818	2.370	107.59	
O-5-HO-5...O-6	0.967	2.944	2.496	108.12	
mean values	0.968	2.849	2.394	108.66	
1e (-301.12)					
O-1-HO-1...O-6	0.966	2.702	2.355	100.38	
O-2-HO-2...O-3	0.967	2.741	2.248	110.52	
O-3-HO-3...O-4	0.967	2.934	2.499	107.14	
O-4-HO-4...O-5	0.968	2.798	2.298	111.19	
O-5-HO-5...O-6	0.968	2.904	2.446	108.64	
mean values	0.967	2.816	2.369	107.58	
1f (-300.29)					
O-1-HO-1...O-3	0.968	2.819	2.217	119.24	
O-2-HO-2...O-3	0.967	2.781	2.302	109.73	
O-3-HO-3...O-4	0.967	2.908	2.461	107.92	
O-4-HO-4...O-5	0.969	2.798	2.293	111.56	
O-5-HO-5...O-6	0.967	2.936	2.482	108.50	
mean values	0.968	2.849	2.351	111.39	
1g (-300.22)					
O-1-HO-1...O-2	0.968	2.767	2.239	113.15	
O-2-OH-2...O-3	0.967	2.778	2.288	110.46	
O-3-HO-3...O-4	0.968	2.910	2.457	108.32	
O-4-HO-4...O-5	0.969	2.801	2.296	111.54	
O-5-HO-5...O-6	0.967	2.934	2.474	108.97	
mean values	0.968	2.838	2.351	110.49	

^a Energies are in kcal/mol.

analogously to that found for the low-energy conformers of **2**. Hydrogen bonds involving the hydroxymethyl group in each of the G+ (**3a**), G- (**3b**), and AP (**3c**) rotamers were generated between HO-1 and O-6, HO-1 and O-3, and HO-1 and O-6 respectively. In each of these rotamers, the anomeric hydroxyl group, HO-2, preferred the exo-anomeric orientation, with the lowest energy structure being **3a**, followed by **3b**, which was 1.1 kcal/mol higher in energy, and then **3c**, whose energy was 1.8 kcal/mol above that of **3a** (see Figure 3).

In the case of pseudosugar **4**, structures **4g**, **4c**, and **4n**, corresponding to the G+, G-, and AP rotamers, respectively, were generated by optimization of the idealized starting geometries. These were not the lowest energy conformations found for this molecule. Manipulation of the hydroxyl group orientations in **4g**, **4c**, and **4n**, followed by full geometry optimization, indicated that there were several stable orientations for each hydroxyl group, many of which differed in energy by less than 0.5 kcal/mol (see

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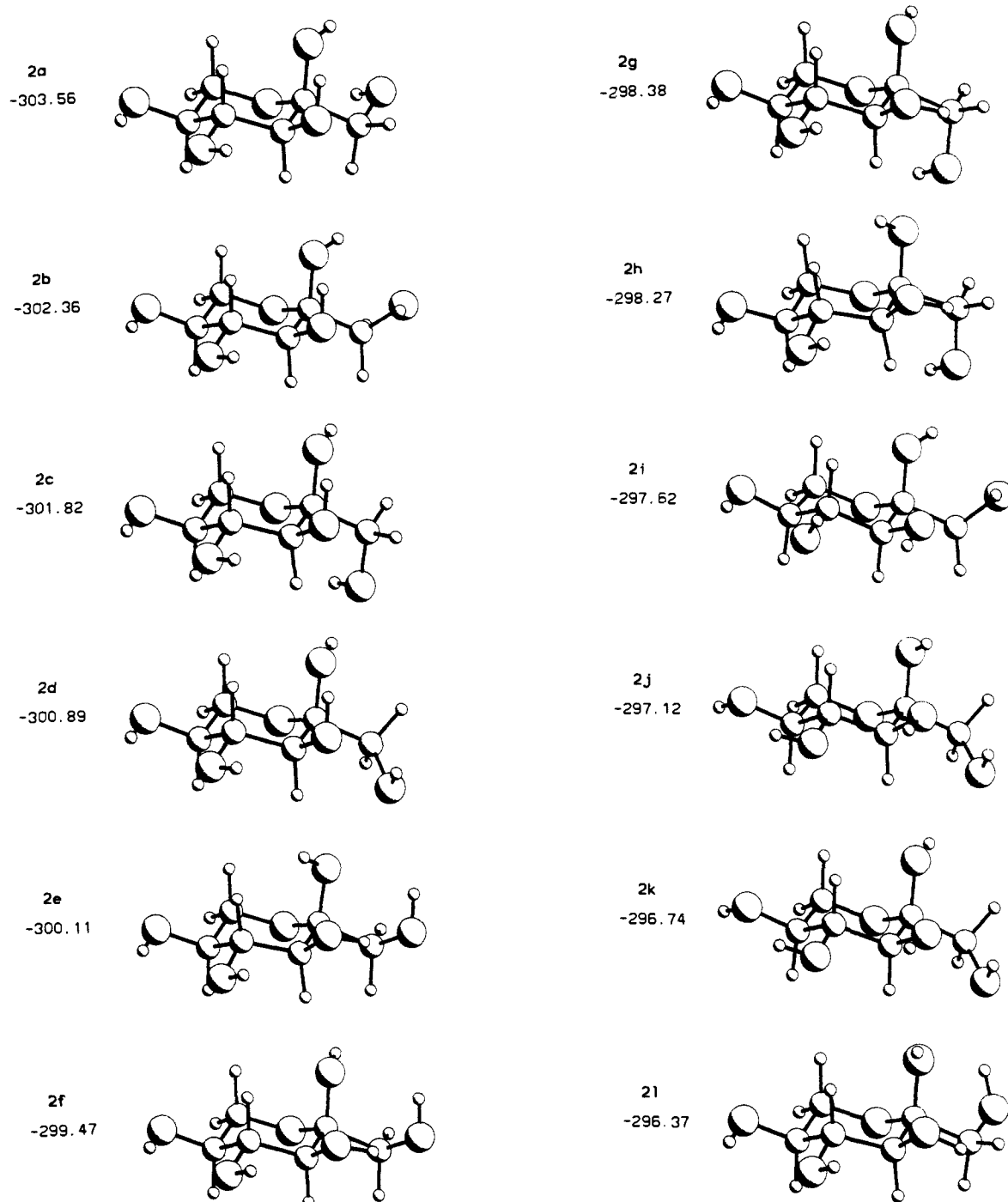


Figure 2. AM1 optimized geometries and heats of formation of α -L-sorbopyranose (2). Structures are listed in order of increasing energy.

Figure 4). In 4, hydroxyl group HO-2 no longer has the electronic and structural properties associated with an anomeric hydroxyl group³⁰ and may be expected to have properties similar to those of the secondary hydroxyl groups HO-3, HO-4, and HO-5. This structural aspect appeared to have the effect of lowering the energy differences between conformations in which O-1, O-2, and O-3 were involved in intramolecular hydrogen bonding. Furthermore, replacement of the ring-oxygen atom by a methylene group removed the stabilizing gauche interaction in the AP rotamer, a situation which would destabilize such rotamers as compared to G+ and G- structures. The subtle geometrical differences between the cyclohexyl and pyranoid ring systems were reflected in the average O...O distance between vicinal hydroxyl groups. On the basis of all of the conformations of 4 this distance was 2.805 Å; the corresponding value based on all of the conformations of structures 1-3 was 2.828 Å. The shorter O...O separations in 4 had the effect of increasing further the number of stable hydroxyl-group orientations in the case of 4 relative to the numbers

in the cases of 1, 2, and 3. Thus, for 4 optimization of the idealized geometries did not lead to global energy minima.

Despite the differing configurations at C-5 among compounds 1-3, in all cases the analogous rotamers resulting from the optimization of the idealized geometries were predicted to have the same hydrogen bond patterns involving O-1, O-2, and O-3. No significant differences in either the relative stabilities or geometries of the rotamers were found. Since O-1 and O-2 in each of 1-3 are believed^{5c-8} to be involved in the interaction with the sweet receptor, we concluded that the low sweetness of 2 relative to that of 1 or 3 is attributable presumably to conformations of these molecules of higher energy than those found by the optimization of the idealized geometries.

The single notable difference between 1 and 2 was found to be in the behavior of HO-4. In 1, HO-4 consistently preferred to form a hydrogen bond with O-5, rather than with O-3, and, hence, in 1, HO-3 might be able to form a hydrogen bond with O-4, a process requiring the breaking of only a hydrogen bond

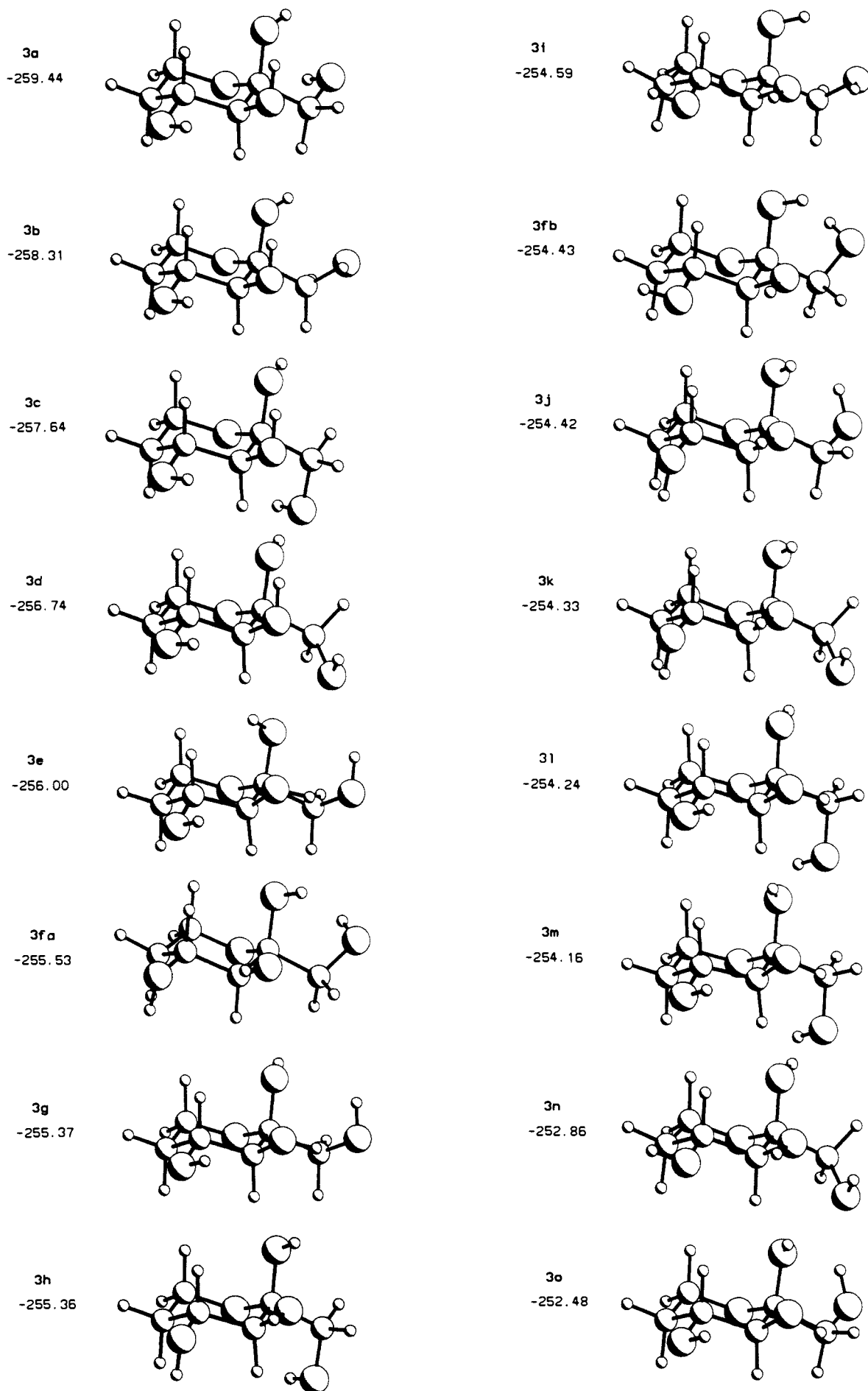


Figure 3. AM1 optimized geometries and heats of formation of 5-deoxy-D-threo-hexulose (3). Structures are listed in order of increasing energy.

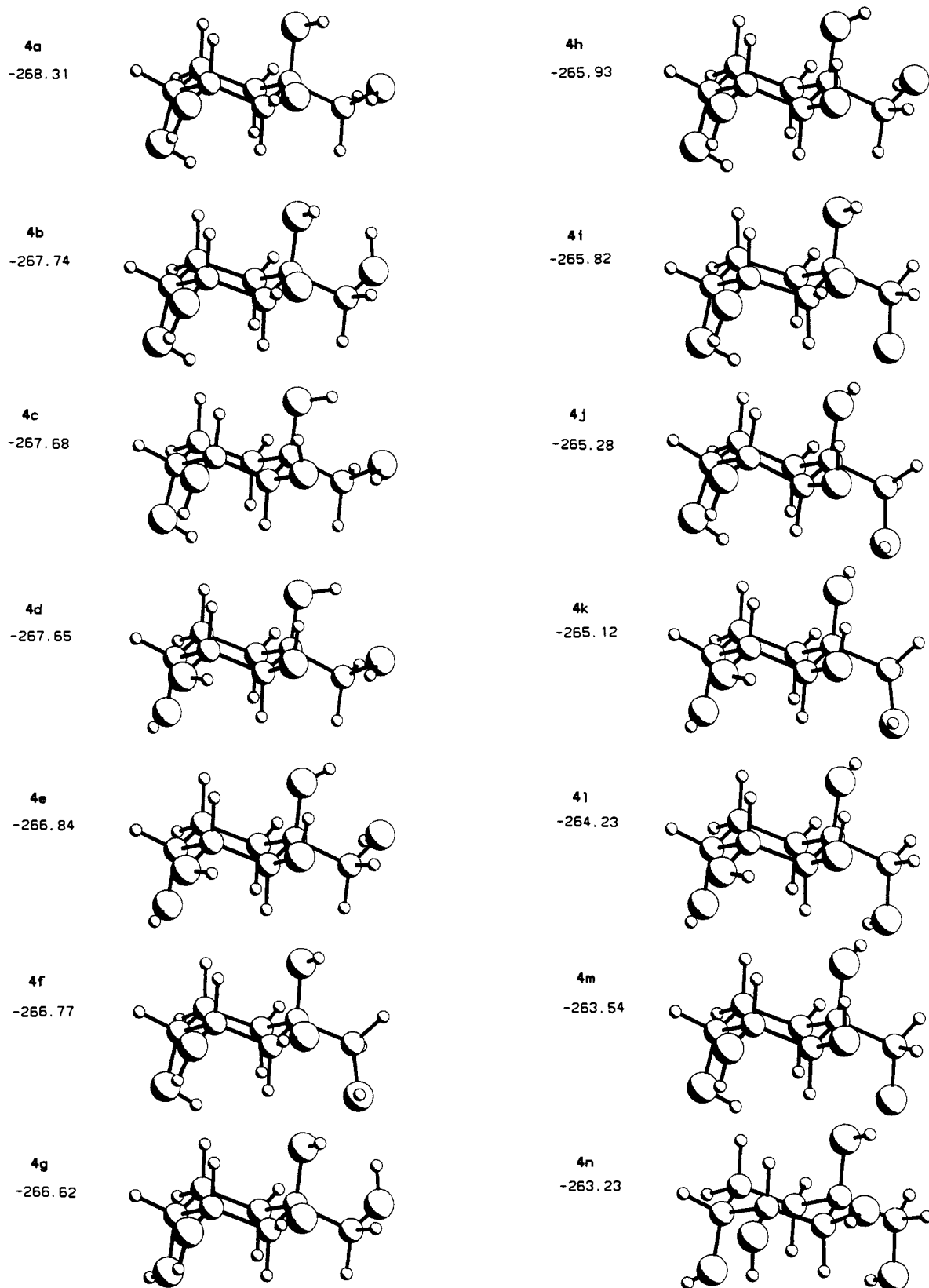


Figure 4. AM1 optimized geometries and heats of formation of pseudo- β -D-fructopyranose (4). Structures are listed in order of increasing energy.

between HO-3 and O-2. In such a case O-3 would be free to act as a hydrogen bond acceptor for HO-1 or HO-2 and, thus, could alter the preferred, low-energy orientation of HO-1 or HO-2. However, in 2, HO-4 consistently formed a hydrogen bond with O-3, and, consequently, in 2, HO-3 might not be able to form a hydrogen bond with O-4, in which case O-3 could not act as a hydrogen bond acceptor for HO-1 or HO-2. Thus, there might be higher energy conformations of 1 and 2 in which the orientations of HO-1 and HO-2 were not analogous, an aspect which

might rationalize, at least partly, the gustatory differences between 1 and 2. To test this hypothesis all of the possible permutations of hydrogen bonds among the hydroxyl groups of each rotamer of 1-4 were generated and fully optimized (see Figures 1-4). The starting geometries were chosen so as to maximize the number of intramolecular hydrogen bonds. In several cases different starting geometries collapsed to the same final geometry.

B. Local Energy Minima. No stable conformations of 1 were found in which HO-4 acted as an hydrogen bond donor in a

Table II. Hydrogen Bond Distances (Å) and Angles (deg) for the AM1 Optimized Geometries of α -L-Sorbosepyranose (**2**)

conformation (heat of formation) ^a	D-H...A	D-H	D...A	H...A	\angle DHA	conformation (heat of formation) ^a	D-H...A	D-H	D...A	H...A	\angle DHA
2a (-303.56)	O-1-HO-1...O-6	0.967	2.810	2.478	99.84	2g (-298.38)	O-1-HO-1...O-6	0.967	2.851	2.485	102.28
	O-2-HO-2...O-1	0.968	2.786	2.290	110.88		O-4-HO-4...O-3	0.967	2.845	2.449	104.22
	O-3-HO-3...O-2	0.968	2.762	2.322	106.75		O-5-HO-5...O-4	0.967	2.852	2.420	106.72
	O-4-HO-4...O-3	0.967	2.924	2.492	106.95		mean values	0.967	2.850	2.451	104.41
	O-5-HO-5...O-4	0.967	2.849	2.421	106.38	2h (-298.27)	O-1-HO-1...O-6	0.967	2.806	2.450	101.40
	mean values	0.967	2.826	2.401	106.16		O-2-HO-2...O-3	0.966	2.777	2.496	96.56
2b (-302.36)	O-1-HO-1...O-3	0.968	3.100	2.401	128.70		O-4-HO-4...O-3	0.967	2.896	2.514	103.48
	O-2-HO-2...O-1	0.967	2.616	2.400	91.81		O-5-HO-5...O-4	0.967	2.861	2.457	104.80
	O-3-HO-3...O-2	0.969	2.714	2.302	104.69		mean values	0.967	2.835	2.479	101.56
	O-4-HO-4...O-3	0.966	2.956	2.539	106.06	2i (-297.62)	O-1-HO-1...O-2	0.969	2.603	2.595	79.77
	O-5-HO-5...O-4	0.967	2.852	2.430	105.93		O-1-HO-1...O-3	0.969	3.105	2.425	126.96
	mean values	0.967	2.847	2.414	107.44		O-2-HO-2...O-1	0.968	2.603	2.322	95.76
2c (-301.82)	O-1-HO-1...O-6	0.967	2.742	2.350	103.48		O-3-HO-3...O-4	0.966	2.938	2.589	101.48
	O-3-HO-3...O-2	0.968	2.743	2.314	105.95		O-5-HO-5...O-4	0.967	2.864	2.454	105.19
	O-4-HO-4...O-3	0.967	2.927	2.486	107.62		mean values	0.968	2.823	2.477	101.83
	O-5-HO-5...O-4	0.967	2.847	2.418	106.40	2j (-297.12)	O-1-HO-1...O-3	0.967	2.791	2.192	118.82
	mean values	0.967	2.815	2.392	105.86		O-2-HO-2...O-3	0.966	2.777	2.290	110.27
2d (-300.89)	O-1-HO-1...O-3	0.968	2.851	2.230	120.89		O-3-HO-3...O-4	0.967	2.867	2.458	105.18
	O-3-HO-3...O-2	0.968	2.739	2.326	104.90		O-4-HO-4...O-5	0.967	2.857	2.432	106.20
	O-4-HO-4...O-3	0.967	2.932	2.494	107.36		mean values	0.967	2.823	2.343	110.12
	O-5-HO-5...O-4	0.967	2.848	2.426	106.01	2k (-296.74)	O-1-HO-1...O-3	0.968	2.745	2.150	118.32
	mean values	0.967	2.843	2.369	109.79		O-3-HO-3...O-4	0.967	2.851	2.407	107.49
2e (-300.11)	O-1-HO-1...O-2	0.968	2.701	2.337	101.45		O-4-HO-4...O-5	0.966	2.859	2.462	104.29
	O-2-HO-2...O-3	0.965	2.745	2.511	93.50		mean values	0.967	2.818	2.340	110.04
	O-3-HO-3...O-1	0.969	2.916	2.177	132.06	2l (-296.37)	O-1-HO-1...O-2	0.968	2.751	2.226	112.92
	O-4-HO-4...O-3	0.967	2.915	2.538	103.20		O-2-HO-2...O-3	0.966	2.794	2.281	112.26
	O-5-HO-5...O-4	0.967	2.863	2.459	104.81		O-4-HO-4...O-3	0.966	2.897	2.538	101.98
	mean values	0.967	2.828	2.404	107.00		O-5-HO-5...O-4	0.967	2.859	2.458	104.58
2f (-299.47)	O-1-HO-1...O-2	0.968	2.772	2.339	106.34		mean values	0.967	2.825	2.376	107.93
	O-3-HO-3...O-1	0.968	2.905	2.156	133.09						
	O-4-HO-4...O-3	0.967	2.852	2.457	104.17						
	O-5-HO-5...O-4	0.967	2.850	2.415	106.81						
	mean values	0.967	2.844	2.342	112.60						

^a Energies are in kcal/mol.

hydrogen bond with O-3, either with or without a hydrogen bond between HO-5 and O-4. In all cases, upon optimization, the hydroxyl groups in **1** rotated so as to generate hydrogen bonds between HO-4 and O-5 and between HO-5 and O-6. In several cases, attempts to find stable "anti-exo-anomeric"³⁴ orientations of HO-2 yielded only the orientations preferred by the exo-anomeric effect. The presence of the anti-exo-anomeric orientation of HO-2 in structures **1e-g** indicated that this orientation existed by virtue of a hydrogen bond between HO-2 and O-3. In these structures O-4 acted as a proton acceptor in a hydrogen bond with HO-3. Further stabilization for the anti-exo-anomeric orientation of HO-2, in the G⁺ rotamer **1g**, was provided through the formation of a hydrogen bond between HO-1 and O-2.

The anti-exo-anomeric conformations, **1e**, **1f**, and **1g**, are approximately 1.0, 1.4, and 3.7 kcal/mol higher in energy than the corresponding exo-anomeric rotamers, **1c**, **1d**, and **1a**, respectively. A comparison of the energies of **1c** and **1e** and of **1d** and **1f** indicated that a destabilization corresponding to only 1-1.5 kcal/mol occurred when HO-2 adopted the anti-exo-anomeric orientation. A comparison of **1c** and **1d** led to an estimate of 0.5 kcal/mol as the energy lost in the breaking of a hydrogen bond

between HO-1 and the ring-oxygen atom, O-6, and the forming of one between HO-1 and O-3.

Of the conformations calculated for **2**, all but **2j** and **2k** exhibited a preference for the formation of hydrogen bonds between HO-5 and O-4 and between HO-4 and O-3. This reversal of the hydrogen bond pattern in **2j** and **2k** resulted in a destabilization of these conformations by approximately 4 kcal/mol, as compared to the corresponding low-energy rotamer **2d**.

The AP rotamers, **2c** and **2d**, differed by approximately 1 kcal/mol, a feature which represents the net destabilization induced by the breaking of a hydrogen bond between HO-1 and O-6 in the case of **2c** and the forming of one between HO-1 and O-3 in the case of **2d**. This energy difference was larger than that calculated for a similar reorganization of hydrogen bonds in **1** and may be reflective of the fact that in **1d** O-3 may be able to function more effectively as a hydrogen bond acceptor with HO-1 than it may in **2d**.

Four conformers of **2** were found in which the anomeric hydroxyl group, HO-2, did not exist in the exo-anomeric orientation, namely, **2e**, **2h**, **2j**, and **2l**. Conformers **2e** and **2l** were generated from the G⁻ and G⁺ rotamers of the hydroxymethyl group, respectively, while in conformers **2h** and **2j** the hydroxymethyl group adopts an AP orientation. The torsion angles between atoms HO-2-O-2-C-2-O-6 in **2e**, **2h**, and **2l** were unusually small, having an average value of 113° as compared to 164° for conformers **1e-g**. This angular distortion may be due, in part, to a repulsive

(34) The term "anti-exo-anomeric" is used to indicate that the anomeric hydroxyl proton (HO-2) adopts a torsion angle with respect to the ring-oxygen atom (O-6) of approximately 180°, as compared to the exo-anomeric orientation, in which this torsion angle is approximately 60°.

Table III. Hydrogen Bond Distances (Å) and Angles (deg) for the AM1 Optimized Geometries of 5-Deoxy-β-D-threo-hexulose (3)

conformation (heat of formation) ^a	D-H...A	D-H	D...A	H...A	∠DHA	conformation (heat of formation) ^a	D-H...A	D-H	D...A	H...A	∠DHA
3a (-259.44)	O-1-HO-1...O-6	0.967	2.804	2.467	100.15	3g (-255.37)	O-1-HO-1...O-2	0.968	2.769	2.325	107.12
	O-2-HO-2...O-1	0.968	2.789	2.293	110.87		O-3-HO-3...O-1	0.968	2.901	2.163	131.90
	O-3-HO-3...O-2	0.968	2.762	2.325	106.60		O-4-HO-4...O-3	0.967	2.842	2.432	105.10
	O-4-HO-4...O-3	0.967	2.916	2.469	107.91		mean values	0.968	2.837	2.307	114.71
	mean values	0.967	2.818	2.389	106.38	3h (-255.36)	O-1-HO-1...O-6	0.967	2.731	2.354	102.46
3b (-258.31)	O-1-HO-1...O-3	0.968	3.092	2.388	129.16		O-2-HO-2...O-3	0.967	2.751	2.267	109.94
	O-2-HO-2...O-1	0.966	2.617	2.406	91.56		O-3-HO-3...O-4	0.967	2.914	2.460	108.44
	O-3-HO-3...O-2	0.968	2.717	2.308	104.44		mean values	0.967	2.799	2.360	106.95
	O-4-HO-4...O-3	0.967	2.939	2.502	107.32	3i (-254.59)	O-1-HO-1...O-3	0.968	2.855	2.179	125.78
	mean values	0.967	2.841	2.401	108.12		O-2-HO-2...O-1	0.968	2.754	2.217	113.85
3c (-257.64)	O-1-HO-1...O-6	0.967	2.742	2.341	104.13		O-2-HO-2...O-3	0.968	2.818	2.772	82.72
	O-3-HO-3...O-2	0.967	2.745	2.319	105.78		O-3-HO-3...O-4	0.967	2.853	2.411	107.38
	O-4-HO-4...O-3	0.967	2.916	2.459	108.68		mean values	0.968	2.827	2.395	107.43
	mean values	0.967	2.801	2.373	106.19	3j (-254.42)	O-1-HO-1...O-2	0.968	2.773	2.235	113.97
3d (-256.74)	O-1-HO-1...O-3	0.968	2.852	2.222	121.63		O-2-HO-2...O-3	0.967	2.768	2.284	110.02
	O-3-HO-3...O-2	0.967	2.739	2.329	104.68		O-3-HO-3...O-4	0.968	2.904	2.437	109.32
	O-4-HO-4...O-3	0.967	2.919	2.465	108.49		mean values	0.968	2.815	2.319	111.10
	mean values	0.968	2.837	2.339	111.60	3k (-254.33)	O-1-HO-1...O-3	0.967	2.790	2.195	118.57
3e (-256.00)	O-1-HO-1...O-2	0.968	2.705	2.335	101.82		O-2-HO-2...O-3	0.966	2.764	2.285	109.69
	O-2-HO-2...O-3	0.965	2.745	2.493	94.61		O-3-HO-3...O-4	0.967	2.902	2.445	108.56
	O-3-HO-3...O-1	0.969	2.906	2.172	131.44		mean values	0.967	2.819	2.308	112.27
	O-4-HO-4...O-3	0.967	2.897	2.501	104.43	3l (-254.24)	O-1-HO-1...O-6	0.967	2.850	2.472	103.04
	mean values	0.967	2.813	2.375	108.07		O-4-HO-4...O-3	0.967	2.831	2.422	105.02
3fa (-255.53)	O-1-HO-1...O-2	0.967	2.579	2.476	85.01		mean values	0.967	2.840	2.447	104.03
	O-1-HO-1...O-6	0.967	3.128	2.822	99.34	3m (-254.16)	O-1-HO-1...O-6	0.967	2.830	2.471	101.71
	O-2-HO-2...O-1	0.967	2.579	2.426	87.89		O-2-HO-2...O-3	0.967	2.802	2.322	109.84
	O-2-HO-2...O-3	0.967	2.808	2.577	93.53		O-4-HO-4...O-3	0.967	2.885	2.489	104.33
	O-3-HO-3...O-4	0.968	2.894	2.406	110.72		mean values	0.967	2.839	2.427	105.29
	mean values	0.967	2.798	2.541	95.30	3n (-252.86)	O-1-HO-1...O-3	0.968	2.772	2.157	120.06
3fb (-254.43)	O-1-HO-1...O-2	0.967	2.576	2.463	85.62		O-3-HO-3...O-4	0.967	2.837	2.389	107.71
	O-1-HO-1...O-6	0.967	3.130	2.823	99.39		mean values	0.968	2.804	2.273	113.89
	O-2-HO-2...O-1	0.967	2.576	2.452	86.23	3o (-252.49)	O-1-HO-1...O-2	0.968	2.758	2.224	113.62
	O-2-HO-2...O-3	0.967	2.798	2.541	95.10		O-2-HO-2...O-3	0.966	2.800	2.270	113.52
	O-3-HO-3...O-4	0.967	2.854	2.423	106.64		O-4-HO-4...O-3	0.966	2.880	2.500	103.25
	mean values	0.967	2.787	2.540	94.60		mean values	0.967	2.813	2.331	110.13

^aEnergies are in kcal/mol.

interaction between HO-2 and HO-3 in the case of **2**, despite the presence of a hydrogen bond between HO-2 and O-3. An examination of **2e**, in which O-1 adopted the G⁻ orientation, indicated that hydrogen bonding between HO-1 and O-2 generated the most distorted torsion angle (103°), while in **2l**, in which O-1 adopted the G⁺ orientation, the torsion angle was the least distorted (136°). The relative energies of **2e**, **2h**, **2j**, and **2l**, when compared to the energies corresponding low-energy exo-anomeric rotamers, **2b**, **2c**, **2d**, and **2a**, were found to be 2.2, 3.5, 3.8, and 7.2 kcal/mol, respectively. The fraction of the energy responsible for the destabilization of conformers **2e**, **2h**, and **2k** attributable to the absence of an exo-anomeric effect may be compensated for by the stabilization gained through the formation of a hydrogen bond between HO-2 and O-3. This hypothesis is supported by the observation that there is a small energy difference between rotamers **2g** and **2h**, which differ only in the orientation of HO-2. Moreover, conformer **2j**, in which HO-2 adopts an anti-exo-anomeric orientation, is approximately 0.4 kcal/mol more stable than the corresponding exo-anomeric rotamer **2k**. Thus, most of

the destabilization of the conformers of **2** having the anti-exo-anomeric orientations may arise from the reorganization of hydrogen bonds between O-2, O-3, and O-4 in these conformers.

On the basis of the above results, the observation that **1** and **2** differed in the nature of the interaction between HO-4 and O-3 may be further generalized. In **1** the ability of HO-4 to act as a hydrogen bond acceptor translated into a stabilization of conformations containing hydrogen bonds between HO-3 and O-4. This feature in turn allowed HO-2 to adopt anti-exo-anomeric orientations that were stabilized by hydrogen bonding between HO-2 and O-3. However, in **2**, the preference of HO-4 to act as a proton donor in a hydrogen bond with O-3 limited the ability of O-3 to act as a proton acceptor in a hydrogen bond with HO-2. While stable conformations of **2** were found in which HO-2 was hydrogen bonded to O-3, they were less stable energetically than similar conformations of **1**.

Removal of the hydroxyl group at C-5 in either **1** or **2** generates the sweet, synthetic deoxy sugar **3**. Since **3** is closely related to both **1** and **2**, it might be expected to adopt conformations present

Table IV. Hydrogen Bond Distances (Å) and Angles (deg) for the AM1 Optimized Geometries of Pseudo- β -D-Fructopyranose (4)

conformation (heat of formation) ^a	D-H...A	D-H	D...A	H...A	\angle DHA	conformation (heat of formation) ^a	D-H...A	D-H	D...A	H...A	\angle DHA
4a (-268.31)	O-1-HO-1...O-3	0.967	2.792	2.128	124.44	4g (-266.62)	O-1-HO-1...O-2	0.967	2.779	2.297	109.82
	O-2-HO-2...O-1	0.969	2.728	2.251	109.18		O-2-HO-2...O-3	0.967	2.768	2.287	109.74
	O-2-HO-2...O-3	0.969	2.799	2.511	96.97		O-3-HO-3...O-4	0.967	2.846	2.356	110.73
	O-3-HO-3...O-4	0.968	2.826	2.320	111.78		O-4-HO-4...O-5	0.967	2.771	2.315	108.03
	O-4-HO-4...O-5	0.968	2.797	2.292	111.63		mean values	0.967	2.791	2.314	109.58
	mean values	0.968	2.788	2.300	110.80		4h (-265.93)	O-2-HO-2...O-1	0.968	2.771	2.240
4b (-267.74)	O-1-HO-1...O-2	0.967	2.780	2.303	109.51	O-3-HO-3...O-2		0.967	2.775	2.439	99.97
	O-2-HO-2...O-3	0.968	2.768	2.286		O-4-HO-4...O-5		0.967	2.805	2.364	107.07
	O-3-HO-3...O-4	0.968	2.840	2.347	110.89	mean values		0.967	2.784	2.348	106.81
	O-4-HO-4...O-5	0.968	2.793	2.284		4i (-265.82)	O-2-HO-2...O-3	0.968	2.752	2.280	109.04
mean values	0.968	2.795	2.305	110.50	O-3-HO-3...O-4		0.967	2.846	2.367	109.98	
4c (-267.68)	O-1-HO-1...O-3	0.968	2.776	2.120	123.62		O-4-HO-4...O-5	0.968	2.793	2.289	111.51
	O-2-HO-2...O-1	0.969	2.740	2.180	115.50		mean values	0.968	2.797	2.312	110.18
	O-3-HO-3...O-2	0.966	2.839	2.705	87.90	4j (-265.28)	O-1-HO-1...O-3	0.968	3.018	2.407	120.73
	O-3-HO-3...O-4	0.966	2.832	2.811	81.37		O-3-HO-3...O-2	0.967	2.814	2.522	97.31
O-4-HO-4...O-5	0.968	2.817	2.362	108.10	O-4-HO-4...O-5		0.968	2.797	2.349	107.58	
mean values	0.967	2.800	2.445	103.30	mean values		0.967	2.876	2.426	108.54	
4d (-267.65)	O-1-HO-1...O-3	0.968	2.810	2.167	122.72	4k (-265.12)	O-1-HO-1...O-3	0.968	2.977	2.329	123.69
	O-2-HO-2...O-1	0.968	2.733	2.195	113.85		O-3-HO-3...O-2	0.967	2.801	2.372	106.24
	O-3-HO-3...O-2	0.968	2.773	2.351	105.64		O-4-HO-4...O-3	0.967	2.852	2.361	110.82
	O-4-HO-4...O-3	0.967	2.868	2.393	109.74		O-5-HO-5...O-4	0.967	2.762	2.302	108.28
	O-5-HO-5...O-4	0.967	2.771	2.324	107.38		mean values	0.967	2.848	2.341	112.26
	mean values	0.967	2.791	2.286	111.87		4l (-264.23)	O-3-HO-3...O-2	0.967	2.752	2.303
4e (-266.84)	O-2-HO-2...O-1	0.967	2.770	2.251	112.50	O-4-HO-4...O-3		0.967	2.859	2.376	110.29
	O-3-HO-3...O-2	0.968	2.766	2.309	107.99	O-5-HO-5...O-4		0.967	2.766	2.300	108.68
	O-4-HO-4...O-3	0.967	2.853	2.373	110.04	mean values		0.967	2.792	2.326	108.79
	O-5-HO-5...O-4	0.967	2.768	2.314	107.86	4m (-263.54)	O-3-HO-3...O-2	0.967	2.755	2.430	99.23
mean values	0.967	2.789	2.312	109.60	O-4-HO-4...O-5		0.967	2.809	2.377	106.47	
4f (-266.77)	O-1-HO-1...O-3	0.967	2.934	2.323	120.46		mean values	0.967	2.782	2.403	102.85
	O-2-HO-2...O-3	0.967	2.809	2.356	107.98		4n (-263.23)	O-2-HO-2...O-3	0.968	2.756	2.293
	O-3-HO-3...O-4	0.968	2.832	2.330	111.51	O-3-HO-3...O-4		0.967	2.876	2.411	109.14
	O-4-HO-4...O-5	0.968	2.796	2.290	111.70	O-5-HO-5...O-4		0.964	2.813	2.663	88.83
mean values	0.968	2.843	2.325	112.91	mean values	0.966		2.815	2.456	102.12	

^aEnergies are in kcal/mol.

in both **1** and **2**. This aspect was indeed found to be the case. The hydrogen bond found between HO-4 and O-3 in **3** was similar to the hydrogen bonds observed in the rotamers of **2** corresponding to the global energy minima. However, unlike the conformations found for **2**, low-energy conformations of **3** were found (**3e**, **3f**, **3h-k**) in which the anomeric hydroxyl group adopted the anti-exo-anomeric orientation. These conformations were stabilized by the presence of a hydrogen bond between HO-2 and O-3 in a manner completely analogous to that seen for both **1** and **2**. The relative energies of these anti-exo-anomeric conformers were in the region 2.2-3.9 kcal/mol above those of the corresponding exo-anomeric rotamers. Furthermore, the anti-exo-anomeric conformer **3e** is approximately 0.6 kcal/mol more stable than the analogous exo-anomeric conformer **3g**.

It appeared that, without the influence of an hydroxyl group at C-5, the hydrogen bonding between HO-4 and O-3 could be readily reorganized so as to allow the formation of an hydrogen bond between HO-2 and O-3.³⁵ In those conformations of **3** in

which O-4 acted as an acceptor atom in an hydrogen bond with HO-3, HO-4 adopted two stable orientations, for example, see **3fa** and **3fb**. These conformers differ in energy by approximately 1.1 kcal/mol, a value representing the difference in energy between tetrahedral and planar, hydrogen bond coordination to O-4. Although both of these types of coordination have been shown to be statistically, equally likely in the solid state,^{36,37} gas-phase results indicate a preference for tetrahedral coordination.³⁸ In the anti-exo-anomeric rotamers **3fa**, **3h**, **3j**, and **3k**, tetrahedral coordination to O-4 was calculated to be more stable than planar coordination by an average value of 1.2 kcal/mol, whereas, planar coordination to O-4 was preferred for the exo-anomeric rotamers **3i** and **3n**.

The presence of stable conformations of **3** in which HO-2 adopts an anti-exo-anomeric orientation, having relative energies similar to those found for **1**, suggested that an anti-exo-anomeric orientation of HO-2 may be pertinent to the sweetness of hexuloses.

In the case of **4**, the results of the optimizations may be summarized as follows. Hydrogen bonding between HO-4 and O-5

(35) This reorganization might be expected to require less energy than was required in the case of **2** on the basis that the stabilization due to the cooperative effect in **3** would be smaller than in **2** (see ref 28).

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may involve either tetrahedral or planar coordination to O-5, the former usually being preferred by approximately 1.1 kcal/mol. When a hydrogen bond was present between HO-4 and O-5, hydroxyl group HO-2 adopted an "anti-exo-anomeric"³⁹ orientation, thereby generating a chain of hydrogen bonds extending between HO-2 and O-3, HO-3 and O-4, and HO-4 and O-5. This hydrogen bond pattern led to the lowest energy structures. Alternatively, when HO-5 formed a hydrogen bond with O-4, a network of hydrogen bonds was generated between HO-5 and O-4, HO-4 and O-3, and HO-3 and O-2. This latter situation was less stable (by approximately 1 kcal/mol) than the former pattern and required that HO-2 adopt the "exo-anomeric" orientation.

In the high-energy structure **4n**, O-4 acted as a proton acceptor in hydrogen bonds with both HO-5 and HO-3, generating a three-center hydrogen bond.

Conclusions

The differences between the conformational preferences of **4** and **1-3** arise primarily from two factors. Firstly, replacement of O-6 by a methylene group subtly alters the ring geometry, and, secondly, the absence of the exo-anomeric effect changes the geometrical preferences of HO-2. In **4** the preference for HO-2 to adopt an "anti-exo-anomeric" orientation is attributable to the lack of an exo-anomeric effect as well as to the presence of an

(39) In a pseudosugar there is no ring-oxygen atom, and the terms anti-exo-anomeric and exo-anomeric are used simply for ease of comparison between **4** and the other structures.

interaction between HO-2 and O-3.

In each of the sweet compounds, **1**, **3**, and **4**, low-energy conformations were found to exist in which HO-2 was hydrogen bonded to O-3. This anti-exo-anomeric orientation of HO-2 was less favored energetically in the case of the less sweet sugar **2**. While hydroxyl group HO-2 traditionally is believed to act as a proton donor in a hydrogen bond with the sweet receptor, previous work by us¹³ has suggested that HO-2 may function as a proton acceptor (see also ref 40). As such, it must be capable of adopting orientations in which the hydroxyl proton is directed away from the proton-donor functionality of the receptor. On the basis of the geometry of the tripartite receptor,⁴¹ HO-2 might act most effectively as a proton acceptor when it adopts an anti-exo-anomeric orientation. Thus, the ability of HO-2 to adopt an anti-exo-anomeric orientation may be related to the strength of the binding between the sweet molecule and the sweet receptor, and hence, may be pertinent to the sweetness of the molecule.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for the award of grants (to W.A.S. and V.H.S.) and a scholarship (to R.J.W.).

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Atomic Polarizability and Electronegativity

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Received October 26, 1989

Abstract: A close relationship between atomic polarizability and electronegativity is demonstrated. It is shown how atomic polarizability can be used in conjunction with the number of s and p valence electrons to derive electronegativities interpreted as either valence electron densities or the electrostatic force exerted on valence electrons. This leads to a new set of electronegativities for every element in the periodic table that can be easily calculated and understood. Such values are in substantially better agreement with traditional Pauling values than those derived as the average of ionization energy and electron affinity. It is further demonstrated that traditional or chemical electronegativities are more closely related to the density functional definition of hardness than to the corresponding definition of electronegativity. This approach offers promise to ongoing theoretical efforts to delineate the role of electronegativity in chemical bonding.

The concept of electronegativity as first proposed by Pauling has become an indispensable tool for all chemists and is also used in physics, biology, and geology.¹ Despite the many variations and extensions of this basic idea, Pauling's original definition as "the power of an atom in a molecule to attract electrons to itself"^{1f} continues to find widespread acceptance. Even the actual numerical values are still widely used and cited.¹

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This appeal reflects the continuing efforts of chemists to view matter from a discrete, atomic perspective.² To be able to understand properties and reactivities of not only isolated molecules but liquids and solids as well in terms of a single number characteristic of each element is unquestionably useful and attractive. The use of electronegativities to understand bond energy differences is widely appreciated.^{1,3} However, there are many other important uses as well. For example, a striking dependence of the superconducting transition temperature on electronegativity is found for both solid elements⁴ and the new high-temperature superconductors.⁵ Further, the theoretical underpinning recently

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