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An AM1 molecular orbital study of α-D-glucopyranose and β-maltose: Evaluation and implications

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ABSTRACT

Chemical reactivity and other characteristics of α-D-glucopyranose and β-maltose were evaluated within a semiempirical molecular orbital (AM1) framework. Theoretically generated structures compared well to those determined by X-ray crystallographic techniques. Calculations suggested that the secondary hydroxy functions (OH-2 and OH-3) of the mono- and di-saccharides were more acidic than the primary alcohol (OH-6), which is consistent with experimental findings. In addition, the enhanced reactivity of the OH-3 locus, which is observed upon OH-2 alkylation of the object sugars, was rationalized in terms of increased OH-3 acidity. The chemical behavior of the monomers examined may be insightful in explaining the reactivity of glucopyranose polymers.

INTRODUCTION

Chemically modified glucopyranose polymers and oligomers represent an important class of carbohydrates with multifarious applications. Alkylated and hydroxyalkylated celluloses and starches have found suitability in many biomedical and food science areas[1–7]. Glucopyranose oligomers such as cyclomaltoheptaose (β-cyclodextrin) and its methylated and hydroxypropylated derivatives have been used as solubilizing pharmaceutical excipients by virtue of the ability of these cone-shaped molecules to form soluble inclusion complexes with drugs and other agents[8–12]. In all cases mentioned, the parent structures are subjected to chemical manipulation through etherification to provide the desired commodity. In most circumstances, it is not advantageous to peralkylate the polymer, meaning that randomly substituted glucopyranose copolymers are obtained whose properties are

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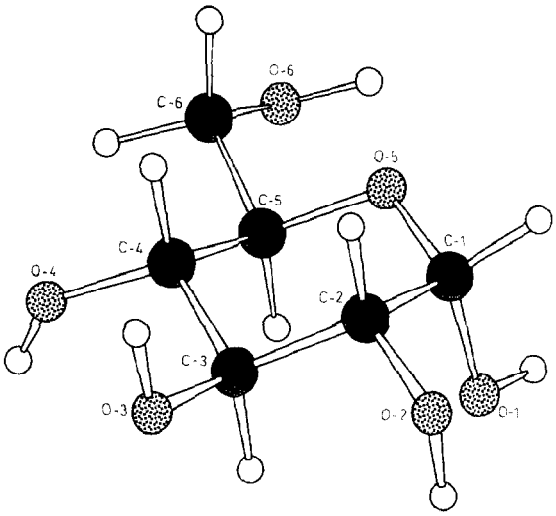


Fig. 1. AM1-generated structure of α-D-glucopyranose with relevant numberings.

dependent on both the degree and nature of the substitution[13]. Interestingly, classical models describing glucose biopolymeric reactivity consider the glucose residues as independent components suggesting that a study of the monomers may shed light on the polymers. To this end, α-D-glucose, as well as the dimer,

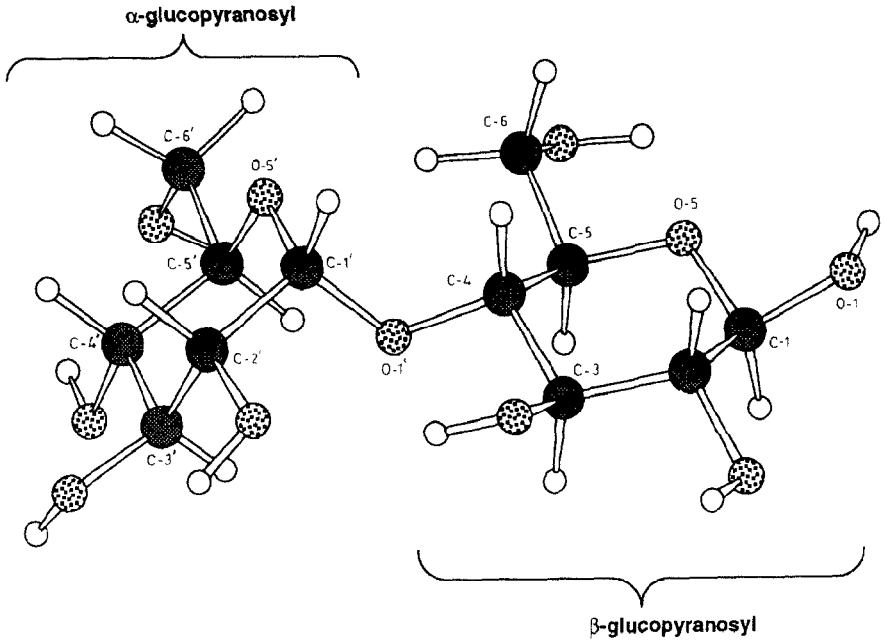


Fig. 2. AM1-generated structure of β-maltose (α- and β-glucopyranosyl residues) with relevant numberings.

β-maltose, were examined within the theoretical framework of the AM1 semiempirical all-valence electron molecular orbital technique[14,15]. The results obtained were then discussed, not only as they apply to the monomers and dimers examined, but also in the context of glucopyranose polymers.

METHODS

Molecular calculations were performed using the AM1 semiempirical molecular orbital approximation installed on a Tektronix CAChe® (Version 2.7) workstation, a reactivity modeling system designed around the Apple Macintosh. Initial structures were generated using the resident templates in the CAChe® molecular

TABLE I

Geometric parameters for AM1-generated and X-ray structures of α-D-glucopyranose and the α- and β-glucopyranosyl residues of β-maltose

	α-D-Glucopyranose		β-Maltose			
			α-Glucopyranosyl		β-Glucopyranosyl	
Bond length (Å)	X-ray	AM1	X-ray	AM1	X-ray	AM1
C-1–C-2	1.539	1.542	1.535	1.523	1.531	1.541
C-2–C-3	1.529	1.537	1.524	1.534	1.529	1.537
C-3–C-4	1.523	1.533	1.523	1.538	1.526	1.538
C-4–C-5	1.534	1.536	1.527	1.536	1.534	1.534
C-5–O-5	1.431	1.432	1.434	1.432	1.423	1.427
O-5–C-1	1.430	1.412	1.403	1.414	1.419	1.424
C-1–O-1	1.400	1.408	1.414	1.414	1.389	1.405
C-5–C-6	1.517	1.531	1.516	1.534	1.518	1.532
Bond angle						
C-1–C-2–C-3	111.1	109.3	109.7	109.5	108.8	109.8
C-2–C-3–C-4	109.8	108.5	107.0	108.9	109.8	111.3
C-3–C-4–C-5	111.1	108.7	110.2	109.7	108.7	109.7
C-4–C-5–C-6	111.5	111.1	111.7	111.3	113.8	113.1
O-5–C-1–C-2	110.1	113.8	110.2	111.9	111.1	112.0
O-6–C-6–C-5	109.9	111.2	111.0	110.3	111.0	105.0
O-2–C-2–C-3	112.2	112.4	111.5	111.8	109.2	109.5
O-3–C-3–C-4	110.6	111.9	106.7	111.4	107.1	110.9
Dihedral angle						
C-1–C-2–C-3–C-4	−51.3	−55.7	−54.7	−55.9	−51.4	−50.7
C-2–C-3–C-4–C-5	53.3	59.9	54.6	56.3	53.9	54.8
C-3–C-4–C-5–O-5	−57.5	−58.7	−55.5	−55.9	−59.6	−56.8
C-4–C-5–O-5–C-1	62.2	55.4	59.6	57.1	64.8	58.6
C-5–O-5–C-1–C-2	−60.9	−52.4	−60.6	−56.7	−61.7	−55.5
O-5–C-1–C-2–C-3	54.1	51.8	57.4	55.4	53.9	50.1

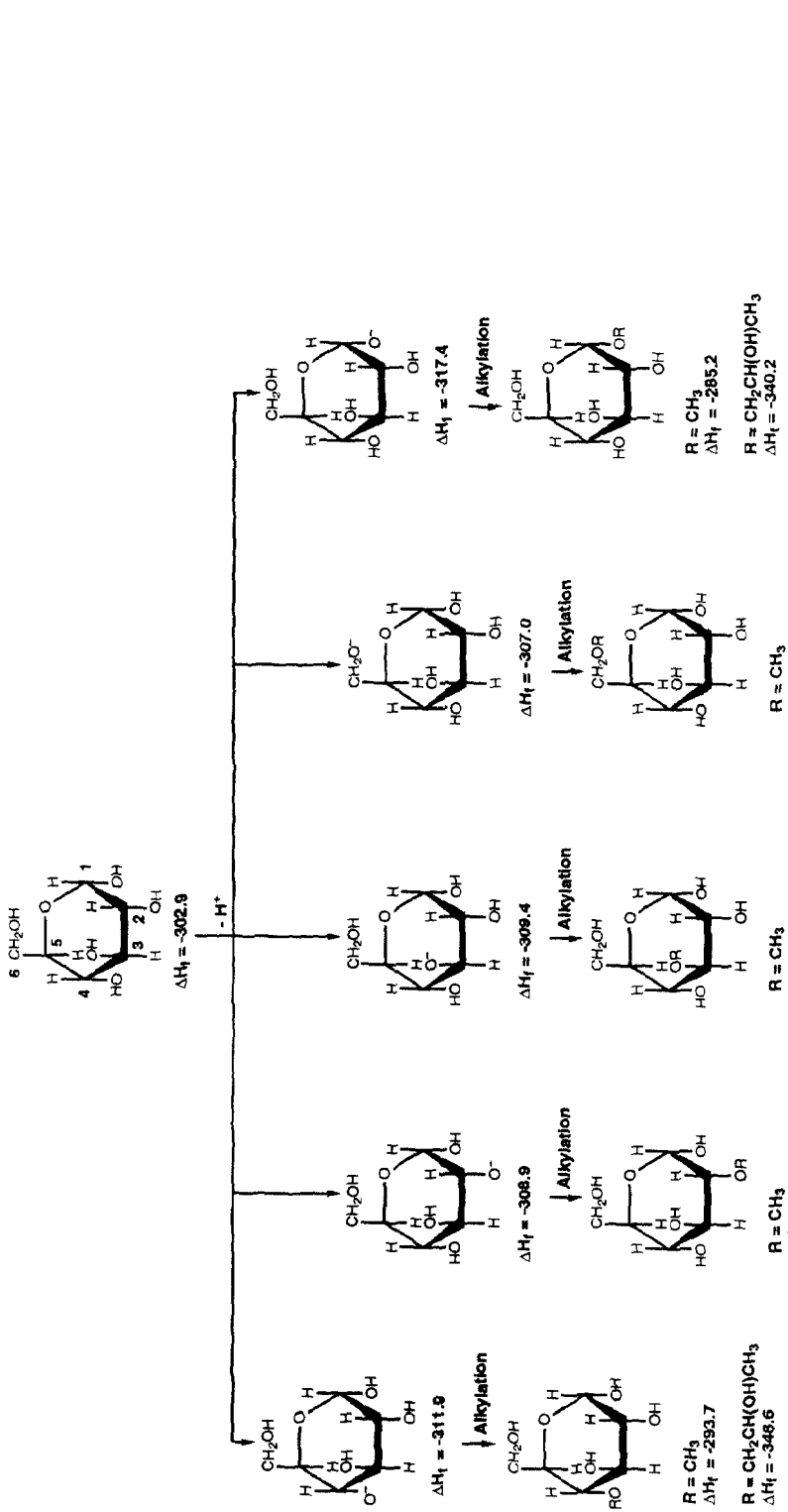
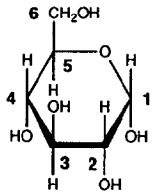


Fig. 3. Deprotonation and alkylation energies for (methylation and (*R*)-2-hydroxypropylation) of α-D-glucopyranose. ΔH_f refers to standard heats of formation in kcal/mol.

editor and minimized using the MM2 molecular mechanics package[16]. The resulting files were then submitted for AM1 optimization, whereby molecular structures and energies [heats of formation (ΔH_f) calculated at standard states in the gas phase in kcal/mol] were obtained by minimizing the total molecular energy with respect to all geometric variables using the Broyden–Fletcher–Goldfarb–Shanno (BFGS) optimization procedure[17,18]. The default SHIFT = 15 eV option was used to allow for 15 eV of damping on self-consistent field iterations to be determined by the rate of convergence, and the PRECISE option was employed to tighten convergence criteria. Vertical ionization potentials were derived from the highest occupied molecular orbital (HOMO) energy using Koopman's theorem[19]. Molecular renderings were produced with the aid of the Chem 3D-plus (Version 2.0.1) software with Cartesian coordinates or *z*-matrices imported from the AM1 output files. Molecular structures obtained from either published X-ray data or the AM1 method were compared with the aid of the FIT routine in the SYBYL modeling interface. All heavy atoms were used in the configurational analysis, and data were

TABLE II

Selected geometric and electronic data for various alkoxy anions of α-D-glucopyranose



Property	α-D-Glucopyranose anion				
	1-O⁻	2-O⁻	3-O⁻	4-O⁻	6-O⁻
Vertical IP (eV)	4.15	3.79	3.76	3.93	3.61
Bond lengths (Å)					
C-1–C-2	1.575	1.570	1.534	1.543	1.543
C-2–C-3	1.535	1.566	1.564	1.526	1.533
C-3–C-4	1.534	1.529	1.568	1.574	1.541
C-4–C-5	1.542	1.537	1.529	1.561	1.527
C-5–O-5	1.407	1.426	1.436	1.441	1.432
O-5–C-1	1.470	1.431	1.419	1.404	1.400
C-1–O-1	1.297	1.403	1.410	1.413	1.419
Atomic partial charge					
O-1	−0.695	−0.328	−0.336	−0.372	−0.395
O-2	−0.374	−0.683	−0.351	−0.330	−0.324
O-3	−0.353	−0.382	−0.711	−0.345	−0.342
O-4	−0.337	−0.364	−0.367	−0.701	−0.440
O-6	−0.362	−0.354	−0.355	−0.364	−0.733

reported in terms of root-mean-square (RMS) deviations in angstroms (Å). For hydroxypropyl derivatives, the (*R*)-2-hydroxypropyl fragment was used.

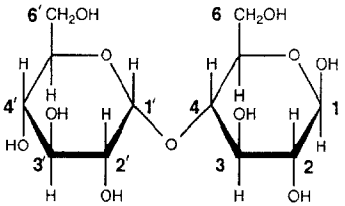
RESULTS

Structural comparisons.—The fully optimized structures and relevant numberings for the model substrates, i.e., α-D-glucopyranose and β-maltose, are given in Figs. 1 and 2, respectively. In addition, geometric parameters derived from the AM1 structures and X-ray crystallographic data are provided in Table I[20–22].

Alkoxide stabilities and deprotonation enthalpies.—The "acidities" of various hydroxy functions in α-D-glucopyranose and β-maltose were examined in a relative fashion by estimating stabilities of the appropriate alkoxy species as reflected by their heats of formation (ΔH_f), as well as by calculating deprotonation enthalpies (DPE)[23]. While ΔH_f values are useful only in comparing structural isomers,

TABLE III

Selected geometric and electronic data for various alkoxy anions of β-maltose



Property	β-Maltose anion						
	α-Glucopyranosyl residue				β-Glucopyranosyl residue		
	2′-O⁻	3′-O⁻	4′-O⁻	6′-O⁻	2-O⁻	3-O⁻	6-O⁻
Vertical IP (eV)	4.50	4.26	4.24	4.13	3.78	4.48	3.68
Bond lengths (Å)							
C-1–C-2	1.573	1.534	1.542	1.544	1.579	1.531	1.543
C-2–C-3	1.563	1.565	1.525	1.535	1.574	1.569	1.534
C-3–C-4	1.540	1.564	1.570	1.542	1.541	1.568	1.534
C-4–C-5	1.531	1.530	1.564	1.528	1.534	1.533	1.529
C-5–O-5	1.430	1.439	1.444	1.431	1.416	1.427	1.427
O-5–C-1	1.414	1.413	1.402	1.405	1.443	1.433	1.412
C-1–O-1	1.437	1.425	1.428	1.424	1.401	1.403	1.406
Atomic partial charge							
O-1	−0.327	−0.284	−0.295	−0.292	−0.333	−0.324	−0.333
O-2	−0.703	−0.373	−0.367	−0.347	−0.667	−0.353	−0.330
O-3	−0.308	−0.704	−0.377	−0.363	−0.309	−0.702	−0.368
O-4	−0.337	−0.364	−0.700	−0.381	−0.313	−0.295	−0.321
O-6	−0.342	−0.346	−0.358	−0.739	−0.360	−0.347	−0.728

TABLE IV

Deprotonation enthalpies (DPE) for various hydroxy groups in α-D-glucopyranose, 2-*O*-[2-(*R*)-hydroxypropyl]-α-D-glucopyranose and β-maltose

Derivative	Deprotonation enthalpy (kcal/mol)
α-D-Glucopyranose	
OH-1	352.6
OH-2	361.1
OH-3	360.6
OH-4	358.1
OH-6	363.1
2-*O*-[2-(*R*)-Hydroxypropyl]-α-D-glucopyranose	
OH-3	352.2
OH-6	365.3
Hydroxypropyl-OH	372.5
β-Maltose	
OH-2′	351.5
OH-3′	349.5
OH-4′	351.9
OH-6′	355.8
OH-2	348.8
OH-3	362.8
OH-6	364.7

deprotonation enthalpies, which are heat of reaction values incorporating product and reactant heats of formation in their magnitude, can be used in intergroup comparisons. The latter parameter is obtained through the following equation:

$$\mathrm{DPE} = \sum \Delta H_f \text{ (products)} - \sum \Delta H_f \text{ (reactants)}$$

or

$$\mathrm{DPE[ROH]} = \left\{\Delta H_f[\mathrm{H^+}] + \Delta H_f[\mathrm{RO^-}]\right\} - \Delta H_f[\mathrm{ROH}]$$

where ΔH_f refers to the heats of formation at standard states for the proton (H^+), the alkoxy sugar (RO^-) and the unionized sugar (ROH). In these determinations, ΔH_f for RO^- and ROH were obtained using the AM1 approximation. Since the ΔH_f for the proton is known not to be well-modeled using semiempirical approaches, the experimental value of 367.2 kcal/mol was used as suggested by Dewar and Dieter[23]. The values obtained for alkoxide stabilities are presented in Figs. 2 and 3 and in Tables II and III for glucopyranose and maltose, respectively. DPE values are collected in Table IV for both species.

Effect of substitution.—α-D-Glucopyranose was substituted in all available hydroxy positions (OH-1, OH-2, OH-3, OH-4, and OH-6) with both methyl and (*R*)-2-hydroxypropyl moieties. In the case of β-maltose, the α-D-glucopyranosyl

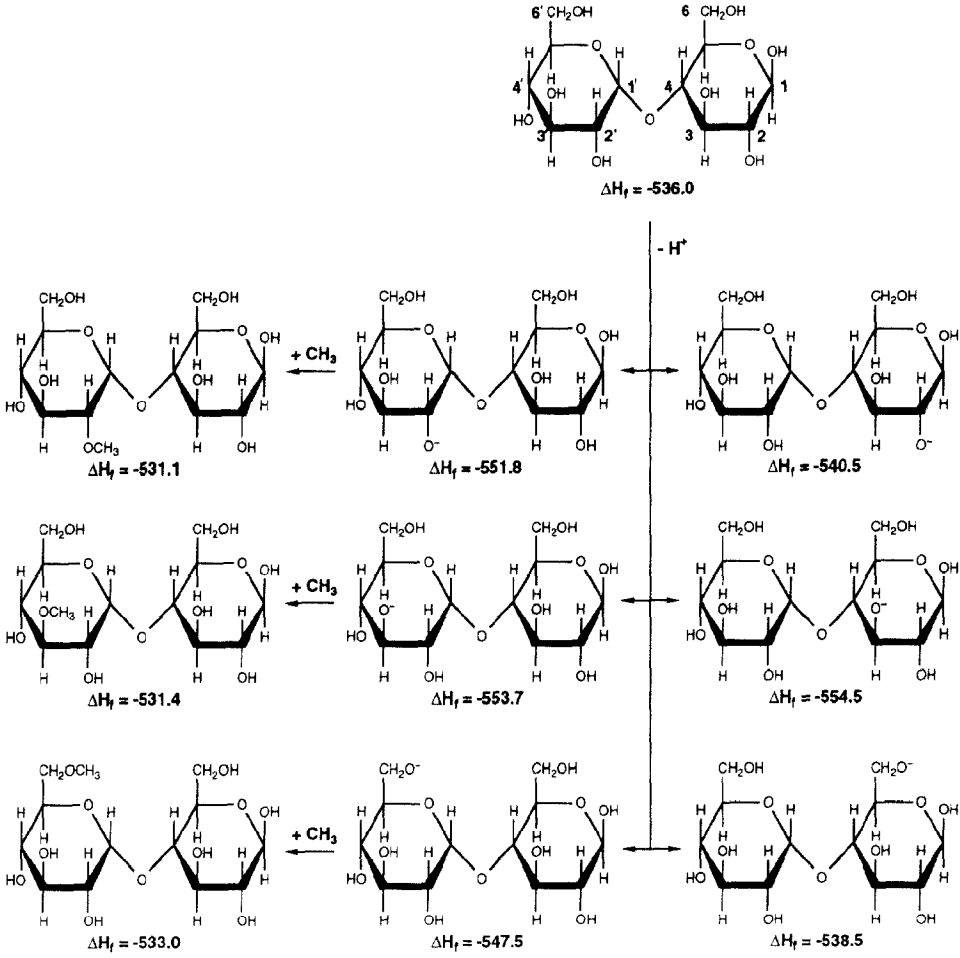


Fig. 4. Deprotonation and methylation energies for β-maltose. ΔH_f refers to standard heats of formation in kcal/mol.

substructure was derivatized to give methyl ethers in the OH-2′, OH-3′, and OH-6′ positions. Heats of formation for the methyl ethers of glucopyranose, as well as the 2-hydroxypropyl glucopyranose derivatives, are given in Fig. 3 and for the methylated maltoses in Fig. 4. In two cases, i.e., the methyl α-D-glucopyranoside and 3-*O*-methyl-α-D-glucopyranose, X-ray crystal structures were available for comparison with AM1-generated structures[24,25].

Effect of O-2 substitution on reactivity at other positions.—A series of calculations were completed with 2-*O*-[(*R*)-2-hydroxypropyl]-α-D-glucopyranose in which anion stabilities and DPEs were calculated for OH-3, OH-6, and hydroxypropyl-OH ionizations. Anion stabilities appear in Fig. 5, while DPE information is given in Table IV. Finally, substitution of 2-*O*-[(*R*)-2-hydroxypropyl]-α-D-glucopyranose with (*R*)-2-hydroxypropyl functions at either the OH-3, OH-6, or hydroxypropyl-OH

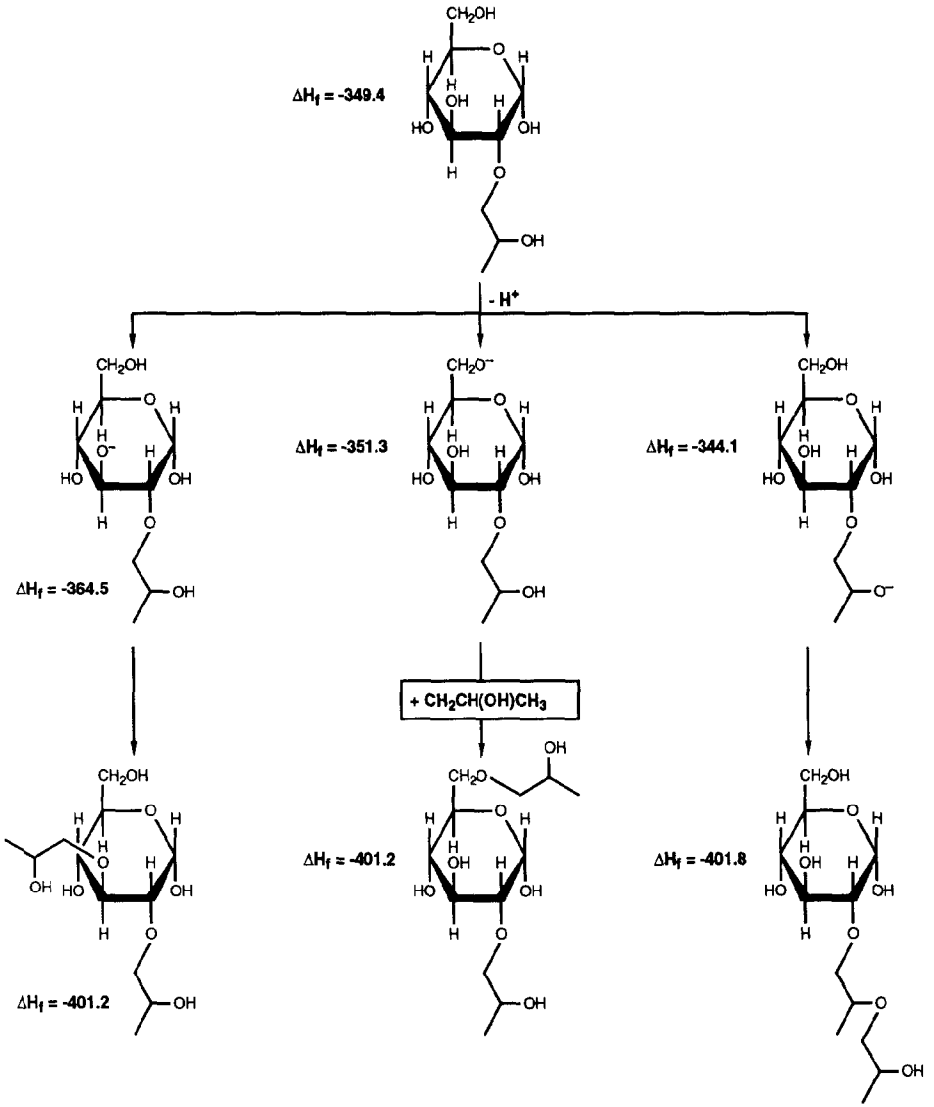


Fig. 5. Deprotonation and 2-(*R*)-hydroxypropylation energies for 2-*O*-[(*R*)-hydroxypropyl]-α-D-glucopyranose. ΔH_f refers to standard heats of formation in kcal/mol.

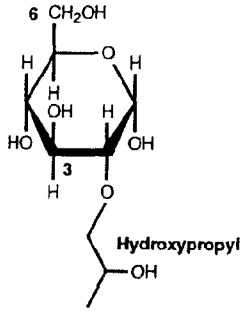
was completed, and associated heats of formation are also presented in Fig. 5. Selected geometric and electronic data are given in Table V.

DISCUSSION

Semiempirical studies of carbohydrates could be of enormous value assuming confidence in the method for this application could be established. It is in that vein

TABLE V

Selected geometric and electronic data for various alkoxy anions of 2-*O*-[2-(*R*)-hydroxypropyl]-α-D-glucopyranose



Property	2-*O*-[2-(*R*)-Hydroxypropyl]-α-D-glucopyranose anion		
	3-O^-	6-O^-	Hydroxypropyl-O^-
Vertical IP (eV)	4.19	3.39	3.14
Bond lengths (Å)			
C-1–C-2	1.538	1.552	1.544
C-2–C-3	1.562	1.534	1.536
C-3–C-4	1.569	1.538	1.537
C-4–C-5	1.530	1.533	1.533
C-5–O-5	1.426	1.432	1.423
O-5–C-1	1.428	1.417	1.430
C-1–O-1	1.403	1.401	1.394
Atomic partial charge			
O-1	−0.333	−0.325	−0.321
O-2	−0.307	−0.297	−0.275
O-3	−0.713	−0.361	−0.326
O-4	−0.378	−0.339	−0.337
O-6	−0.355	−0.751	−0.343
O-Hydroxypropyl	−0.353	−0.345	−0.717

that the present investigation was conducted. While some minimal basis set ab initio[26] and semiempirical studies at the CNDO level of sophistication have been applied to simple sugars[27,28], the use of the AM1 method to study carbohydrate reactivity is novel. Importantly, other uses of semiempirical tools in the carbohydrate area are conspicuous. Thus, the anomeric effect has been the subject of several investigations where semiempirical methods have been successfully used[29,30]. Given these circumstances, careful comparisons between X-ray crystal structure and experimental heats of formation were completed at the onset of this work to provide some level of confidence in the method selected for the purposes selected. As shown in Table I, semiempirically derived structures for α-D-gluco-

pyranose and maltose closely mirror experimentally obtained crystal structures both in terms of bond lengths and ring puckering[20]. Conformational analysis reveals that the two structures of α-D-glucopyranose vary by an RMS deviation of 0.1 Å. Importantly, since the semiempirical methods explicitly treat electrons, they can provide electronic and molecular orbital information wich may have geometric ramifications. As suggested above, pyranoses demonstrate the anomeric effect in which orbital overlap favors axial orientation at the anomeric carbon[31,32], resulting in distortion of bond lengths associated with the anomeric carbon. Thus, the shortening heterocyclic O-5–anomeric carbon (C-1) and C-1–O-1 bonds relative to other ring bonds is predicted using the AM1 method.

The theoretically determined structure of β-maltose was also found to closely agree with X-ray crystallographic data as demonstrated in Table I[21,22]. Conformational analysis indicates a good RMS fit with a deviation of 0.3 Å. Other structures determined in the course of the present studies including methyl α-D-glucopyranoside and 3-*O*-methyl-α-D-glucopyranose were also found to closely compare to X-ray crystal data when such information was available[24,25].

When α-D-glucopyranose was subjected to deprotonation, alkoxides were formed with energies (ΔH_f) indicating the following order of stability OH-1 > OH-4 > OH-3 > OH-2 > OH-6 (Fig. 3). For those hydroxy functions available for substitution in biopolymers such as starch and cellulose, the OH-2 and OH-3 were fairly close in energy, differing by less than 0.5 kcal/mol, while the OH-6 was more than 2.2 kcal/mol less stable than the averaged secondary hydroxy anions stabilities. These differences are reflected in the DPE values (Table IV) that suggest the OH-2 and OH-3 are more acidic than the corresponding OH-6 group. These trends are likewise observed in the ionization of β-maltose and suggest that the primary alcohol is more difficult to ionize than either secondary hydroxy species (Fig. 4). These results are consistent with a variety of experimental findings, which showed that, for glucopyranose oligomers such as cyclodextrins, base titration resulted in significant changes in the ^{13}C NMR resonances of the C-2 and C-3 pyranose ring carbons, while the NMR evaluations showed little change in the C-6 resonance, suggesting that the secondary (OH-2, OH-3), but not the primary (OH-6) hydroxy groups, were involved with the initial ionization process[33]. The greater acidity of the secondary hydroxy functionalities has also been suggested in cellulose[34]. The differences in pK_a values for the primary and secondary hydroxy groups has been exploited synthetically to provide selective alkylation. Thus, in preparing ethers of cyclodextrins or cellulose, a low base environment promotes preferential ionization of the secondary hydroxy groups which, due to their increased nucleophilicity, enhances alkyl substitution at these sites[35–37].

The acidities of component hydroxy groups are not, however, the only parameters affecting product composition. The accessibility of the nucleophilic functions, as well as the relative stability of the product formed, are also important. To examine these variables, methylated derivatives of α-D-glucopyranose and β-maltose and hydroxypropyl ethers of α-D-glucopyranose were evaluated. In the

glucopyranose series, the relative stability of methyl ether isomers (Fig. 3) was 6-OCH_3 > 4-OCH_3 > 2-OCH_3 > 3-OCH_3 > 1-OCH_3 with relative differences of ΔH_f ($\Delta\Delta H_f$) of 0, 2.3, 2.9, 3.6, and 10.76 kcal/mol, respectively, when the 6-OCH_3 isomer was used as a comparative benchmark. In the hydroxypropyl series, the isomeric stabilities were 6-*O*-[(*R*)-2-hydroxypropyl (HP)] > 2-*O*-(2HP) > 4-*O*-(2HP) > 3-*O*-(2HP) > 1-*O*-(2HP), and the $\Delta\Delta H_f$ base on the 6-*O*-(2HP) isomers were 0, 3.52, 4.38, 5.06, and 12.8 kcal/mol, respectively. For the OH-2, OH-3, and OH-6 positions, the predicted order of substitution is the same and indicates that the primary alcohols provide the lowest energy isomers due to lower steric interaction and lower nonbonded congestion. Interestingly, the 2-hydroxypropyl group provides for a greater $\Delta\Delta H_f$ between the most and least stable isomers compared with methyl substitution consistent with the greater bulk of the 2-hydroxypropyl function. These calculations suggest that if there is no difference in the nucleophilicity of the OH-2, OH-3, and OH-6 positions, that substitution at the more accessible OH-6 will thermodynamically predominate. This appears to occur experimentally in cases when base concentrations are high, a situation which ionizes all hydroxy groups, since preferential alkylation occurs at the primary OH-6 functionality. Such findings have been observed in both cellulose and cyclodextrins[35–37].

The data above suggest that the stability of OH-2 and OH-3 ethers is similar, i.e., the difference in the ΔH_f of the 2-OCH_3 and 3-OCH_3 isomers is only 0.7 kcal/mol. This proposes that, all things being equal, alkylation at the OH-2 or OH-3 loci should occur to a similar extent. Experimental evidence is supportive of the theoretical conclusions in cases where glucopyranose monomers or derivatives thereof are examined. For example, methylation of 1,4,6-tri-*O*-protected glucopyranose residues, such as methyl 4,6-*O*-ethylidene-β-D-glucopyranoside or methyl 4,6-*O*-benzylidene-β-D-glucopyranose, gives rise to equal proportions of the 2-*O* and 3-*O* ether derivatives[38]. Interestingly, the alkylation of glucopyranose biopolymers suggest that the OH-3 position may react somewhat slower than the OH-2 or OH-6 positions, although recent data dispute this differential reactivity[39]. If there are indeed differences in OH-2 and OH-3 reactivity, these effects may be due to a matrix phenomenon such as hydrogen bonding.

In extending these ideas to glucopyranose polymers, the calculations reported herein are consistent with Spurlin's statistical kinetic model for ether substitution in cellulose[40]. In his model, all sugar residues are treated independently, consistent with the use of glucopyranose as a model for starch or cellulose. In the Spurlin treatment, the extent of substitution at a particular hydroxy function is theorized to be governed by the relative reactivity of the hydroxy groups, again a precept compatible with the current investigation. An important tenet of the construct is that substitution in a particular glucopyranose residue may affect the reactivity of other positions in that residue to further substitution. In at least one case, that of carboxymethylation, it appears that an initial substitution has no effect on subsequent reactivity[13]. On the other hand, in the case of methylation, ethylation,

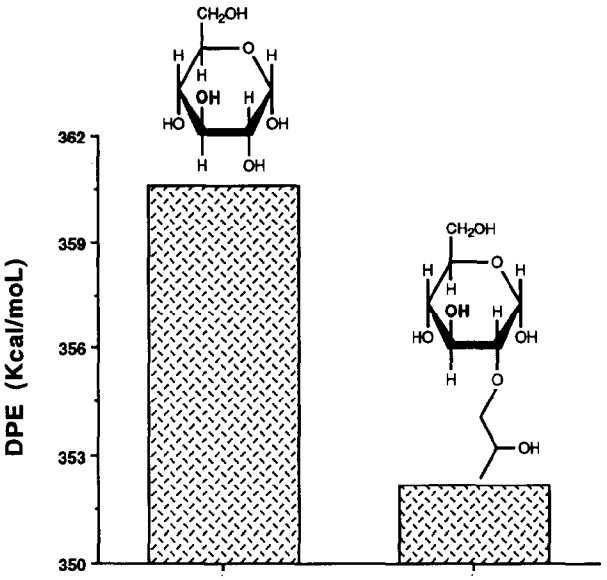


Fig. 6. Deprotonation enthalpies (DPE) for ionization of the OH-3 group of α-D-glucopyranose and 2-*O*-[(*R*)-2-hydroxypropyl]-α-D-glucopyranose.

hydroxyethylation and hydroxypropylation of cellulose[41–43] and hydroxypropylation of cyclodextrin[35,36], the experimental data support the idea that substitution at the OH-2 position enhances reactivity at the OH-3 but not at other loci. A case in point is the hydroxypropylation of cyclodextrin. In the reaction, the proportion of the 2,3-bis-*O*-(2-hydroxypropyl) isomer increases disproportionately as a function of 2-*O*-hydroxypropylation. To examine this tendency, 2-*O*-[(*R*)-2-hydroxypropyl]-α-D-glucopyranose was used as a model residue, and alkoxide stabilities and DPEs were determined for ionization at the OH-3, OH-6, and hydroxypropyl-OH positions. As shown in Table IV and Fig. 5, the order of alkoxide stability of the anions of 2-[(*R*)-2-hydroxypropyl]-α-D-glucopyranose and α-D-glucopyranose was found to be OH-3 > OH-6 > 2-hydroxypropyl-OH. Importantly, substitution of a 2-hydroxypropyl group at the OH-2 position of glucopyranose appears to lower the DPE of the OH-3 by 8.4 kcal/mol relative to the unsubstituted sugar (Fig. 6). Thus, several factors may be involved in the activation of the OH-3 group when the OH-2 function is substituted, including decreases in the pK_a for the OH-3 position.

These data also point to the relatively low reactivity of the hydroxy function associated with the added 2-hydroxypropyl group, as the DPE for this moiety is more than 20 kcal/mol higher than OH-3 ionization and 7 kcal/mol higher than OH-6 dissociation. Experimentally, little, if any, poly(propyleneglycol) formation is observed in hydroxypropylation of cyclodextrin consistent with the low reactivity suggested herein[35]. Interestingly, while such side reactions do not occur in hydroxypropylation, they have been detected in hydroxyethylation[41]. Finally, while there is a significant difference in the stability of the intermediate alkoxides, the

bis-*O*-(2-hydroxypropyl) derivatives are of similar energy, indicating that steric interactions and hydroxy availability are comparable in the three structures.

CONCLUSIONS

The theoretical studies on glucopyranose and maltose provided herein suggest that semiempirical manipulation of these substrates can provide chemically useful information. These data give an electronic basis for the higher acidities of the secondary glucopyranose hydroxy functions, as well as a steric rationale for the greater accessibility of the primary hydroxy groups in various substitution reactions. In addition, the calculations presented suggest that a considerable part of the chemistry of starch and cellulose can be investigated through examination of the monomers, which is consistent with the classical work of Spurlin[40].

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